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Edited by
Peter Boyle and Bernard Levin

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Editors	Peter Boyle Bernard Levin
Regional Editors	Ketayun Dinshaw Miklos Kasler Twalib Ngoma Luis Pinillos Ashton Murat Tuncer Ping Zhao
Assisting Editors	Philippe Autier Paulo Boffetta Pierre Hainaut Sylvia Franceschi Hiroko Ohgaki Sean Tavtigian
Coordinating Editors	John Daniel Eric Duell Caroline Granger
Layout	messaggio studios
Illustrations	Roland Dray Sharon Grant Georges Mollon
Printed by	naturaprint
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Contributors

Rosita Accardi
Clement Adebamowo
Ben Anderson
Philippe Autier
Robert Baan
Mariano Barbacid
Paolo Boffetta
Mathieu Boniol
Peter Boyle
Jo Brady
Anne Brédart
Paul Brennan
Jean-Benoît Burrion
Elodie Caboux
Franco Cavalli
Young-eun Cho
Gary Clifford
Vincent Cogliano
Maria-Paula Curado
David Currow
Jean-Marie Dangou
Ketayun Dinshaw
Sylvie Dolbeault
Jean-François Doré
Mary Doroshenk
Eric Duell
Mary Farfán
Jill Farrington
Rodrigo Feijó
Jacques Ferlay
Pietro Ferrari
Silvia Franceschi
Pierre Hainaut
Uzma Hasan
Mia Hashibe
Mary Heanue
Julia Heck
Zdenko Herceg
Lisa-Maree Herron
Rayjean J. Hung
Mazda Jenab
Miklos Kasler
David Kerr
Namory Keita
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Patrick Maisonneuve
James McKay
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Gordon McVie
Richard Muwonge
Maria-Claudia Nascimento
Twalib Ngoma
Hiroko Ohgaki
Shigeru Omi
Claudio Pelucchi
Luis Pinillos Ashton
Samlee Plianbangchang
Martyn Plummer
Amelie Plymoth
Qing Qing
Kunnambath Ramadas
Giorgia Randi
Darius Razavi
Sabina Rinaldi
Ulrik Ringborg
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Massoud Samiei
Rengaswamy Sankaranarayanan
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Ghislaine Scelo
Mary Jane Schier
Vladimir Semiglazov
Hai-Rim Shin
Sudhir Srivastava
Eva Steliarova-Foucher
Kurt Straif
Bakary Sylla
Sean Tavtigian
Massimo Tommasino
Murat Tuncer
Larry von Karsa
Joachim Weiss
Yi-Xin Zeng
Yawei Zhang
Ping Zhao
Tongzhang Zheng

For a complete list of contributors and their affiliations see pages 493-496

Contents

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Foreword

The International Agency for Research on Cancer (IARC) was founded by Resolution of the World Health Assembly in September 1965. At this time, although data were sparse, cancer was widely considered to be a disease of westernised, high-resource, industrialised countries. Today the situation has changed dramatically, with the majority of the global cancer burden now found in low- and medium-resource countries.

The global burden of cancer has more than doubled during the past 30 years. In 2008, it is estimated that there were over 12 million new cases of cancer diagnosed, 7 million deaths from cancer and 25 million persons alive with cancer. The continued growth and ageing of the world's population will greatly affect the cancer burden. By 2030, it could be expected that there could be 27 million incident cases of cancer, 17 million cancer deaths annually and 75 million persons alive with cancer within five years of diagnosis.

The greatest impact of this increase will fall on the low- and medium-resource countries. Such countries are, arguably, harder hit by cancer than the high-resource countries. These countries frequently have a limited healthcare budget and a high background level of communicable disease. Cancer treatment facilities are not universally available and life-saving therapies are frequently unavailable for economic reasons. Cancer, and other chronic diseases that are becoming more common, can cause devastating damage to entire families when the head of household and frequently the only source of income for a frequently an extended family, succumbs to cancer.

The rapid increase in the cancer burden represents a crisis for public health and health systems worldwide. A major issue for many countries, even among high-resource countries, will be finding sufficient funds to treat all cancer patients effectively and provide palliative, supportive and terminal care for the large numbers of cancers which will be diagnosed in the coming years.

However, there are prospects for cancer prevention in all resource settings. Tobacco smoking is the best-understood major human carcinogen. One third of cancers in high-resource countries are caused by tobacco smoking, which also causes a large proportion of deaths from other chronic disease including vascular disease and chronic obstructive pulmonary disease. The worst of the tobacco epidemic has yet to materialise in low-resource countries. There is a 40-year temporal gap between big changes in tobacco prevalence in a population and the peak of the disease epidemic caused by this habit. Tobacco control is a major task for countries irrespective of their resource setting.

Modifiable risk factors for cancer have been identified, including alcohol consumption, excessive exposure to sunlight, lack of physical activity, overweight and obesity, dietary factors, occupational exposures and chronic infection. Effective prevention will reduce the risk of cancer, and effective screening will allow many others to be successfully treated for their disease.

In low-resource countries, many common cancers such as primary liver cancer, cervix cancer, nasopharynx cancer, Kaposi Sarcoma and stomach cancer are caused by chronic infections with different agents. In these circumstances, there are now prospects for prevention via vaccination for hepatitis B (liver cancer) and human papillomavirus (cervix cancer). The major issue in the poorest countries is delivery of the prevention action at a price that is affordable for the countries' health systems.

Identification of risk factors for cancers is not a simple task, and delivering effective prevention can be even more difficult. Prevention research must take on a higher profile and greater importance in the broad cancer research strategy and in those cancer plans currently being developed. An additional advantage of prevention is that many key risk factors for cancer are shared with other common conditions such as vascular disease and diabetes.

A complete understanding of the mechanisms of the development of cancer is very unlikely to come about in the foreseeable future, making impossible reliance on a single approach to prevent cancer and deaths from the disease. Translational research in its broadest meaning is of paramount importance, covering the spectrum from translating cutting-edge scientific discovery into new approaches to cancer treatment to translating information about cancer risk factors into changes in population behaviour.

Priorities clearly must be identified to tackle the global cancer burden. Such priorities must include a focus on low- and medium-resource countries and the identification, delivery and evaluation of effective cancer control measures. Focus should be on the four pillars of cancer control: prevent those cancers which can be prevented; treat those cancers that can be treated; cure those cancers that can be cured; and provide palliation whenever palliation is required.

Peter Boyle
Director
International Agency for Research on Cancer

1

Global Cancer Control

1.1 Introduction: Needs and Prospects for Cancer Control

Cancer can quite easily be thought of as a *modern* disease but there are good reasons why this may only appear to be the case. Firstly, cancer and heart disease are the major diseases and causes of death in old age, and it was only really during the latter stages of last century that large proportions of people began living to the seventh, eighth and ninth decades of life—decades at which chronic diseases are commonest.

Life expectancy in Ancient Egypt was around 40 years; this fell during the Dark and Middle Ages before rebounding to the same level in the middle of the 19th century. The large increase in life expectancy to current levels (Table 1.1.1) has been brought about by the cure or control of a large number of otherwise fatal diseases such as plague, cholera, diabetes, malnutrition, diseases of infancy and other infectious diseases such as tuberculosis.

The declines in death rates over the roughly hundred-year period 1848–54 to 1971 in England and Wales are remarkable. Major killers such as tuberculosis have seen a drop in mortality from 2901 per million over the period 1848–54 to 13 per million in 1971. Scarlet fever, diphtheria, whooping cough, measles, smallpox, puerperal fever, syphilis, typhus and non-respiratory tuberculosis have been virtually eliminated as a cause of death (Table 1.1.2). This has been a golden era for medicine and public health.

A second point is that better clinical diagnosis has led to more cases of cancer being diagnosed, a proportion of which would have previously been missed. There has been a remarkable improvement in imaging [1] and other diagnostic techniques, which have contributed substantially to an increased chance of diagnosis and to a more accurate diagnosis of cancer.

While there are reasons for an artefactual increase in the cancer burden, there has undoubtedly been a real increase in the number of people who develop cancer due to an increased exposure to etiological agents. The impact of cigarette smoking on lung cancer is salutary in making what was an otherwise extremely rare form of cancer at the beginning of the twentieth century into the commonest cancer in many populations a century later.

Men			
Highest Life Expectancy		Lowest Life Expectancy	
Andorra	80.6	Swaziland	39.8
Iceland	80.2	Sierra Leone	41.0
Hong King	79.4	Angola	41.2
Japan	79.0	Mozambique	41.7
Switzerland	79.0	Zambia	42.1
Australia	78.9	Lesotho	42.0
Sweden	78.7	Central African Rep	43.3
Israel	78.6	Afghanistan	43.9
Macau	78.5	Zimbabwe	44.1
Canada	78.3	Rwanda	44.6
New Zealand	78.2	Liberia	44.8
Singapore	78.0	Guinea-Bissau	44.9
Norway	77.8	Congo	45.2
Spain	77.7	Nigeria	46.4
Cayman Islands	77.5	Somalia	46.9
Italy	77.5	Cote d'Ivoire	47.5
Netherlands	77.5	Burundi	48.1
Malta	77.3	Malawi	48.1
Women			
Highest Life Expectancy		Lowest Life Expectancy	
Andorra	86.6	Swaziland	39.8
Japan	86.1	Lesotho	42.3
Hong Kong	85.1	Mozambique	42.4
Spain	84.2	Zambia	42.5
Switzerland	84.2	Zimbabwe	42.7
France	84.1	Afghanistan	43.8
Australia	83.6	Sierra Leone	44.2
Italy	83.5	Angola	44.3
Iceland	83.3	Central African Rep	46.1
Virgin Islands (US)	83.3	Liberia	46.6
Sweden	83.0	Nigeria	47.3
Canada	82.9	Congo-Kinshasa	47.7
Faroe Islands	82.8	Rwanda	47.8
Israel	82.8	Guinee-Bissau	47.9
Macau	82.8	Malawi	48.4
Cayman Islands	82.7	Cote d'Ivoire	49.3
Puerto Rico	82.7	Somalia	46.9
Austria	82.6	South Africa	49.7

Table 1.1.1 *Countries with highest and lowest life expectancy in men and women, 2005-2010 (Abstracted from Pocket World in Figures (2008 Edition). The Economist, London).*

Isaac Adler (1849-1918) wrote the first major medical text dealing with the pathology and clinical aspects of primary lung cancer [2]. He wrote:

"Is it worthwhile to write a monograph on the subject of primary malignant tumours of the lung? In the course of the last two centuries an ever-increasing literature has accumulated around this subject. But this literature is without correlation, much of it buried in dissertations and other out-of-the-way places, and, with but a few notable exceptions, no attempt has been made to study the subject as a whole, either the pathological or the clinical aspect having been emphasised at the expense of the other, according to the special predilection of the author. On one point, however, there is nearly complete consensus of opinion, and that is that primary malignant neoplasms of the lungs are among the rarest forms of the disease. This latter opinion of the extreme rarity of primary tumours has persisted for centuries."

Similar to lung cancer, several other major modern diseases were newly described and evolved rapidly during the twentieth century. For example, according to Poole-Wilson et al. [3], myocardial infarction was first described in a patient in 1910 by Obrastzow and Straschenko [4] and by Herrick [5]. Acute appendicitis was first described by Reginald Fitz in 1886 [6].

Cancer is not a modern disease

Cancer is not a modern disease but has clearly existed for many centuries. It is however a more common phenomenon in man nowadays than previously, in large extent due to the growth of the world's population and the relatively advanced age to which people now live, since it is a disease that is more common in elderly ages than in younger ages.

Researchers have attempted to seek early evidence of cancer from study of fossil remains. A tumour has been reported from the tail of a dinosaur, but there remains some doubt as to whether this is a true malignant tumour or a callous consequent to an injury to the animal's tail, some 80 feet from its brain [7]. Moodie and Abel [8] then described a tumour of the dorsal vertebrae in a cretaceous mosasaur (a large lizard) but there was never conclusive proof of malignancy. This, once again, could likely have been the result of injury as was another lesion, described as an osteosarcoma, found in the fossilised remains of the femur of a cave bear [9].

Cause of Death	1848–54	1971
Tuberculosis	2901	13
Bronchitis, influenza	2239	603
Scarlet fever, diphtheria	1016	0
Whooping cough	423	1
Measles	342	0
Smallpox	263	0
URT infections	75	2
Cholera, dysentery	1819	33
Typhoid (typhus)	990	0
Non-Respiratory TB	753	2
Infections in Infants	1322	0
Puerperal fever	62	1
Syphilis	50	0
Other Infections	635	52

Table 1.1.2 *Death rates (per million) from various causes in England and Wales in 1848–1854 and 1971 (Data abstracted from Cairns [59])*

Evidence has been found in bony (skeletal) remains of both true bone tumours and destructive lytic lesions, and radiographic examination has also been able to detect smaller, occult deposits suggestive of disseminated disease [10]. The femur of a *homo erectus* (Pithecanthropus) dating from 450 000 BC initially gave the appearance of a tumour but could equally likely to have been *myositis ossificans*. There is also the possibility that a lesion found in the calvarium of a skeleton from the Twentieth Dynasty of Ancient Egypt (c. 1200 BC) exhibits malignant destruction of the jaw, sinus and palate with a surrounding zone of osteitis. Radiography has revealed 26 lesions in the skull of a man (aged around 30 years) with the appearance of multiple myeloma (or at least multiple secondary deposits) [11].

While there is suggestive but little conclusive evidence of cancer in fossilised or bony remains, there is clear evidence of the existence of cancer from study of Egyptian mummies. Granville [12] reported the dissection of an ancient Egyptian female mummy that revealed widespread disease of the ovaries with abdominal extensions, considered as bilateral malignant cystadenoma. Interestingly, while analysis of 88 adult and 5 child mummies revealed tumours of the bone, nasopharynx and mouth, they failed to find common modern-day tumours such as breast, colon, stomach and lung.

Cancer has been described by writers in ancient Greece, Rome and Persia, and it has been noted and treated in medieval texts. The American Egyptologist Edwin Smith brought to light what has become to be known as the Edwin Smith Surgical Papyrus, dating from about 2500 BC, which is devoted to surgical case histories, and number 45 in this series contains some of the earliest writings on cancer:

".....if thou examinest a [woman] having bulging tumours on [her] breast and thou findest that swellings have spread over [her] breast, it thou puttest they hand upon [her] breast upon these tumours thou findest them very cool, there being no fever at all therein when thy hand touches [her], they have no granulation, they form no fluid, they do not generate secretions of fluid and they are bulging to thy hand. Thou shouldest say concerning [her], "One having bulging tumours. There is no treatment."

(Translated by Professor James Breasted in 1930 [13]).

Another papyrus describes a tumour of the uterus treated by local vaginal application of fresh dates and limestone with and without pig's brain. Writings from ancient India (Ayuruedic books) suggest that cancer was able to be diagnosed correctly over 2500 years ago but was considered incurable. Tumours of the oral cavity, pharynx, oesophagus, pelvis and rectum are described, but no mention is made of cervix, breast, lung or bone cancers.

The aphorisms of Hippocrates of Cos (born 460 BC) contain a variety of references to malignant disease. Number 38 states: *"Every cancer not only corrupts the part it has seized but spreads further"*. Galen (131-200 AD) noted that *"cancerous tumours develop with greatest frequency in the breasts of women"*. He described a tumour raised above the skin, extending along the lymphatic vessels radially on all sides and often with red streaks: such tumours may ulcerate and discharge a dark, reddish, evil-smelling secretion. Galen likened the lesion to a crab: *karkinos* in Greek and *cancer* in Latin. He recognised that surgery was the only chance of cure and must be done at an early stage when excision of the whole lesion was possible.

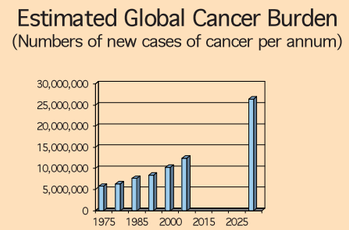
The captured Greek physician, Democedes, was called upon by King Darius of Persia to treat Atossa, the Queen, who had a lump in her breast that increased in size and eventually ulcerated: modesty had prevented her showing it to anyone until it had reached a large size.

Little progress or mention was made of cancer until the 18th century, when Bernard Peyrihle proposed a viral theory of cancer. John Hunter gave a long account of surgery for cancers of the female breast, uterus, lips and stomach and advised that tumours may be hereditary, and that palpitation of the mass should be gentle in case rough handling spread the disease. He noted that *"no cure has been found"*. In 1775, Percival Pott [14] described the occupational cancer of the scrotum that occurred in chimney sweeps. In 1761, John Hill suggested that snuff was responsible for nasal cancer and polyps [15]. Prior to this, in 1743 Ramazzini [16] had reported an excess of breast cancer in nuns in Padua.

Treatment advances came in the nineteenth century. In 1881, Billroth performed a successful gastrectomy for stomach cancer and in 1884, Godlee removed a brain tumour. William Marsden founded his Cancer Hospital in 1851 with two aims: care of the cancer patient and cancer research. The century closed with the discoveries of Roentgen and the Curies, which led to radiological diagnosis and radiotherapy, and the work of Beatson on hormonal manipulation in breast cancer.

Different forms of cancer have been recognised and treated for centuries, and it is advances in civilisation and the associated improvement in life expectancy that has contributed to making cancer such a common disease worldwide. In the United Kingdom in 1880 approximately half of the population died before 45 years of age and this decreased to around 3% in 1980. In 1880 in the United Kingdom, 25% of the population reached the age of 70; in 1990 the corresponding figure was 70% [17]. More recently, the effective prevention of cardiovascular diseases led to an acceleration of the decline of premature mortality and an increase in life expectancy and, inadvertently, cancer. More and more men and women are alive today at ages when cancer is more common than ever before, and the phenomenon is not restricted to a handful of developed countries.

Is such an increase as estimated for the year 2030 in the global cancer burden consistent with current trends? In 1975 it was estimated [1] that the global cancer burden was 5.9 million. The figure contains subsequent estimates made for 1980 [2], 1985 [3], 1990 [4], 2000 [5], 2002 [6] and 2030 (in this chapter). The global burden doubled in the last third of the twentieth century and the trend from this year (2008) to 2030 looks feasible when the long-term trends are examined.



1. Parkin DM, Stjernswärd J and Muir CS. Estimates of the worldwide frequency of twelve major cancers. Bull World Health Organ. 1984;62(2):163-82

2. Parkin DM, Läärä E, Muir CS. Estimates of the worldwide frequency of sixteen major cancers in 1980. Int J Cancer. 1988 Feb 15;41(2):184-97.

3. Parkin DM, Pisani P, Ferlay J. Estimates of the worldwide incidence of eighteen major cancers in 1985. Int J Cancer. 1993 Jun 19;54(4):594-606

4. Parkin DM, Pisani P, Ferlay J. Estimates of the worldwide incidence of 25 major cancers in 1990. Int J Cancer. 1999 Mar 15;80(6):827-41

5. Parkin DM. Global cancer statistics in the year 2000. Lancet Oncol. 2001 Sep;2(9):533-43.

6. Ferlay J, Bray F, Pisani P and Parkin DM. GLOBOCAN 2002: Cancer Incidence, Mortality and Prevalence Worldwide IARC CancerBase No. 5. version 2.0, IARCPress, Lyon, 2004.

Priority setting requires knowledge of the cancer burden

Priority setting for cancer control and cancer services in any region needs to be based on knowledge of the cancer burden and the local mix of predominant cancer types. Unfortunately, neither the number of new cases of cancer nor the number of deaths caused by cancer is available from many parts of the world—in 2000, less than 20% of the world's population was covered by Cancer Registration and 35% by vital statistics schemes based on medically-certified cause of death. Furthermore, this coverage was not spread equally over the globe: in Africa less than 13% of the population was covered by such schemes, and in Asia about 9% was covered; by contrast, 95% of the population of Latin America was covered. The corresponding figures for cancer incidence statistics was 8% for Africa, 7% for Asia and 13% in Latin America.

The International Agency for Research on Cancer (IARC) estimated that for the year 2008 there were 12.4 million incident cases of cancer, 7.6 million deaths from cancer and 28 million persons alive with cancer within five years from initial diagnosis. IARC also estimated that just over half of incident cases and two thirds of cancer deaths arise in low- and medium-income countries. In 2008, the world population was estimated to be 6.7 billion and was expected to rise to 8.3 billion by 2030 [18]. During this period the populations of high-income countries are expected to increase by 4% while the increase is expected to be approximately 30% in low- and medium-income countries. Additionally, the proportion of the population in low- and medium-income countries aged over 65 is expected to increase by 5% to 10%. In view of the strong association between cancer rates and age, these will combine to increase the cancer burden by 2030, with low- and medium-income countries most affected.

There are several clearly identified causes of cancer [19-22] and several strategies that can lead to reductions in cancer incidence and mortality [23]. Currently, the most common forms of cancer differ between high-income countries and the remainder. In high-income countries, cancers of the lung, breast, prostate and colorectum dominate, and one third of cancers are caused by tobacco use and 10% by chronic infection [24]. Cancer control priorities include tobacco control, (high-tech) screening for small tumours, and curative treatment.

In low-resource and medium-resource countries, cancers of the stomach, liver, oral cavity, and cervix dominate [25,26]. This pattern is changing rapidly, with large increases in many parts of the world where lung, breast, and colorectal cancer have been historically uncommon. One quarter of the cancer burden in low-resource countries appears to be attributable to chronic infection, but 12% is currently caused by tobacco, and this proportion is growing [26]. Cancer control priorities in these countries include tobacco control and (low-tech) screening for down-staging, with treatment frequently aimed at palliation.

The great problems facing low- and medium-resource countries into this century are the growth and ageing of the population and the *westernisation* of their lifestyle, particularly the growth in the prevalence of tobacco smoking [25]. Changes in lifestyle habits including changing nutritional practices, increase in sedentary lifestyle, weight gain and obesity and sociological changes, notably increasing age at first birth and decreasing parity in women, are leading to large increases in breast and colorectal cancer in particular.

Tobacco is the best identified human carcinogen and is carcinogenic in all its forms of use [27,28]. It is clear, and has been for several years now, that the effect of tobacco on cancer risk, and indeed on overall mortality, is far in excess of any other common risk factor or treatment effect [29]. Information nowadays taken for granted (*half of smokers die of a smoking-related disease; half of these deaths are in middle age; each smoking-related death in middle age loses over 20 years of a non-smoker's life expectancy; there are over twenty fatal diseases causally linked to cigarette smoking; even if a smoker stops smoking in middle age he starts to win back some of non-smokers' life expectancy*), has evolved from the extensive follow-up of the British Doctors study [30].

Tobacco use has taken hold in populations in low- and medium-resource countries, and substantial increases have taken place in smoking prevalence in recent years. Given the substantial delay—which approaches 40 years—between big changes in smoking prevalence in populations being reflected in big changes in disease rates, the peak of the tobacco-smoking related cancer epidemic in low- and medium-countries has still to materialise. The Tobacco Epidemic will be driving the Cancer Epidemic in low- and medium-resource countries for years to come.

Low-resource and medium-resource countries are, arguably, harder hit by cancer than the high-resource countries [25]. Low-income countries are those with annual gross national income per capita of less than US$765. Such countries often have a limited health budget and a high background level of communicable disease. Cancer treatment facilities are not universally available, and life-extending therapies are often unavailable generally for economic reasons. Cancer and other chronic diseases, which are becoming more common, can cause devastating damage.

Middle-resource countries are those with an annual gross national income *per capita* of less than US$9300. Such countries risk being somewhat overlooked as high-income countries

increasingly focus on (expensive) new technologies and drugs to treat cancer, and many seek to help provide basic diagnostic and treatment facilities in low-income countries.

Many middle-income countries have diagnostic and treatment structures in place but face severe economic pressure to upgrade equipment and to pay for the new drugs used to treat cancer. Many hospitals need to be upgraded to high-income country standards and there is a need to accelerate training and to increase in the complement of specialised oncologists, radiotherapists, oncology nurses and all other medical, paramedical and technical personnel necessary. The situation in two middle-income countries, Hungary and Turkey, is summarised in the boxes in this chapter.

The first big step towards cancer prevention and control world-wide is to understand the magnitude and nature of the cancer burden in different regions of the world and then move towards an understanding of avoidable causes and other priorities. Recent increases in data availability in low-income countries allow a better, although still imperfect, picture of the global cancer burden.

Evolution of the global cancer burden

Around the year 2000, less than 20% of the world's population was covered by cancer registration and 33% by mortality schemes based on medically certified deaths. However, this is not equally spread over the globe: in Africa less than 13% of the population is covered by a death certificate scheme, in Asia only 8.5% of the population is covered, and 95% of the population of Latin America is covered. The corresponding population coverage for cancer incidence statistics is 8% in Africa, 7% in Asia and 10% in Latin America.

In the absence of data from large portions of the population, it is necessary to make estimations; the methods used to compute these are described in detail in *GLOBOCAN 2002* [31]. In summary, incidence and mortality rates (number of cases or deaths per 100 000 persons per year) were estimated by country, sex and cancer site, for 5 age groups (0-14, 15-44, 45-54, 55-64, 65+) using the most recently available data collected at the IARC up to the year 2004 or 2005 wherever possible [32-34]. The numbers of cases and deaths were computed by multiplying these estimated rates by the estimated 2008 population estimates for the corresponding country [18]. The results are presented according to World Health Organization Region.

Mortality data are available from the WHO Mortality Database [35] are available by sex and cancer site up to 2005 for many countries of the world, although the degree of detail and quality of the data vary considerably. Only regional mortality data are available for some countries, and these data were used to estimate national rates. For countries where mortality data were unavailable or were known to be of poor quality, estimates of mortality were made from incidence, by use of country or region-specific survival.

Various methods were used to estimate the sex- and age-specific incidence rates of cancer for a country. Wherever available, the most recent national incidence rates or estimates have been used. For countries where local or regional incidence and national mortality data were available, national incidence was estimated by applying a set of age-, sex- and site-specific incidence/mortality ratios, obtained from the aggregation of representative cancer registries data, to the country's national mortality. Incidence/mortality ratios are obtained from a Poisson regression model of the selected registry incidence data offset by corresponding mortality data, including terms for sex and age. This method is regularly used by the Descriptive Epidemiology Group of IARC, and has been shown to estimate cancer incidence accurately. Where local and/or regional incidence data are available and no information on death is available, regional rates were used to estimate national rates. For those countries for which no data were available, the country-specific rates were calculated from the simple average of those of neighbouring countries as described in *GLOBOCAN 2002* [31].

Global Cancer Burden

It has been estimated that 58.8 million people died in 2004 [36]. Half of these deaths involved people less than 60 years of age, and there were 22 million deaths in people aged 70 years and older and 10.7 million deaths in people aged 80 years and over. Approximately one death in five was in a child under 5 years of age. Deaths from cancer represent around one eighth of all deaths, although there will be more people who will have died *with cancer* although it was not the direct cause of death.

Mortality data provide important information but are restricted to giving insight into the absolute lack of health in any population. Cancer incidence data have the substantial advantage of providing a clearer picture of the cancer problem and have a key role to play in service planning and related activities. It is also clear, at least in qualitative terms, that the cancers which are common in certain parts of the world are not so common in others. It is essential to have estimates of the burden of cancer and its different types in different parts of the world.

WHO African Region (AFRO)

The estimated population of the AFRO Region in 2008 was 812 million (404 million men and 408 million women), most of whom are young (Figure 1.1.1a). The effectiveness of national population censuses in several African countries is not reliable, and a very small proportion of the total population of the AFRO Region is covered by medically-certified causes of death (7.2% of the population) or is covered by population-based cancer registries which provide incidence data (8.3% of population). The estimates of population and cancer burden for AFRO have a large measure of inaccuracy present.

It is estimated that there were 667 000 incident cases of cancer in 2008 (314 000 in men and 353 000 in women) and 518 000 deaths from cancer (approximately 252 000 in men and 266 000 in women) (Figure 1.1.1b). In men, the commonest cancer, and the commonest cause of cancer-related mortality, was Kaposi Sarcoma, which is an undoubted consequence of the HIV/AIDS epidemic, followed by cancers of the liver, prostate and oesophagus. In women, cervix cancer was the most common form of cancer and cancer death. Breast cancer was second most common in incidence and mortality, followed by liver cancer and Kaposi Sarcoma (Figure 1.1.1b).

WHO Region of the Americas (AMRO/PAHO)

Each country in the Region of the Americas (AMRO/PAHO) has a national census. In North America (United States of America and Canada) the entire population is covered by a national death certificate scheme and 90% of the population by population-based cancer registration. In Central and Latin America, 95% of the population is covered by a national mortality scheme and 13% by population-based cancer registration. Estimates will be better in North America than in Central and Latin America.

The estimated population of the AMRO/PAHO region was 831 million in 2000, with marginally more women than men (Figure 1.1.2a). The population pyramid demonstrates a population that contains a significant number of middle-aged men and women, quite dissimilar to the young population of the AFRO Region (Figure 1.1.2a).

There were an estimated 2 617 000 incident cases of cancer in 2008, 1.338 million in men and 1.279 million in women. Overall, there were an estimated 1 258 000 deaths from cancer in 2008: in men there were an estimated 651 000 deaths from cancer and 607 000 cancer deaths in women. Prostate cancer was the commonest incident cancer in men although there were more deaths from lung cancer (Figure 1.1.2b). Lung cancer was the second commonest incident form of cancer in men followed by cancer of the colorectum, stomach and

Fig. 1.1.1 *Population pyramid (Figure 1.1.1a), Cancer Incidence and Mortality (Figure 1.1.1b) in World Health Organization African Region (AFRO).*

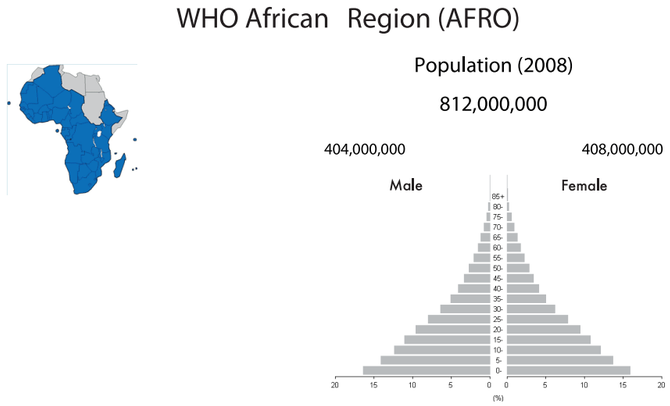


Fig. 1.1.1a

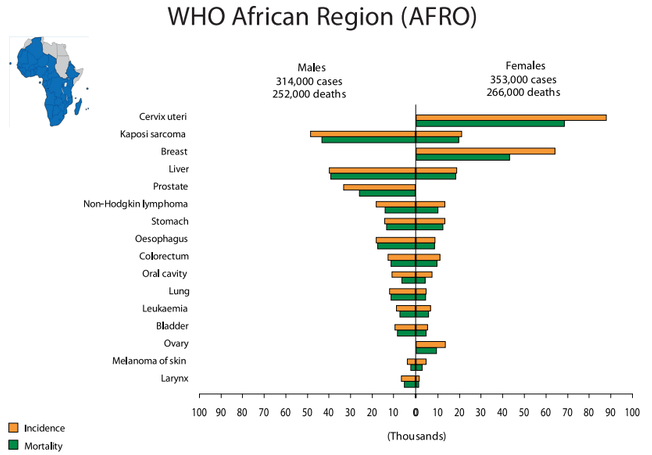


Fig. 1.1.1b

lymphoma (Figure 1.1.2b). In women, breast cancer was the commonest incident form of cancer although, as in men, there were more deaths from lung cancer. Lung cancer was the second commonest form of cancer in women followed by colorectal cancer, cervix cancer and cancer of the corpus.

There are substantial differences between North America (United States and Canada) and Central and South America. The population pyramids of these regions are remarkably different. In North America (total population 346 million) there is a clearly ageing population (Figure 1.1.3a) while in Central and Latin America (total population 577 million) there is a young population (Figure 1.1.3b).

In North America there were an estimated 1 606 000 incident cases of cancer (849 000 in men and 757 000 in women) and 669 000 deaths from cancer (349,000 in men and 320,000 in women) in 2008. Prostate cancer clearly predominates incidence, followed by lung cancer, colorectal cancer, bladder cancer, melanoma and lymphoma (Figure 1.1.3c). Lung cancer is the commonest form of death from cancer, followed by prostate cancer and colorectal cancer (Figure 1.1.3c). In women, breast cancer is the commonest incident form of cancer, followed by cancer of the lung, colorectal cancer and cancer of the corpus (Figure 1.1.3c). Lung cancer is the commonest cause of cancer death in women, followed by breast cancer and colorectal cancer (Figure 1.1.3c).

In the southern part of the PAHO Region (Central and South America and the Caribbean) in 2008 there were 1 011 000 incident cases of cancer (489 000 in men and 522 000 in women) and 589 000 cancer deaths (302 000 in men and 287 000 in women). In men the commonest incident form of cancer is prostate cancer followed by lung cancer, stomach cancer and colorectal cancer (Figure 1.1.3d). Lung cancer is the most frequent cancer cause of death followed by prostate, stomach and colorectal (Figure 1.1.3d). In women, the commonest form of cancer is breast cancer followed by cervix

Fig. 1.1.2 *Population pyramid (Figure 1.1.2a), Cancer Incidence and Mortality (Figure 1.1.2b) in World Health Organization PAHO Region (PAHO).*

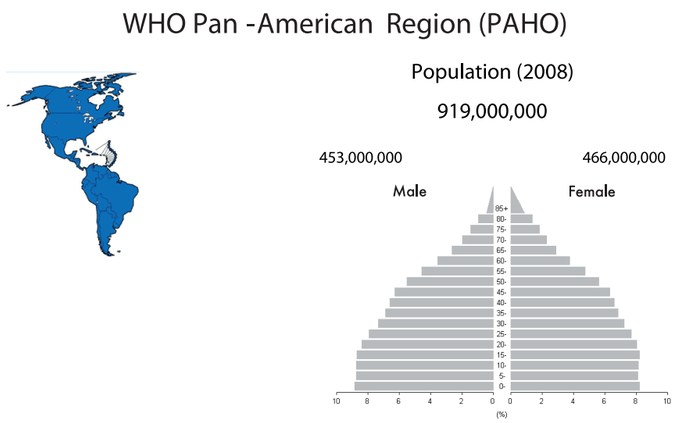


Fig. 1.1.2a

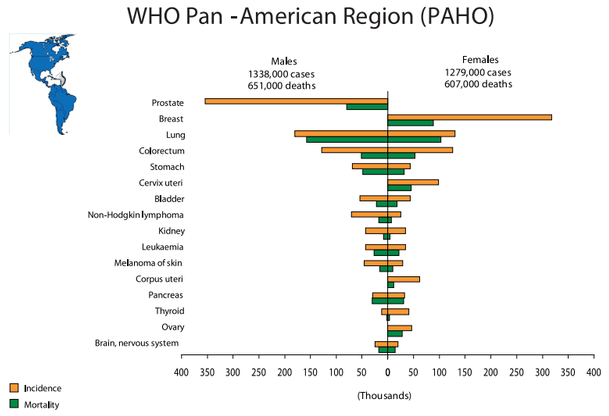


Fig. 1.1.2b

Fig. 1.1.3 *Population pyramid for Northern American component (Figure 1.1.3a) and Central and Latin American component (Figure 1.1.3b) and Cancer Incidence and Mortality for Northern American component (Figure 1.1.3c) and Central and Latin American component (Figure 1.1.3d) for World Health Organization PAHO Region.*

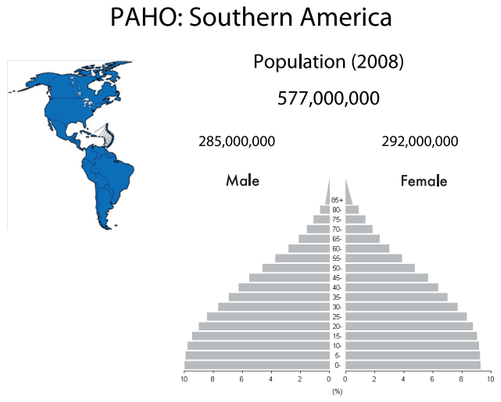


Fig. 1.1.3a

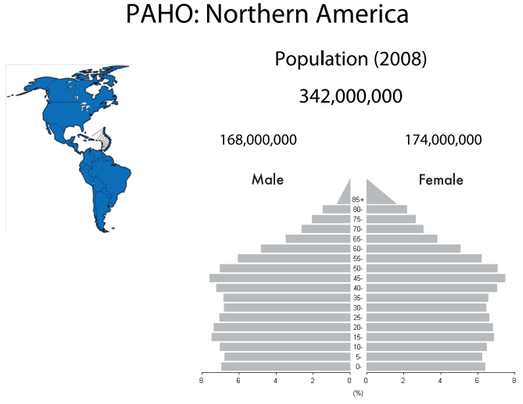


Fig. 1.1.3b

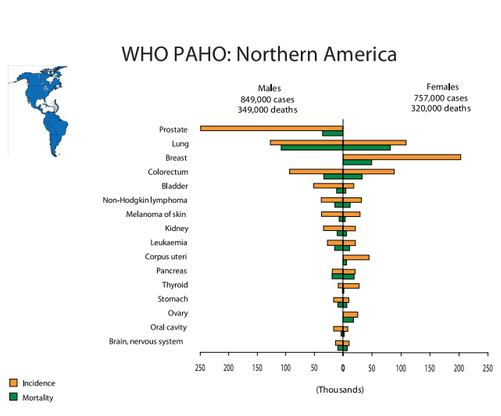


Fig. 1.1.3c

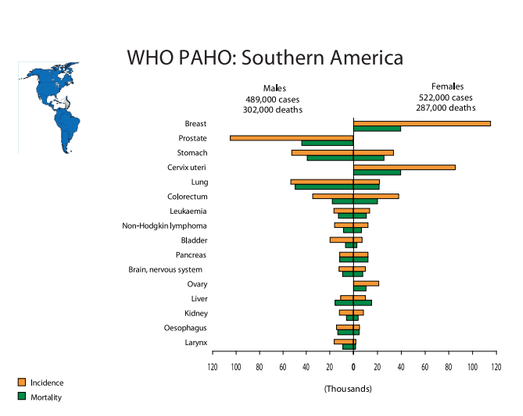


Fig. 1.1.3d

cancer, colorectal cancer, stomach cancer and lung cancer. Breast cancer, cervix cancer, stomach cancer, lung cancer and colorectal cancer are the commonest forms of cancer death (Figure 1.1.3d).

WHO South East Asia Region (SEARO)

The effectiveness of national population census in several Asian countries is uncertain, and only a small proportion of the total population of the SEARO Region has mortality data available or is covered by population-based cancer registries which provide incidence data. When considering the estimates of population and cancer burden for SEARO, these observations must be taken into account while also noting that the overall burden and the cancer pattern is dominated by India, which comprises 67% of total population of the Region.

It is estimated that the population of the SEARO Region in 2008 was 1.768 billion, with a slight predominance of men than women. The population pyramid demonstrates a young population (Figure 1.1.4a).

It is estimated that in 2008, there were 1 589 000 incident cases of cancer in 2008 (758 000 in men and 831 000 in women) and 1 072 000 deaths from cancer (approximately 557 000 in men and 515 000 in women) (Figure 1.1.4b). In men, the commonest cancer was lung cancer, followed by oral cancer, pharyngeal cancer, oesophagus cancer, stomach cancer, colorectal cancer, liver cancer and larynx cancer (Figure 1.1.4b). Lung cancer was the commonest form of cancer deaths in men (Figure 1.1.4b). If oral cavity and pharynx are combined, then this site is the predominant site of incident cancer and cancer death in men. In women, cervix cancer and breast cancer were the commonest incident and fatal forms of cancer by a considerable margin (Figure 1.1.4b). The different case mix between men and women results in more deaths in men than in women, based on fewer incident cases.

Fig. 1.1.4 *Population pyramid (Figure 1.1.4a), Cancer Incidence and Mortality (Figure 1.1.4b) in World Health Organization South-East Asia Region (SEARO).*

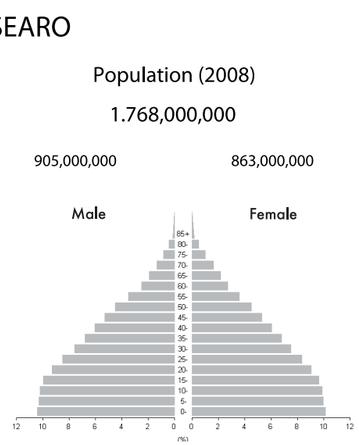


Fig. 1.1.4a

Fig. 1.1.4b

WHO Eastern Mediterranean Region (EMRO)

As in SEARO and WPRO, the effectiveness of national population census in several countries is uncertain, and only a small proportion of the total population of the EMRO Region has mortality data available or is covered by population-based cancer registries that provide incidence data. When considering the estimates of population and cancer burden for EMRO, these must be taken into account.

The estimated 2008 population of the EMRO Region was 561 million, with a slight predominance of men over women. The population pyramid demonstrates a young population (Figure 1.1.5a).

It is estimated that in 2008, there were 467 000 incident cases (228 000 in men and 239 000 in women) and 323 000 deaths from cancer (approximately 228 000 in men and 153 000 in women) (Figure 1.1.5b). In men, the commonest cancers were lung cancer and bladder cancer, although there were more deaths from lung cancer (Figure 1.1.5b). In women, breast cancer was the commonest incident and fatal form of cancer by a considerable margin from cervix cancer (Figure 1.1.5b).

WHO Western Pacific Region (WPRO)

The effectiveness of national population census in several Asian countries is uncertain, and only a small proportion of the total population of the WPRO Region has mortality data available or is covered by population-based cancer registries that provide incidence data. When considering the estimates of population and cancer burden for WPRO, these observations must be taken into account while simultaneously noting that the cancer pattern and burden are driven by China, which comprises 75% of the total population of the Region, and where there is a high frequency of cancers with a poor prognosis (lung, liver, oesophagus, stomach). A high mortality/incidence ratio should be expected in this region.

Fig. 1.1.5 *Population pyramid (Figure 1.1.5a), Cancer Incidence and Mortality (Figure 1.1.5b) in World Health Organization Eastern Mediterranean Region (EMRO).*

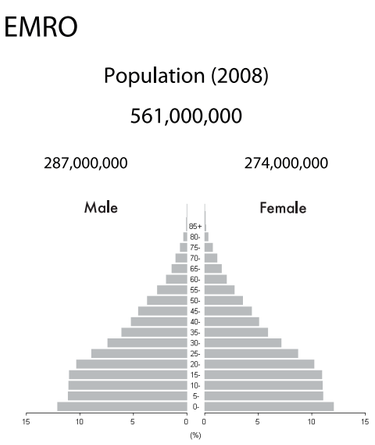


Fig. 1.1.5a

Fig. 1.1.5b

The population of the WPRO Region in 2008 was estimated to be 1.780 billion, with marginally more men than women (Figure 1.1.6a). The population pyramid demonstrates an ageing population with a bulge in the numbers in middle age (Figure 1.1.6a).

It is estimated that in 2008 there were 3 689 000 incident cases of cancer (2 213 000 in men and 1 476 000 in women) and 2 575 000 deaths from cancer (approximately 1 629 000 in men and 946 000 in women) (Figure 1.1.6b). In men, the commonest incident cancer was stomach cancer, closely followed by lung cancer and liver cancer and then oesophagus cancer and colorectal cancer (Figure 1.1.6b). Lung cancer, liver cancer, stomach cancer and oesophageal cancer were the commonest forms of cancer death in men (Figure 1.1.6b). In women, breast cancer was the commonest incident form of cancer, followed by stomach cancer, lung cancer, colorectal cancer, liver cancer and cervix cancer (Figure 1.1.6b). Lung cancer was the commonest cancer cause of death in women followed by stomach cancer, liver cancer, oesophagus cancer, breast cancer and colorectal cancer (Figure 1.1.6b).

WHO European Region (EURO)

National censuses of the population in countries of the EURO Region provide fairly good data. In addition, 98.3% of the population of the Region is covered by mortality statistics and 36.5% of the population is covered by population-based cancer registration.

The population of the EURO Region in 2008 was estimated to be 891 million, with marginally more women than men (Figure 1.1.7a). The population pyramid demonstrates an ageing population with a bulge in the numbers in middle-age and decreasing numbers of births in younger age categories (Figure 1.1.7a).

It is estimated that in 2008 there were 3 422 000 incident cases of cancer (1 821 000 in men and 1 601 000 in women) and 1 847 000 deaths from cancer (approximately 1 034 000 in men and 813 000 in women) (Figure 1.1.7b). In men, the commonest incident cancer was lung cancer followed by prostate cancer, colorectal cancer, bladder and stomach cancer (Figure 1.1.7b). Lung cancer, colorectal cancer, prostate cancer and stomach cancer were the commonest forms of cancer death in men (Figure 1.1.7b). In women, breast cancer was the commonest incident form of cancer, followed by colorectal cancer, lung cancer, corpus cancer and stomach cancer (Figure 1.1.7b). Breast cancer was also the commonest cancer cause of death in women, followed by colorectal cancer, lung cancer and stomach cancer (Figure 1.1.7b).

Countries of Central and Eastern Europe have experienced an ongoing economic transition for over a decade. It was decided to restrict attention to the countries of the WHO EURO Region that were outside the European Union and the European Economic Area. This provided a sub-region with a total population of 413 million. The population pyramid demonstrates a reduced number of births in recent years and a marked predominance of women at older age groups (Figure 1.1.8a).

There were an estimated 1 049 000 incident cases of cancer in 2008 (523 000 in men and 526 000 in women) and 644 000 cancer deaths (359 000 in men and 285 000 in women) (Figure 1.1.8b). The commonest incident forms of cancer in men were lung cancer, stomach cancer, colorectal cancer, prostate cancer and bladder cancer (Figure 1.1.8b). Lung cancer, stomach cancer and colorectal cancer were the commonest forms of cancer death (Figure 1.1.8b). In women, breast cancer was the commonest form of cancer followed by colorectal cancer, stomach cancer, cervix cancer and corpus cancer (Figure 1.1.8b). Breast, colorectal and stomach cancer were the commonest forms of cancer death in women (Figure 1.1.8b).

Fig. 1.1.6 *Population pyramid (Figure 1.1.6a), Cancer Incidence and Mortality (Figure 1.1.6b) in World Health Organization Western Pacific Region (WPRO).*

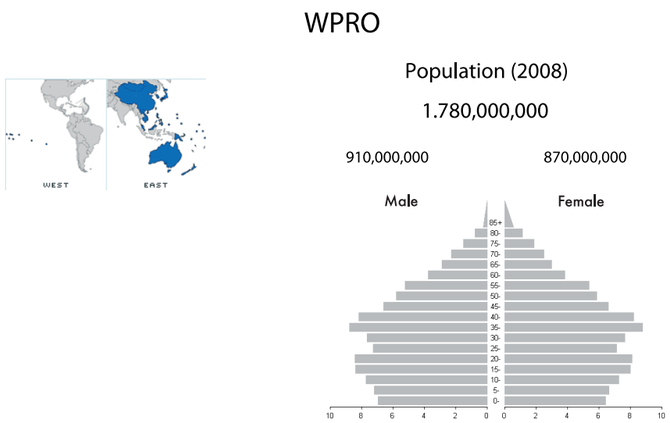


Fig. 1.1.6a

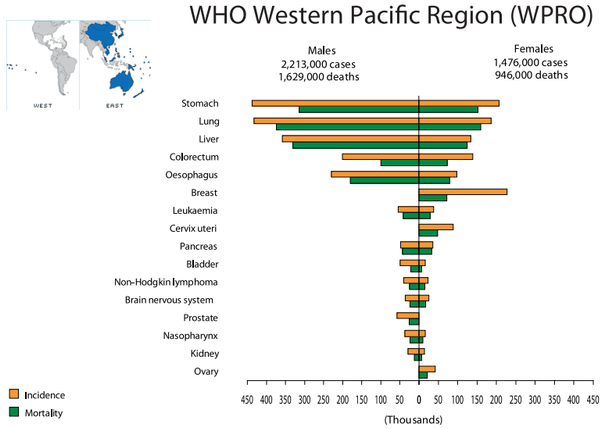


Fig. 1.16b

Fig. 1.1.7 *Population pyramid (Figure 1.1.7a), Cancer Incidence and Mortality (Figure 1.1.7b) in World Health Organization European Region (EURO).*

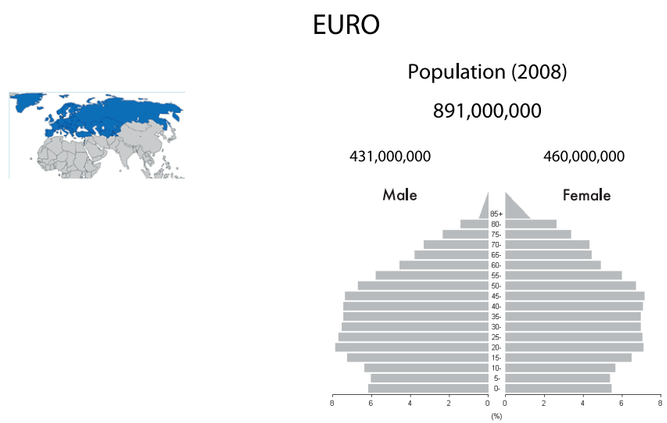


Fig. 1.1.7a

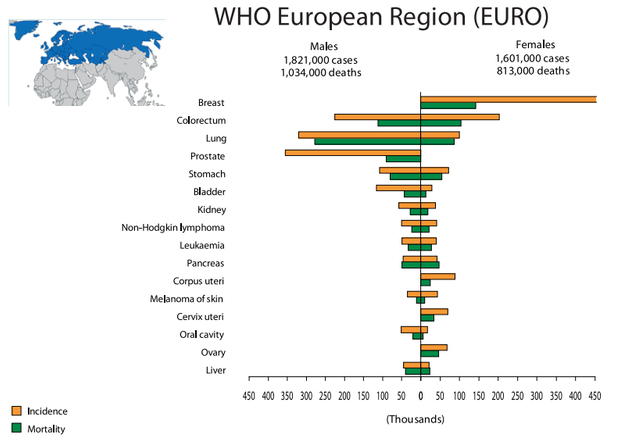


Fig. 1.1.7b

Worldwide

Globally, there were an estimated 12.4 million incident cases of cancer in 2008 (6 672 000 in men and 5 779 000 in women) and 7.6 million deaths from cancer (4 293 000 in men and 3 300 000 in women). Over half of the incident cases occurred in residents of four WHO regions with a large proportion of countries of low- and middle-income—AFRO, EMRO, SEARO and WPRO (Figure 1.1.9). Globally, lung cancer was the commonest incident cancer and cause of cancer-related mortality in men; in women, the most common incident cancer and cause of cancer-related death was breast cancer.

The global cancer burden: Factors driving the increase

There are three clear scenarios under which the global cancer burden could increase over time. First of all, the increase in the world's population anticipated from 6.1 billion in 2000 through 6.7 billion in 2008 to attain 8.3 billion by 2030 will lead to an increase in the cancer burden even if the age-specific rates remain constant. Secondly, given the very large increases in cancer risk with age, if the population size and the age-specific rates remain constant, then the burden will increase if the population ages. Figure 1.1.10 clearly shows that the world population will age considerably by 2030 as well as increasing significantly.

Aging is a major issue for the future cancer burden. Aging has proceeded more gradually in more developed countries than in less developed countries, affording these nations time to adjust to this structural change. Japan is the major exception, doubling its percentage of population age 65 or older in just 26 years. Other countries in East and Southeast Asia (especially China, South Korea, Taiwan and Thailand) are on a similarly rapid trajectory, fuelled by dramatic and relatively recent drops in fertility. It took 115 years for the proportion of France aged 65 and over to double from 7% (1865) to 14% (1980). In Singapore it will take

Fig. 1.1.8 *Population pyramid (Figure 1.1.8a), Cancer Incidence and Mortality (Figure 1.1.8b) in World Health Organization European Region (EURO) with European Union and European Economic Area countries omitted.*

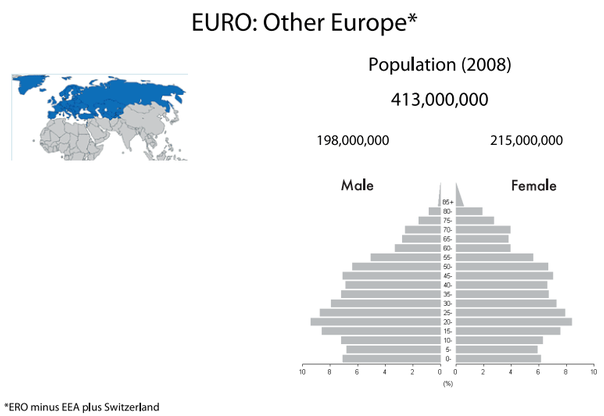


Fig. 1.1.8a *Population Pyramid for modified EURO Region, 2008*

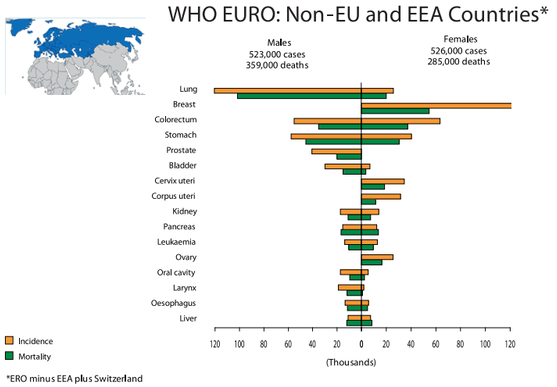


Fig. 1.1.8b

**WHO EURO Region minus European Union Member States (Austria, Belgium, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Poland, Portugal, Slovakia, Slovenia, Spain, Sweden and United Kingdom) and members of the European Economic Area (Iceland and Norway) and Switzerland.*

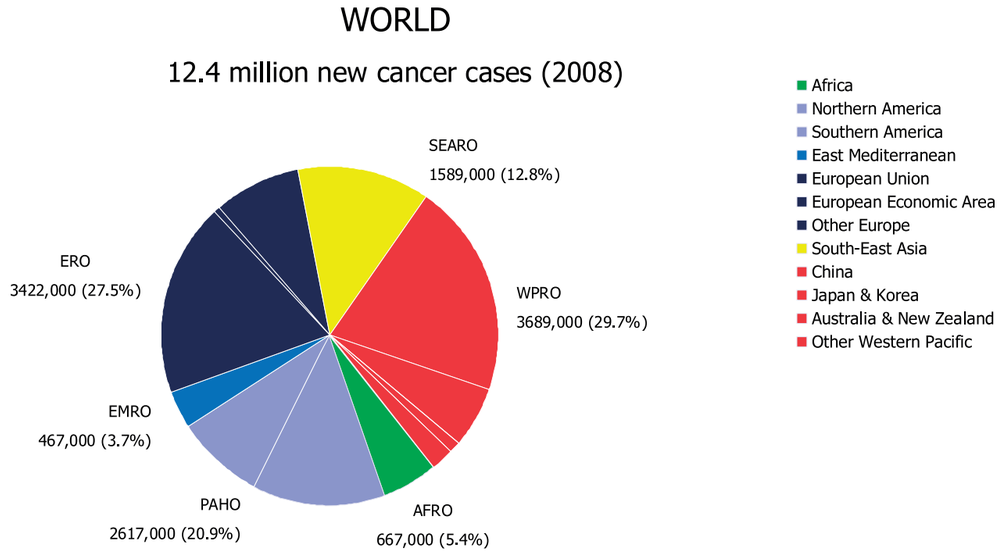


Fig. 1.1.9 *Distribution of Global Cancer burden by World Health Organization Region (2008)*

an estimated 19 years for the proportion of the population to double from 7% (2000) to 14% (2019)(Figure 1.1.11).

In China, due to vast improvements in health over the past five decades, life expectancy at birth has increased by two thirds, from 40.8 to 71.5 years, between 1955 and 2005. The percentage of elderly people (over 65) in China is projected to triple from 8 percent to 24 percent between 2006 and 2050. Because chronic health problems become more common in old age, China's population aging has led to increases in the country's prevalence of chronic disease and disability [37,38].

The third element that can lead to an increase in the cancer burden, even when the population size remains constant and the age distribution remains unchanged, is an underlying increase in the incidence rates. In France, cancer incidence rates increased by 1.3% per annum between 1978 and 2000 [19,21]. In the Indian cancer registries, between 1983 and 1997, the incidence rate increased at an annual rate of 0.5% per annum. In China (Qidong), between 1973 and 1997, the incidence rate increased at an annual 1.4% per annum. In Latin American registries between 1985 and 1997 the incidence rate increased at an annual rate of 1.0% per annum [39-46].

The growth and ageing of the world's population and the continual increase in the underlying incidence rates in low- and middle-income countries will contribute to increases in the global cancer burden. The global cancer burden under a range of scenarios of percentage increases is presented in Table 1.1.3. It is clear that population growth and ageing contribute much more to the future cancer burden than an underlying increase in the incidence rates (Table 1.1.3). Under the zero increase in cancer incidence scenario, the global burden will increase from 10.9 million in 2002 to nearly 20 million in 2030. Similar figures and conclusions are available for mortality data (Table 1.1.4).

By extrapolation of these data, taking into account demographic changes and factoring in a yearly increase in cancer incidence of 1%, it could be expected that by 2030 there will be approximately 26.4 million incident cases of cancer and 17.0 million cancer deaths a year (Table 1.1.4). The extrapolations made are likely to produce conservative estimates of the cancer burden

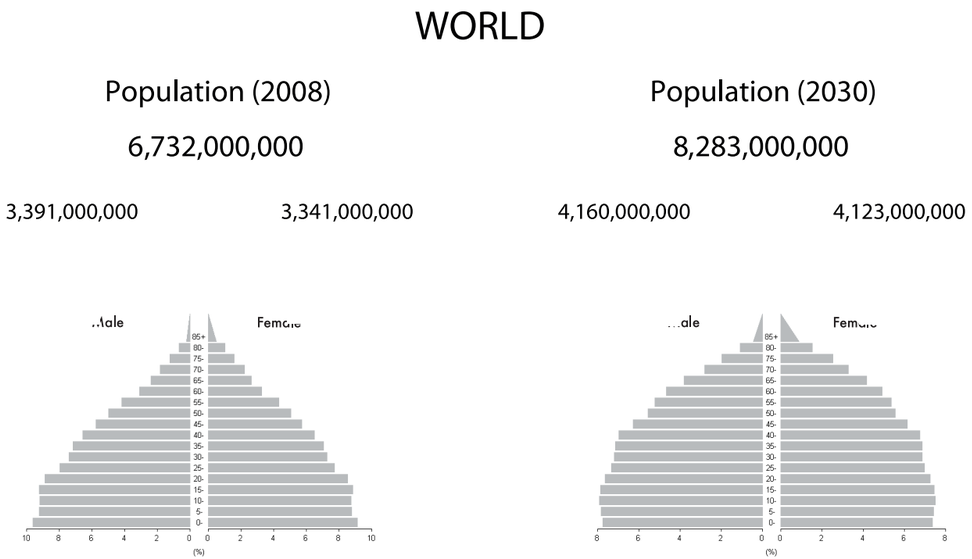


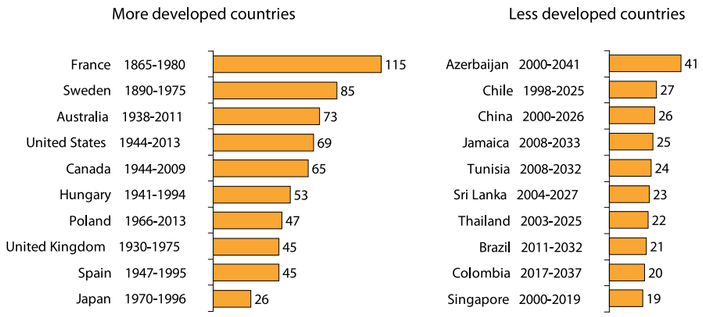
Fig. 1.1.10 *Estimates of global population by gender and age, 2000 and 2030*

when the 1% annual increase in incidence rates is assumed.

Action Required. At present, the most common forms of cancer differ between high-resource countries and those of low and middle resource. In high-resource countries, cancers of the lung, breast, prostate and colorectum dominate; a third of cancers are caused by tobacco use and 10% by chronic infection. In countries of low and middle resources, cancers of the stomach, liver, oral cavity and pharynx and cervix dominate; a quarter of these seem to be caused by chronic infection, although the proportion of cancer caused by tobacco is growing. However, the pattern is changing rapidly, with large increases in many parts of the world where lung, breast and colorectal cancer have been historically uncommon.

Priority setting for cancer control and cancer services in any region needs to be based on knowledge of the cancer burden and the local mix of cancer types which predominate. Unfortunately, neither the number of new cases of cancer nor the number of deaths caused by cancer is available from many parts of the world, and only estimates can be made based on the partial incidence and mortality data available. Such estimates are a first crucial step in providing insight into the cancer burden in all regions of the world, thereby allowing a process of priority identification and priority setting to be engaged.

Currently about half the world's population is covered by death registration schemes with a medically certified cause of death. This analysis has been restricted to data from such schemes to allow comparability in the methods of estimation and the sources used. However, there are a number of ongoing schemes in different regions of the world that give insights into causes of death in a larger proportion of the world population [47]. For example, in India



* Dates show the span of years when percent of population age 65 or older rose (or is projected to rise) from 7 percent to 14 percent.

Fig. 1.1.11 *Number of years for percentage of population age 65 or older to rise from 7% to 14%*

there is a sample registration system and an urban system of medically certified causes of death. In China, there is a Disease Surveillance Points system in place and an urban death registration scheme [37,38].

However, the estimates made here, for all their imperfections, reflect the cancer burden in different parts of the world and serve as a basis for establishing priorities in cancer control activities. Their first impact is to establish clearly that cancer is a worldwide problem.

Although data were sparse when IARC was founded in 1965 [48], cancer was then widely considered to be a disease of developed, high-income countries [39]. The situation has changed dramatically with at least half of the global cancer burden found in low-resource and medium-resource countries. In 2008, five cancers in every ten occurred in residents of four WHO Regions that are mainly constituted of low-resource and medium-resource countries: the African Region (AFRO)(5.4%), the Eastern Mediterranean Region (EMRO)(3.7%), the South East Asia Region (SEARO)(12.8%) and the Western Pacific Region (WPRO)(29.7%) (Figure 1.1.9).

The continued growth and ageing of the world's population will greatly affect the future cancer burden. Given these demographic changes (Figure 1.1.10), and factoring in an annual increase in cancer incidence and mortality of 1%, by 2030 it could be expected that there will be 26.4 million incident cases of cancer and 17.0 million cancer deaths annually (Tables 1.1.3 and 1.1.4). An annual increase of 1% per annum in the incidence rate seems reasonable, and may well be conservative.

These estimates made herein correspond closely with those made by other groups [34, 49-52] (Table 1.1.5). For example, the estimates of the global cancer deaths made by the American Cancer Society [32] for 2007 are 7.6 million, and the calculation presented herein estimates the same number of cases in 2008. The World Health Organization [52] has made an estimate of 11.5 million deaths in 2030, comparable to our estimate of 12.9 million under the hypothesis of no increase in cancer death rates. Although there are clear indications that the incidence rate of cancer is rising in many parts of the world, the assumption of the same percentage increase in death rate could be questioned. For example, if the overall increase in incidence is driven by forms of cancer for which the case fatality rate is low, then the mortality rate may not rise so quickly. On the other hand, if the increase in incidence is driven by forms of cancer for which fatality is high, then the increase in mortality may be greater than that in incidence. Assuming the same change in mortality rates as incidence is in many respects the optimal course, although the estimates of the burden of cancer deaths may be less reliable than those of the global burden.

The growth and ageing of the population of countries of low or middle income, together with westernisation of lifestyle and the rapid growth of tobacco smoking, are contributing to dramatic changes on the burden of cancer. Changes in lifestyle habits (including adoption of a more sedentary lifestyle, weight gain and obesity) and sociological changes (notably increasing age at first birth and decreasing parity in women) are leading to large increases in breast and colorectal cancer in particular. Indeed, in view of the substantial delay—about 40 years—between changes in smoking prevalence in populations being reflected in changes in disease rates, the peak of the tobacco-smoking related cancer epidemic in countries of low and middle income has probably yet to materialise.

The cancer burden will increase in each of the WHO Regions. In the African region (AFRO), the burden will increase from 700 000 in 2008 to 1 200 000 cases in 2030 if there is no increase in the incidence rate or 1 600 000 if there is a 1% annual increase in incidence factored in (Table 1.1.6). In the Western Pacific Region (WPRO), the burden will increase from 3 700 000 in 2008 to 6 100 000 cases in 2030 if there is no increase in the incidence

rate, or 8 100 000 if there is a 1% annual increase in incidence (Table 1.1.6). Similar estimates are presented for mortality data (Table 1.1.7).

Evidently, the greatest effect of this increase will fall on low-resource and medium-resource countries where, in 2001, almost half of the disease burden was already from non-communicable disease [53]. Low-resource and medium-resource countries are, arguably, harder hit by cancer than the high-resource countries. The effects will be considerable in terms of the treatment needs and the costs of treatment, especially in low- and medium-resource countries still faced with the burden of infectious disease and a low budget for health. Cancer treatment facilities are not universally available, and life-extending treatment is often unavailable, generally for economic reasons. The increasing burden of cancer and other chronic diseases could thus cause devastating damage to entire families in several circumstances, including when the head of household and the only source of income for a frequently extended family succumbs to cancer, or when death of the mother results in girls stopping their education to look after the household.

Necessity and Prospects for Cancer Control. Epidemiology provides compelling evidence that a large proportion of human cancer may be avoidable. Different populations throughout the world experience different levels of different forms of cancer, and these levels change with time. Groups of migrants acquire the cancer pattern of their new home, sometimes within decades (as demonstrated by migrants to Australia) [54]. From evidence such as this the environmental theory of carcinogenesis has developed [20,55], and it is widely held that upwards of 80%, and perhaps 90%, of human cancer may be attributable to environmental factors, defining "environment" in its broadest sense to include a wide range of (sometimes poorly defined) lifestyle aspects, including dietary, social and cultural practices.

Annual Percentage Change	Men	Women	Both sexes
-1.50(%):	7.183	5.893	13.076
-1.25(%):	7.712	.326	14.038
-1.00(%):	8.277	6.791	15.068
-0.75(%):	8.883	7.287	16.171
-0.50(%):	9.531	7.819	17.351
-0.25(%):	10.225	8.388	18.614
0.00(%):	10.968	8.997	19.965
0.25(%):	11.762	9.649	21.411
0.50(%):	12.611	10.346	22.957
0.75(%):	13.520	11.091	24.611
1.00(%):	14.491	11.888	26.380
1.25(%):	15.530	12.740	28.270
1.50(%):	16.640	13.651	30.291

Table 1.1.3 *Number of new cancer cases (millions) expected globally in 2030 (based on 2002 rates and annual percentage changes)*
For comparison purposes, there were 10.9 million cancer cases in 2002

Annual Percentage Change	Men	Women	Both sexes
-1.50(%):	4.837	3.605	8.442
-1.25(%):	5.193	3.870	9.063
-1.00(%):	5.574	4.154	9.728
-0.75(%):	5.982	4.458	10.440
-0.50(%):	6.419	4.783	11.202
-0.25(%):	6.886	5.131	12.017
0.00(%):	7.386	5.504	12.890
0.25(%):	7.921	5.902	13.823
0.50(%):	8.493	6.329	14.821
0.75(%):	9.104	6.785	15.889
1.00(%):	9.759	7.272	17.031
1.25(%):	10.458	7.794	18.252
1.50(%):	11.206	8.351	19.556

Table 1.1.4 *Number of cancer deaths (millions) expected globally in 2030, (based on 2002 rates and annual percentage changes).*
For comparison purposes, there were 6.7 million cancer deaths in 2002

Source	Year estimated	Deaths (millions)	Incidence (millions)	Notes
American Cancer Society [32]	2007	7.6	12.0	a
IARC	2008	7.6	12.4	
World Health Organization	2005	7.6	none	a
U.I.C.C [52]	2002	6.7	10.9	
Globocan 2002 [31]	2002	6.7	10.9	
Institute of Medicine [49]	2001	7.0	none	
Mathers and Loncar [50]	2030	11.5	none	
IARC	2030	12.9	20.0	b
IARC	2030	17.0	26.4	c

Table 1.1.5 *Various estimates of the global cancer burden*

a, Estimates based on Globocan [31];
b, Assumes no change in underlying rate;
c, assumes a 1% per annum increase in incidence.

Region	2008	2030[a]	2030[b]
AFRO	0.7	1.2	1.6
EURO	3.4	4.1	5.5
EMRO	0.5	0.9	1.2
PAHO	2.6	4.8	6.4
SEARO	1.6	2.8	3.7
WPRO	3.7	6.1	8.1
WORLD	12.4	20.0	26.4

Table 1.1.6 *Estimated (2008) and projected numbers (millions) of cancer cases*
a, No temporal change in incidence rates during the period;
b, under scenario of 1% per annum increase in incidence rates.

Region	2008	2030[a]	2030[b]
AFRO	0.5	0.9	1.3
ERO	1.8	2.6	3.4
EMRO	0.3	0.6	0.9
PAHO	1.3	2.3	3.1
SEARO	1.1	1.9	2.6
WPRO	2.6	4.4	5.9
WORLD	7.6	2.9	17.0

Table 1.1.7 *Estimated (2008) and projected numbers (millions) of cancer deaths*
a, No temporal change in incidence rates during the period;
b, under scenario of 1% per annum increase in incidence rates.

In theory, therefore, the large majority of human cancer diagnosed each year may be avoidable, but avoidable causes of many common cancers have not yet been clearly identified. A prerequisite of cancer prevention lies in identifying the determinants of cancer risk. Cancer control embraces a number of important elements with the aim of reducing the incidence of cancer and, failing primary prevention, reducing mortality either by finding disease at an earlier and more 'curable' stage or by improving survival stage-for-stage through improvements in therapy. There are a number of disciplines involved within this embrace, including epidemiology, clinical science, behavioural science and health education. It is a complex and at times uncoordinated package, and many details will be presented in individual sections below.

Cancer would chiefly be an economic problem if it were not for the fact that half of the people who develop cancer die from their disease. Thus the concept of Cancer Control has been developed to attack the cancer problem at various points:

(i) Primary Prevention

The most obvious ways to prevent people dying from cancer are either to find cures for the different forms of the disease or to find ways to stop the development of clinical cancer in the first instance. At present, cancer prevention involves determining the causes of cancer (risk determinants) among those factors shown to be associated with the development of the disease by epidemiological studies (risk factors). Avoiding a changing exposure to risk determinants would result in a reduction in cancer risk.

The evidence that cancer is preventable is compelling. Different populations around the world experience different levels of different forms of cancer [56], and these levels change with time in an orderly and predictable manner [57]. Groups of migrants quickly leave behind the cancer levels of their original home and acquire the cancer pattern of their new residence sometimes within one generation [54, 58]. Thus those Japanese who left Japan for California left behind the high levels of gastric cancer in their homeland and exchanged it for the high levels of breast and colorectal cancer present among inhabitants of their new home. Furthermore, groups whose lifestyle habits differentiate themselves from other members of the same community frequently have different cancer risks (c.f. Seventh Day Adventists and Mormons [59]. Although all of the avoidable causes of cancer have not yet been clearly identified (e.g. in France, one third of cancer deaths can be explained by known risk factors [22]), it is thought that risk determinants exist for about one half of cancers. Thus, primary prevention in the context of cancer is an important area of public health.

The American Cancer Society has established a goal of reducing cancer mortality in the United States by 25% and cancer incidence by 50%by 2015. There has been significant progress in recent years in addressing the cancer problem. Cancer death rates have decreased by 18.4% among men and 10.5% among women since the early 1990s.

The *Annual Report to the Nation on the Status of Cancer, 1975-2005, Featuring Trends in Lung Cancer, Tobacco Use and Tobacco Control* is a joint report of the American Cancer Society, the US Centers for Disease Control and Prevention (CDC), the National Cancer Institute (NCI), and the North American Association of Central Cancer Registries (NAACR) [Jemal et al. *Journal of the National Cancer Institute* 2008; 100: 1672-1694].

The cancer death rate in the United States continues to go down and now cancer incidence–the rate at which new cancers are diagnosed also–appears to be dropping. Cancer death rates for both sexes combined declined about 1.8% per year from 2002 through 2005, almost double the 1.1% per year decrease seen from 1993 through 2002. For the first time in the 10-year history of the report, incidence rates for all cancers combined decreased, falling by 0.8% per year from 1999 to 2005.

Cancer death rates in the United States declined for 10 of the 15 most common causes of cancer death among both men and women, but increased for a few individual cancers, such as esophageal and bladder cancers among men, pancreatic cancers in women, and for cancers of the liver in both.

The decline in cancer incidence was largely due to declines in the most common cancers: lung, colorectal and prostate cancer for men and breast and colorectal cancer for women. Lung cancer death rates in women leveled off from 2003 through 2005, but incidence rates are still rising, though more slowly than they have risen in the past. Lung cancer death rates have been decreasing in men since the 1990s.

There are still significant differences in lung cancer deaths in different parts of the United States. In California, for instance, the lung cancer death rate dropped by about 2.8% per year among men between 1996 and 2005. That decline is more than double that seen in some Midwestern and Southern states, and may be due in part to California's strong tobacco control policies.

(ii) Secondary Prevention

It is very frequently the case that the probability of successful treatment of cancer is increased, sometimes very substantially, if the cancer can be diagnosed at an early stage. Awareness of the significance of signs and symptoms is important, but all too often cancers that exhibit symptoms are at an advanced stage. *Screening* is a term frequently applied to the situation where tests are used to indicate whether a (generally asymptomatic) individual has a high or low chance of having a cancer. Detecting cancers at an early, asymptomatic stage could lead to decreases in the mortality rate for certain cancers.

(iii) Tertiary Prevention. An obvious way to prevent cancer death is to cure those cancers which develop. However, there have been few major breakthroughs in cancer treatment in the sense of turning a fatal tumour into a curable one. Notably successes have been in testicular teratoma [60], Hodgkin disease [61], children's leukaemia, Wilm's tumour and choriocarcinoma. Progress in survival of the major cancers has been very much less than hoped. Adjuvant chemotherapy and tamoxifen have improved survival in breast cancer [62], adjuvant chemotherapy has also contributed to improvements in prognosis of ovarian cancer and colorectal cancer [63], and there has been additional progress that could be attributed specifically to certain treatments.

General progress in medical science has led to modern anaesthesia making more patients candidates for surgery, and the surgery itself safer; better control of infection and bacterial diseases; better imaging, which has improved tumour localisation and staging; and better devices being available to deliver the appropriate doses of radiation and drugs. Thus, more patients can get better and more appropriate therapy and hence have a better prognosis.

The quality of life issue has not been neglected, with breast conservation therapy now almost supplanting traditional, radical mastectomy in the majority of women; as well as more plastic breast reconstruction, less amputation of limbs for bone and soft-tissue sarcomas, and better colostomies being some important advances. Although increased attention has been given to issues of palliative, supportive and terminal care, there is still much work to be done (see Chapter 1.8).

Achieving cancer control: The example of the European Union

Turning theoretical knowledge of cancer risk factors into screening efficacy is a challenge. In the European Union, the High-level Cancer Experts Committee set a target in 1985 of reducing the number of deaths expected in the year 2000 by 15%, i.e. from 1 000 000 to 850 000 according to their calculations. Against this background of cancer as an important public health problem that is one of the commonest causes of premature and avoidable death in Europe, the *European Code Against Cancer* was introduced to be a series of recommendations that if followed could lead in many instances to a reduction in cancer incidence and also to reductions in cancer mortality. The recommendations were all evidence-based and were practicable to apply.

The *European Code Against Cancer* was originally drawn up and subsequently endorsed by the European Commission High-level Cancer Experts Committee in 1987. In 1994, the European Commission invited the European School of Oncology to assemble a group of international experts to examine and consider revision of the scientific aspects of the recommendations given in the current Code. This exercise took place and a new version was adopted by the Cancer Experts Committee at its meeting of November 1994 [64]. A further revision took place in 2003, producing the third version of the Code [65].

Any recommendation made to reduce cancer occurrence should not be one that could lead to an increased risk of other diseases. The recommendations which comprise the revised *European Code Against Cancer* should, if followed, also lead to improvements in other aspects of general health (Table 1.1.8). It is also important to recognise from the outset that each individual has choices to make about their lifestyle, some of which could lead to a reduction in their risk of developing cancer. These choices, and the rationale underlying their recommendation, are presented below.

The Code initially contained ten points [64] but was increased to eleven points for the third version [65]. If followed, this would lead to reductions in cancer incidence and/or mortality. The first point in the Code is the most important, while the others are not necessarily in order of importance in terms of how many cases or deaths could be prevented.

1. *Do not smoke; if you smoke, stop doing so. If you fail to stop, do not smoke in the presence of non-smokers.*

It is estimated that 25–30% of all cancers in developed countries are tobacco-related. From the results of studies conducted in Europe, Japan and North America, between 87 and 91% of lung cancers in men, and between 57 and 86% of lung cancers in women, are attributable to cigarette smoking. For both sexes combined the proportion of cancers arising in the oesophagus, larynx and oral cavity attributable to the effect of tobacco, either acting singly or jointly with the consumption of alcohol are between 43 and 60%. A large proportion of cancers of the bladder and pancreas and a proportion of cancers of the kidney, stomach, cervix and nose and myeloid leukaemia are also causally related to tobacco consumption. Because of the length of the latency period, tobacco-related cancers observed today are related to the cigarette smoking patterns over several previous decades. On stopping smoking, the increase in risk of cancer induced by smoking rapidly ceases. Benefit is evident within 5 years and is progressively more marked with the passage of time.

Smoking also causes many other diseases, most notably chronic obstructive pulmonary disease (commonly called chronic bronchitis) and an increased risk of both heart disease and

stroke. The death rate of long-term cigarette smokers in middle age (from 35 to 69 years of age) is three times that of life-long non-smokers, and approximately half of regular cigarette smokers who started smoking early in life, eventually die because of their habit. Half the deaths take place in middle age, when smokers lose approximately 20–25 years of life expectancy compared to non-smokers; the rest occur later in life when the loss of expectation of life is 7–8 years. There is now, however, clear evidence that stopping smoking before developing cancer or some other serious disease avoids most of the later risk of death from tobacco, even if cessation of smoking occurs in middle age. While the rate at which young people start to smoke will be a major determinant of ill-health and mortality in the second half of this century, it is the extent to which current smokers give up the habit that will determine mortality in the next few decades and which requires the urgent attention of public health authorities.

Tobacco smoke released to the environment by smokers, commonly referred to as environmental tobacco smoke (ETS) and which may be said to give rise to enforced "passive smoking", has several deleterious effects on people who inhale it. It causes a small increase in the risk of lung cancer and also some increase in the risk of heart disease and respiratory disease and is particularly harmful to small children. Smoking during pregnancy increases the risk of stillbirth, diminishes the infant's birth weight, and impairs the child's subsequent mental and physical development, while smoking by either parent after the child's birth increases the child's risk of respiratory tract infection, severe asthma and sudden death.

Although the greatest hazard is caused by cigarette smoking, cigars can cause similar hazards if their smoke is inhaled, and both cigar and pipe smoke cause comparable hazards of cancers of the oral cavity, pharynx, extrinsic larynx and oesophagus.

Worldwide, it is estimated that smoking killed four million people each year in the 1990s and that altogether some 60 million deaths were caused by tobacco in the second half of the 20th century. In most countries, the worst consequences of the tobacco epidemic are yet to emerge, particularly among women in developed countries and in the populations of developing countries

This first point of the European Code Against Cancer is refers to the most important cause of cancer [65] and should be viewed as containing three distinct messages:

Many aspects of general health can be improved and many cancer deaths prevented, if we adopt healthier lifestyles:	
1.	Do not smoke; if you smoke, stop doing so. If you fail to stop, do not smoke in the presence of non-smokers.
2.	Avoid Obesity.
3.	Undertake some brisk, physical activity every day.
4.	Eat a variety of vegetables and fruits every day: eat at least five portions daily. Limit your intake of foods containing fats from animal sources.
5.	If you drink alcohol, whether beer, wine or spirits, moderate your consumption to two drinks per day if you are a man or one drink per day if you are a woman.
6.	Care must be taken to avoid excessive sun exposure. It is specifically important to protect children and adolescents. For individuals who have a tendency to burn in the sun active protective measures must be taken throughout life
7.	Comply strictly with regulations aimed at preventing occupational or environmental exposure to known cancer-causing substances. Follow advice of National Radiation Protection Offices.
There are Public Health programmes which could prevent cancers developing or increase the probability that a cancer may be cured:	
8.	Women from 25 years of age should participate in cervical screening. This should be within programmes with quality control procedures in compliance with "EU Guidelines for Quality Assurance in Cervical Screening".
9.	Women from 50 years of age should participate in breast screening. This should be within programmes with quality control procedures in compliance with "EU Guidelines for Quality Assurance in Mammography Screening".
10.	Men and women from 50 years of age should participate in colorectal screening. This should be within programmes with built-in quality control procedures.
11.	Participate in vaccination programmes against Hepatitis B Virus infection.

Table 1.1.8 *European Code Against Cancer (Third version)[65]*

Do not smoke. Smoking is the largest single cause of premature death.

Smokers: stop as quickly as possible. In terms of health improvement, stopping smoking before having cancer or some other serious disease avoids most of the later excess risk of death from tobacco even if smoking is stopped in middle age.

Do not smoke in the presence of non-smokers. The health consequences of your smoking may affect the health of those around you.

2. *Avoid obesity.*

3. *Undertake some brisk, physical activity every day.*

Obesity is an established and major cause of morbidity and mortality. It is the largest risk factor for chronic disease in Western countries after smoking, increasing in particular the risk for diabetes, cardiovascular disease and cancer. Most countries in Europe have seen the prevalence of obesity (defined as a body mass index of ≥30 kg/m^2) rapidly increase over the years.

Many studies have examined the relationship between physical activity and the risk of developing cancer. The protective effect of physical activity on cancer risk improves with increasing levels of activity–the more the better–though such a recommendation should be moderated in individuals with cardiovascular disease. Regular physical activity that involves some exertion may be needed to maintain a healthy body weight, particularly for people with sedentary lifestyles. This could involve half an hour per day three times per week. More vigorous activity several times per week may give some additional benefits regarding cancer prevention.

4. *Increase your daily intake and variety of vegetables and fruits: eat at least five servings daily. Limit intake of foods containing fats from animal sources.*

Diet and nutritional factors commenced to be the focus of serious attention in the aetiology of cancer from the 1940s onwards. Initially dealing with the effects of feeding specific diets to animals receiving chemical carcinogens, research turned to the potential of associations with human cancer risk. Initially this was conducted through international comparisons of estimated national per capita food intake data with cancer mortality rates. It was consistently found that there were very strong correlations in these data, particularly with dietary fat intake and breast cancer. As dietary assessment methods became better, and certain methodological difficulties were identified and overcome, the science of nutritional epidemiology emerged.

5. *If you drink alcohol, whether beer, wine or spirits, moderate your consumption to two drinks per day if you are a man or one drink per day if you are a woman.*

There is wide variability among European Union countries in terms of *per capita* average alcohol consumption and preferred type of alcoholic beverage. Although three groups of countries are traditionally identified according to the prevalent drinking culture (wine drinking in the South, beer drinking in the Central Europe and spirit drinking in the North), there is considerable variability within such groups and within countries, and new patterns are evolving rapidly (e.g. increasing consumption of wine in Northern countries; increasing prevalence of binge drinking, in particular among women).

There is convincing epidemiological evidence that the consumption of alcoholic beverages increases the risk of cancers of the oral cavity, pharynx and larynx and of squamous-cell carcinoma of the oesophagus. Risk of breast cancer and colon cancer is also increased by alcohol consumption. The risks tend to increase with the amount of ethanol drunk, in the absence of any clearly defined threshold below which no effect is evident.

6. *Care must be taken to avoid excessive sun exposure. It is specifically important to protect children and adolescents. For individuals who have a tendency to burn in the sun active protective measures must be taken throughout life.*

Skin cancer is predominantly, but not exclusively, a disease of white-skinned people. Its incidence, furthermore, is greatest where fair-skinned peoples live at increased exposure to ultraviolet light, such as in Australia. The main environmental cause of skin cancers is sun exposure, and the ultraviolet light is deemed to represent the component of the solar spectrum involved in skin cancer occurrence. Exposure to artificial sources of sunlight, such as from sunbeds or sunlamps, is also known to increase risk of melanoma, with the effect particularly prominent if exposure starts as a teen or young adult.

7. *Apply strictly regulations aimed at preventing any exposure to known cancer-causing substances. Follow all health and safety instructions on substances which may cause cancer. Follow advice of national radiation protection offices.*

The prevention of exposure to occupational and environmental carcinogens has followed the identification of a substantial number of natural and man-made carcinogens, and has led to significant reductions in cancer occurrence. The message in this item of the code solicits responsible behaviour for individuals in three respects: (1) from those who have to provide timely and clear instructions, primarily legislators and regulators who should adapt scientific consensus evaluations into European Union law, and control compliance with these regulations; (2) from those who should follow these instructions and comply with the laws to protect the health of others, for instance managers, hygienists and doctors in industry; (3) from every citizen who in order to protect their own health and the health of others, ought to pay heed to the presence of carcinogenic pollutants and follow instructions and regulations aimed at mitigating or preventing exposure to carcinogens. The control of the prevalence and level of exposure to occupational and environmental carcinogens through general preventive measures has historically played a more important

role in preventing cancers than individual measures of protection.

Apart from individual lifestyle choices, there are public health programmes that could prevent cancers developing or increase the probability that a cancer may be cured.

Early detection is an important factor in reducing the death rate from cancer, whether it is achieved by personal actions or through participation in early detection programmes. Awareness of different visual body signs or symptoms that could easily be observed by anyone and that are possibly related to cancer is important. It is unequivocally established that cancer survival is better for early, localised disease than for the later stage, advanced form of the disease. Thus the earlier in the process that a cancer can be diagnosed and treated then the better this is for the patient. Much effort has gone into cancer screening and the development of methods for finding cancers at an earlier stage in their development and increasing prospects for cure. It is possible to make recommendations based on the available evidence.

8. *Women from 25 years of age should participate in cervical screening. This should be within programmes with quality control procedures in compliance with EU guidelines for quality assurance in cervical screening.*

The effectiveness of screening for cervical cancer has never been demonstrated in a randomised trial. There is, however, sufficient non-experimental evidence showing the efficacy of screening using a cervical smear (Pap) test performed every 3–5 years. The effects are somewhat smaller at a population level. In some of the Nordic countries, the reduction was about 80% in women in the age groups exposed most intensively to screening. In the mid-1980s, after several years of organised screening, the overall incidence was 5–15 per 100 000 woman-years.

Cervix cancer screening should be offered to all women over 25 years. There is limited evidence of benefit of screening in women over 60 though the likely yield of screening is low in women over age 60, since the incidence of high-grade cervical lesions declines after middle age. Screening this age group is associated with potential harm from false-positive results and subsequent invasive procedures. Stopping screening in older women is probably appropriate among women who have had 3 or more consecutive previous (recent) normal Pap smear results. Yield is also low after hysterectomy, and there is scant evidence to suggest that screening produces improved health outcomes.

9. *Women from 50 years of age should participate in breast screening. This should be within programmes with quality control procedures in compliance with "EU guidelines for quality assurance in mammography screening".*

There is considerable evidence that breast cancer screening with mammography is effective at reducing mortality from breast cancer. A well-organised programme with a good compliance should lead to a reduction in breast cancer mortality of at least 20% in women aged over 50. The value of screening women under 50 years is uncertain. No trials having large enough statistical power to analyse these women separately have been completed. What recommendations should be made for mammographic screening of women aged 40–49 is an important question that cannot now be answered; over 40% of the years of life lost due to breast cancer diagnosed before the age of 80 years are attributable to cases presenting symptomatically at ages 35–49 years, frequently an age of considerable social responsibility.

Mammographic screening is only one step in the total management of the woman with breast cancer. As has been shown from long-term established programmes in the United Kingdom, Sweden, Finland and the Netherlands, recognition of the importance of the multidisciplinary team in the assessment of mammographic abnormalities had spread into the symptomatic sector, leading to the development of integrated multidisciplinary breast care centres. Staffed by dedicated surgeons, radiologists and pathologists working alongside breast care nurses, counselling and other support personnel, these centres offer the necessary care for women with breast cancer.

10. *Men and women from 50 years of age should participate in colorectal screening. This should be within programmes with built-in quality control procedures.*

The identification of a well-determined pre-malignant lesion, the adenomatous polyp, together with the good survival associated with early disease, make colorectal cancer an ideal candidate for screening. In the past quarter century, progress has been made in our ability to screen patients for colorectal cancer or its precursor state, using advances in imaging and diagnostic technology. Faecal occult blood guaiac test cards were first employed in the 1960s, the flexible sigmoidoscope was introduced in the mid-1970s to replace the rigid sigmoidoscope which had been first introduced in 1870, and colonoscopy has been available since 1970.

Despite the evidence showing that screening is worthwhile, most citizens of developed countries have not been screened for colorectal cancer by any means. While this situation persists the chance is being missed to prevent about one quarter of the colorectal cancer deaths that occur each year in the European Union.

11. *Participate in vaccination programmes against Hepatitis B infection.*

Chronic infection with hepatitis B virus (HBV) and hepatitis C virus (HCV) accounts for the majority of liver cancer cases in Europe. In a large case-series of liver cancer from six European Liver Centres, only 29% of liver cancer patients had no marker of either HBV or HCV infection.

An effective vaccine against HBV has been available for 20 years now. Several countries in the European Union (e.g. Denmark, Finland, Ireland, the Netherlands, Sweden and the United Kingdom) do not perform routine vaccination against HBV in children, on account of the low prevalence of HBV infection in the general population (http://www.who.int/), whereas other countries (e.g. Belgium, France, Germany) report coverage below 50%. There is scope for reconsidering national policies regarding universal vaccination against HBV, since selective vaccination of high-risk groups rarely works and travelling and migration facilitate the mixing of high- and low-risk populations. Although infection with HBV in young adulthood (typically through sexual intercourse or contaminated needles) carries a much lower risk of chronic hepatitis and liver cancer than does infection at birth or during childhood, it frequently induces acute hepatitis.

Impact of cancer control activities: The example of Europe

During the lifespan of the 'Europe Against Cancer' program, cancer mortality in the (then-15) Member States of the European Union (EU) had started to decline; the estimated number of deaths in 2000 was 940 510, which was 9.0% fewer than the 1 033 083 deaths expected on the basis of application of the age-specific mortality rates from the mid-1980s to the 2000 population [66,67]. When all the mortality data for 2000 were eventually available (and only Belgium is still an estimate, with 1997 being the most recent year for which data are available), there were 935 219 cancer deaths in the EU, which is 9.5% fewer than expected. These declines have subsequently been confirmed [68,69].

Bosetti et al. [69] present confirmation that these downward trends are continuing in the enlarged Member States of the EU (26 Member States, since Cyprus did not have data available). It is wonderfully reassuring to gaze at the downward trends in mortality rates in almost all forms of cancer. Now there can be more emphasis placed on the cancer sites where the mortality rates are rising. Notable among these are liver and pancreas cancer in both men and women, and the dramatic increases taking place in lung cancer in women. These continual upward trends are now more prominent when mortality rates from all other forms of cancer are in decline [69].

This decline was previously predicted by Quinn et al. [70], who made statistical forecasts of the trends in the EU-15 until 2020. While rates of most cancers were predicted to fall, in some countries rates in men were set to stabilise. While this was good news, it was tinged with the sad realisation that the stable rate achieved among men would be twice as high in Hungary as it would be in Sweden [70].

Cancer control is necessary and possible

There is strong evidence that cancer is, and will be for the immediate future, a major public health problem. The majority of human cancers may be avoidable, and for several of them avoidable causes have already been identified. In global terms, the greatest impact would be from the control of tobacco smoking and the control of breast cancer. While tobacco control could be achieved using a series of government and societal actions [29], prospects for the prevention of breast cancer, for example, are more remote.

Failing primary prevention, screening for breast, cervix and colorectal cancer could have a significant effect on reducing mortality from these common diseases. Screening for other forms of cancer will emerge as public health strategies once there has been proper evaluation; the current situation with prostate cancer is salutary in this respect.

With the expansion in the absolute numbers of cases of cancer set to continue into the next century, the role of prevention in cancer control strategies will increase in importance, as will the central role of epidemiology. This latter will also have to change: arguably the time has come to de-emphasise the chase for risk factors and to re-focus on the implementation of current knowledge in populations where many thousands, if not millions, of frequently premature deaths could be avoided.

A major challenge for many countries is finding sufficient funds to develop the capacity to treat the large numbers of cancers that will be diagnosed in the coming years. Effective prevention will reduce the risk of cancer and effective screening will allow many others to be successfully treated for their disease. Prevention actions can be implemented today to reduce the burden of major cancer killers: e.g. tobacco control against lung cancer and other forms of cancer [27, 28] and vaccination against cancers of the cervix and liver. Cancer control in developing nations must serve to de-stigmatise cancer and raise governmental and public awareness and dispel the myth equating cancer diagnosis with death.

Radiotherapy is an essential component of the treatment of cancer, and whether used for cure or palliation, radiotherapy has been shown to be cost effective. In high-income countries, over half of new cases receive one course of radiotherapy and up to one quarter of cancer patients may receive a second course. In low and middle-resource countries the need for radiotherapy is much greater due to late-stage presentations and the types of cancer that predominate. Breast and cervical cancers, the two leading female cancers globally, are highly treatable when detected early, and radiotherapy plays a major role in treatment protocols. Cervical cancer is the commonest form of cancer in women in Africa, and radiotherapy is an undeniable necessity. Simultaneously, it is essential to alter the 70%:30% balance of palliation over cure that exists at present [71].

Most low- and middle-resource countries have limited access to radiotherapy, although over 30 African and Asian countries have no services at all. In Africa the actual supply of radiotherapy is 20% of needs, while in the Asia-Pacific Region, with over 3 million new cases of cancer each year and the need for 4000 radiotherapy machines, only 1200 or so machines exist [72]. Total global shortages in low- and middle-resource countries are over 7000 radiotherapy machines, and it is clear that accessible, affordable, and suitable radiotherapy technologies are needed.

The *Programme of Action on Cancer Therapy* (PACT), established by the International Atomic Energy Agency (IAEA) and partners, aims principally to ensure effective and sustainable transfer of radiation technology to underserved regions of the world where need exists and to integrate radiotherapy into the broader public health priorities on cancer as part of *National Cancer Strategies*. In addition, PACT has the potential to serve as a focus to establish a series of evidence-based, appropriate actions to reduce cancer incidence and cancer mortality and increase the amount of effective palliation that can be delivered. The international cancer control community requires a focus [26], which PACT could provide.

The Millennium Development Goals (MDGs) (United Nations, 2005) have galvanised unprecedented efforts to meet the needs of the world's poorest communities. Achieving the MDGs has become a competitive challenge for many countries and will be of immense value to populations world-wide. Cancer prevention and control must acquire the same focus as provided by the MDGs [26,73]. In many parts of the world, the absence of a specific MDG on cancer (or indeed chronic disease) has led to cancer control taking on something of a lesser role in terms of allocated priority. There needs to be greater incentive developed for low-resource and medium-resource countries to prioritise cancer and other chronic diseases. A similar argument has been made regarding cardiovascular disease [74], and there is a wider recognition that this is necessary [75,76].

Although increasingly many medium-resource countries assign high priority in their national health strategies to chronic diseases including cancer, the donor community and most bilateral development agencies do not as yet consider cancer control a high priority. If cancer is not given higher priority through focused global efforts, health-care systems in low-resource and middle-resource countries will encounter even further problems as the number of cancer cases increases. More and more people will die prematurely and needlessly from cancer, with devastating social and economic consequences for households, communities and countries alike. Cancer could become a major impediment to socioeconomic development in low resource and economically emerging nations.

Current Opportunity

The timing is now right to address this growing cancer burden, part of the neglected epidemic of chronic disease and a neglected development goal [26,74,76]. The WHO Resolution on Cancer Control (WHA58.22) [77] provides a strong impetus for countries to develop programmes aimed at the reduction of cancer incidence and mortality. Although this is a strong incentive, there is an overwhelming and urgent need for leadership and coordination in this area. Compared to other global health communities, the global cancer control community is diffuse and often ineffective.

This has important implications for public health as well as other elements of health services around the world. There will be a need for more medical, nursing and related staff to treat these patients, there will need to be more hospitals and treatment facilities available, and this will all be a major expense as well as a major logistical problem for the near future. The implications for planning are that cancer control activities will need to increase to help reduce the mortality burden that is otherwise likely to materialise.

Priorities must be realistic and achievable, and include a focus on low-resource and medium-resource countries and the identification, delivery and assessment of effective cancer control measures. Depending on resources and competing health priorities, all steps must be taken to prevent those cancers which are preventable; to treat those cancers which are treatable; to cure those cancers which are curable; and to provide palliation and supportive care to patients throughout their cancer trajectory.

In the chapters that follow in this volume, current knowledge of cancer causes and prevention prospects will be outlined to serve as a basis for cancer control planning and prioritisation in regions at different resource settings.

CANCER CONTROL IN MEDIUM-INCOME COUNTRIES: THE CASE OF HUNGARY

Hungary, situated in central Europe, has an estimated 2008 population of 10.1 million, two thirds of whom live in urban areas. There are 3.3 doctors and 7.9 hospital beds per 1000 population; 7.9% of Gross Domestic Product (GDP) is spent on healthcare.

National Institute of Oncology

With a single regulation in 1952, the Ministry of Health created the National Institute of Oncology on the former territory of the Siesta sanatorium, thus creating the centre of Hungarian oncology and significantly affecting the whole of the Hungarian fight against cancer. According to the functions set down in its charter, the National Institute of Oncology became the epidemiological, organisational, methodological, treatment, research, and training centre for Hungarian oncology, and it remains so today. After the National Institute of Oncology moved to its new location, the 300 beds initially available at the Institute slowly increased to 348. Although this number has not changed significantly since then, the structure of the clinical departments underwent changes on several occasions in response to the challenges of the times.

At the time, the clinical department of the National Institute of Oncology consisted of seven clinical inpatient departments: Surgery (61 beds), Gynaecology (65 beds), Urology (49 beds), two Departments of Radiology (57 beds and 68 beds), Internal Medicine, and Temporary Post-treatment Care. The Institute also included X-ray diagnostics, a central medical laboratory, outpatient care, a pathological and histological laboratory, a radiation physics and isotope laboratory, a pharmacy, and the methodological-organisational-statistical department, managing the nationwide network of oncology care centres. The Oncopathological Research Institute (OPI) has been carrying out its diagnostic and experimental activities within five departments (Pathology, Experimental Morphology, Experimental Pharmacology, Cellular Biology, and Biochemistry) in the same complex since 1954, and has always maintained strong organisational connections with the National Institute of Oncology.

In 1956, Prof Dr Tibor Venkey was named Director-General. The chemotherapy and diagnostic internal medicine department was formed in the first half of 1953; in 1955, the Onco-dermatology Department was created. In 1958, the Isotope Department was launched; last, in 1959, the Department of Laryngology became a separate organisational unit. At the end of 1955 a separate outpatient care department was formed with the appointment of seven outpatient care consultants, easing the burden on the physicians in the clinical departments. (In 1958, the Institute was equipped with a cobalt gun, which entailed the reorganisation of the department of radiotherapy.)

Between 1959 and 1970, Dr János Vikol was the Director-General of the Institute. He played a vital role in involving the Institute in the cancer control programmes of the World Health Organization (WHO), thereby laying the foundations for the exceptional international performance of the Institute. In 1966, Dr Vikol was put in charge of the Cancer Control Section of the WHO, which involved frequent visits abroad; therefore the Institute was managed by Dr Iván Rodé as temporary Director in 1968. Under Dr Rodé's leadership, the scope of radiotherapy further expanded. In 1970 was installed a 25 MeV circular accelerator (betatron), unique at that time, allowing tumours located deep within the body to be successfully treated due to its high energy and accurate dose counts.

In 1971, Prof Dr Sándor Eckhardt was appointed superintendent, leading to a number of changes in the operation of the institute. The structure of the institute has mirrored the development in the field of cancer, allowing for the approximation of the European standards with regard to tumour treatment and research. The international recognition and integration of the National Institute of Oncology was significantly improved by the election of Prof Eckhardt as the president of UICC.

Professor Eckhardt also further strengthened the Oncology Committees according to tumour localisation. Until 1970, the physicians of the institute had held joint meetings to discuss the controversial cases and make diagnostic and therapeutic decisions. Since the number of patients consulted was continuously growing, it seemed necessary to establish expert committees for gynaecological tumours, abdominal and accessory cavity tumours, haemoblastoses, breast tumours, skin melanoma, and head-neck tumours (1970). Institute members held clinico-pathological conferences on a monthly basis, where, apart from the autopsy results, they evaluated the results of the more interesting biopsies, along with the clinical history of the patients.

In 1971 the Department of Internal Medicine, which had previously had 24 beds and one outpatient office, was expanded to 60 beds and two outpatient offices. In addition to these, an immunology laboratory was added in 1974 for the examination of the immunological changes sometimes concomitant with malignancies. By 1976 the Department had 65 inpatient beds and 14 physicians, and the Internal Medicine outpatient centre examined, treated and checked more than 6000 patients.

The management of the Institute has been carried out by a Board of Directors since 1987. This relative organisational, material and intellectual freedom proved inspirational for research, resulting in considerable development over the subsequent decade.

In 1992, Prof Dr Miklós Kásler became the superintendent of the National Institute of Oncology, and restructured the Institute with three centres in line with the three distinct activities at the Institute: the Centre for Clinical Oncology, the Centre for Pathology and the Centre of Research. In 2002, the Director General established a management structure more suited to constantly changing financial conditions and to the European norms. As a result of the international activities of Prof Kásler, Hungary participated in the development of the European Code against Cancer (2004) and the National Cancer Control Programme meetings organised by the UICC and WHO. Prof Kásler headed the Educational Team of the Organization of European Cancer Institutes; he is presently assisting the international integration of the National Institute of Oncology as a member of the steering committee of the European Alliance against Cancer. The development (1993) and expansion (1997, 2005) of the Hungarian National Cancer Control Programme are both linked with the name of Miklós Kásler. He was appointed president of the National Programme against Cancer Council in February 2005. In this role, Dr Kásler commenced the European harmonisation of the Hungarian oncology care system.

The main feature of the Institute of Oncology is its capability to provide patients with complex clinical onco-therapeutic treatment (surgery, chemotherapy, and radiation therapy). The personal conditions paired with the state-of-the-art tumour diagnostics (CT, MRI, imaging, laboratory, pathological) equipment provide high-quality diagnostic and monitoring capabilities with the help of a highly trained expert team well-versed in imaging, laboratory, and pathological diagnostics.

Cancer in Hungary

Hungary's cancer mortality statistics have long been dramatically elevated. At present, there are about 300 000 cancer patients, and 33 530 people died of malignant diseases in 2003. Cancer is the second most frequent cause of death in Hungary, following cardiovascular disease. Cancer occurs so frequently that the prevention, up-to-date treatment, and control of cancer have become major public health challenges. At present in Hungary there are 601 specialists in medical oncology and 120 radiotherapists, some of whom have medical oncology as a second specialisation.

The first National Cancer Control Programme (NCPP) was established in 1993, and evolving cancer patterns and trends in Hungary have provided the basis for evaluating priorities for cancer control. These priorities include:

1. Primary prevention: Health education, oncology-related programmes on TV, development of new education programmes for the medical and paramedical staff;
2. Secondary prevention: Improvement of screening for breast, colorectal, cervix and head and neck tumours, and promotion of research related to early detection;
3. Treatment: Establishment of treatment protocols;
4. Establishment of a National Cancer Registry (fulfilled 1999); and
5. Rehabilitation.

Evolution of the Hungarian National Cancer Registry

The Országos Rákregiszter GRID (ORG) project was established to develop the next generation of the National Cancer Registry (NCR) for Hungary. The NCR started operation in 1999, and its central mission is the collection, management and analysis of medical data on people who have been diagnosed with malignant or neoplastic disease.

The ORG project is a consortium of the Department of Distributed Systems (DSD) of SZTAKI, Arvato Systems Hungary Inc. and the National Institute of Oncology. It has been responsible for building new online infrastructure to collect and validate medical data, which will greatly improve the quality of NCR data on cancer and thus provide a much stronger statistical base for decision-makers and medical researchers. One of the other important objectives of the ORG project is to broaden the range of data collected, including relevant healthcare, environmental, political, demographical and economic data associated with a given geographical territory in addition to the standard cancer-specific medical and demographic data.

The ORG Cancer Registry finished its test phase in 2007, and the old and the new systems are running in parallel in order to eliminate any remaining errors in the system, train personnel, and prepare for the final switch from the old system to the new one.

Sources

Additional information on the National Cancer Control Programme can be accessed at: http://www.eum.hu/index.php?akt_menu=2652&archiv=1
Additional information on the National Cancer registry can be accessed at: http://dsd.sztaki.hu/projects/org/en/

CANCER CONTROL IN MEDIUM-INCOME COUNTRIES: THE CASE OF TURKEY

Cancer control practices in Turkey started in 1947 when the Turkish Cancer Research and Control Institution was established. The Ahmet Andicen Oncology Hospital was started in Ankara in 1955, and the Department of Cancer Control in Primary Health Services was established in 1962, becoming the Department of Cancer Control in the Ministry of Health in 1970. The Department is responsible for the regulation of preventive services and treatment cervices in relation to cancer control, and for implementing, executing and inspecting cancer treatment resources. In 1970, the week of 1-7 April was designated as National Cancer Week, and this continues to this day.

In 2008, the estimated population of Turkey was 73.2 million. There are 1.4 doctors per 1000 population and 2.6 hospital beds per 1000 population. An estimated 7.7% of Gross Domestic Product (GDP) was spent on healthcare in 2008. There are an estimated 150 000 new cases of cancer in Turkey each year. In men, the commonest cancers are those of the trachea, bronchus and lung (33%); stomach (9%); urinary bladder (9%); colon and rectum (8%); prostate (6%) and larynx (6%). In women, the commonest cancers are those of the breast (24%); colon and rectum (9%); stomach (7%); ovary (6%); trachea, bronchus and lung (6%); leukaemia (5%); and cervix (5%) and corpus (5%).

Cancer treatment facilities. Cancer treatment in Turkey is available in public hospitals, university hospitals and in private institutions. The majority of oncologists generally work in large centres having high standards. There are three oncology institutes in Turkey (Oncology Institute of Hacettepe University, Oncology Institute of Istanbul University and the Oncology Institute in Dokuz Eylul University) and 44 centres for cancer diagnosis and treatment.

At the beginning of 2007, there were 170 specialists in medical oncology in Turkey; this is less than optimum and recognised as one of the key bottlenecks in the development of cancer treatment services. Certain steps that will go into effect in the near future have been taken to address this situation. However, a serious impediment remains the high costs of many chemotherapeutic drugs which could overwhelm the health budget of the country.

"Interpreting Cancer Control as simply Treatment Services is a problem all over the world. Awareness that cancer is a preventable and controllable disease has been recognised only very recently." (A Murat Tuncer, 2008).

Turkey has an active programme in radiation oncology, with approximately 300 active radiation oncologists and an increasing number of radiation oncologists in training. However, lack of a domestic radiotherapy equipment manufacturer has a led to a number of problems frequently entailing long delays between launching a bid and having the new, modern equipment installed and working. There also remains a shortage of medical physicists.

Oncology nursing is recognised, and there have been training courses in the country since 1987 with the (Turkish) Association for Oncology Nursing having been established in 1989. There are currently over 500 oncology nurses in Turkey.

Cancer prevention and early diagnosis. A project for the creation of cancer registries was established in 1992. Today, the main priority in the cancer control plan, which is now accepted as national policy, is the collection of reliable and accurate data on cancer incidence. In 2006, priority was given to create and develop cancer registries in Ankara, Antalya, Samsun, Erzurum, Trabzon, Izmir, Edirne and Eskisehir. In addition, steps are being taken to establish a Cancer Early Diagnosis and Screening Centre (KETEM) in every city (by the end of 2008 there will be 83 such centres). This KETEM project was initiated jointly by the European Union and the Turkish Ministry of Health in 1996 and was launched in 2004. Moreover, population-based screening programmes for cervix and breast cancer, designed according to established EU criteria for quality control, are rapidly gaining ground throughout the country.

Tobacco is recognised as the major cause of cancer in Turkey, and a *Law on Tobacco Control and Preventing the Damages of Tobacco Products* (law 5727 of 3rd January 2008) has been passed. This law bans smoking in bars, restaurants and public places. It represents an important investment for the future of cancer control in Turkey.

A detailed description of the current situation in Turkey can be found in the following publication:

Cancer Control in Turkey. Editor: Prof Dr A Murat Tuncer. Department of Cancer Control, Turkish Republic Ministry of Health, Ankara, 2008

REFERENCES

1. Fass L (2008). Imaging and cancer: A review. *Mol Oncol* 2: 115-152.

2. Adler I (1912). *Primary malignant growths of the lungs and bronchi. A pathological and clinical study*. New York: Longmans & Co.

3. Poole-Wilson PA, Jacques A, Lyon A (2006). Treatment of angina: a commentary on new therapeutic approaches. *Eur Heart J* 8: a20-a25.

4. Obrastzow WP and Straschenko ND (1910). Zur kenntis der thrombose der koronararterien des herzens. *Z Klin Med* 71: 116-132.

5. Herrick JB (1912). Clinical features of sudden obstruction of the coronary arteries. *JAMA* 1912: 2015-2020.

6. Fitz RH (1886). Perforating inflammation of the vermiform appendix: with special reference to its early diagnosis and treatment. *Trans Assoc Am Physicians. 1886;1:107-144.*

7. Moodie RL (1917). Studies in paleopathology. I. General consideration of the evidences of pathological conditions found among fossil animals. *Ann Med Hist* 1: 374-393.

8. Moodie R and Abel O (1924). Nevere studies uber krankheiter fossiler wirbeltiese. *Verh Zool Bot Ges Wien* 73: 1004.

9. Esper of Erlangen (1774). *cited in Moodie [7]* .

10. Gray PH (1967). Radiography of ancient Egyptian mummies. *Med Radiogr Photogr* 43: 34-44.

11. Ritchie WA and Warren SL (1932). The occurrence of multiple bony lesions suggesting myeloma in the skeleton of a pre-Columbian Indian. *Am J Roentgenol* 28: 622-628.

12. Granville AB (1825). An essay on Egyptian mummies, with observations on the art of embalming among the ancient Egyptians. *Philos Trans R Soc Lond* 115: 269-316.

13. Breasted JH (1930). *The Edwin Smith surgical papyrus*. Chicago: The University of Chicago Press.

14. Pott P (1775). *Chirurgical observations relative to the cataract, the polypus of the nose, the cancer of the scrotum, the different kinds of ruptures, and the mortification of the toes and feet*. London: T.J. Carnegy.

15. Redmond DE (1970). Tobacco and cancer: the first clinical report, 1761. *N Engl J Med* 282: 18-23.

16. Ramazzini B (1743). *De morbis artificum diatriba*. Venetiis: Apud Josephum Corona.

17. Zatonski W and Boyle P (1996). Health transformations in Poland after 1988. *J Epidemiol Biostat* 1: 183-187.

18. United Nations Department of Economic and Social Affairs (2007). *World population prospects: the 2006 revision*. New York: United Nations.

19. Boyle P, Autier P, Bartelink H, et al. (2003). European Code Against Cancer and scientific justification: third version (2003). *Ann Oncol* 14: 973-1005.

20. Doll R and Peto R (1981). The causes of cancer: quantitative estimates of avoidable risks of cancer in the United States today. *J Natl Cancer Inst* 66: 1191-1308.

21. IARC, Académie Nationale de Médecine, Académie des Sciences, et al. (2007). *IARC Working Group Reports, Volume 3, Attributable causes of cancer in France in the year 2000*. Lyon, France: International Agency for Research on Cancer.

22. Peto J (2001). Cancer epidemiology in the last century and the next decade. *Nature* 411: 390-395.

23. Boffetta P, Tubiana M, Hill C, et al. (*In Press*). The causes of cancer in France. *Ann Oncol*.

24. Stewart BW, Kelihues P (2003). *World cancer report*. Lyon, France: International Agency for Research on Cancer.

25. Boyle P (2006). The globalisation of cancer. *Lancet* 368: 629-630.

26. Parkin DM (2006). The global health burden of infection-associated cancers in the year 2002. *Int J Cancer* 118: 3030-3044.

27. IARC (2004). *IARC monographs on the evaluation of carcinogenic risks to humans, Volume 85, Betel quid and areca nut chewing and some areca-nut-derived nitrosamines*. Lyon, France: International Agency for Research on Cancer.

28. IARC (2004). *IARC monographs on the evaluation of carcinogenic risks to humans, Volume 83, Tobacco smoke and involuntary smoking*. Lyon, France: International Agency for Research on Cancer.

29. Boyle P, Gray N, Henningfield J, et al. (2004). *Tobacco : science, policy and public health*. Oxford: Oxford University Press.

30. Doll R, Peto R, Boreham J, et al. (2004). Mortality in relation to smoking: 50 years' observations on male British doctors. *BMJ* 328: 1519.

31. Ferlay J, Bray F, Pisani P, et al. (2004). *GLOBOCAN 2002: Cancer incidence, mortality and prevalence worldwide*. Available from: http://www-dep.iarc.fr/

32. American Cancer Society (2007). *Cancer Facts & Figures 2007*. Atlanta: American Cancer Society.

33. Boyle P and Ferlay J (2005). Cancer incidence and mortality in Europe, 2004. *Ann Oncol* 16: 481-488.

34. Ferlay J, Autier P, Boniol M, et al. (2007). Estimates of the cancer incidence and mortality in Europe in 2006. *Ann Oncol* 18: 581-592.

35. WHO. *WHO Statistical Information System (WHOSIS)*. Available from: http://www.who.int/whosis Date Accessed: December 1, 2008.

36. WHO (2008). *The global burden of disease : 2004 update*. Geneva: World Health Organization.

37. Yang G, Hu J, Rao KQ, et al. (2005). Mortality registration and surveillance in China: History, current situation and challenges. *Popul Health Metr* 3: 3.

38. Yang GH, Huang ZJ, Tan J (1996). Priorities of disease control in China-analysis on mortality data of National Disease Surveillance Points System. *Zhonghua Liu Xing Bing Xue Za Zhi* 17: 199-202.

39. Doll R, Payne P, Waterhouse J (1966). *Cancer incidence in five continents : A technical report*. Geneva: International Union against Cancer.

40. Doll R, Muir CS, Waterhouse J (1970). *Cancer incidence in five continents, Volume II*. Geneva, International Union against Cancer.

41. Waterhouse J, Muir C, Correa P, et al. (1976). *IARC Scientific Publications, Number 15, Cancer incidence in five continents, Volume III*. Lyon, France: International Agency for Research on Cancer.

42. Waterhouse J, Muir C, Shanmugaratnam K, et al. (1982). *IARC Scientific Publications, Number 42, Cancer incidence in five continents, Volume IV*. Lyon, France: International Agency for Research on Cancer.

43. Muir C, Waterhouse J, Mack T, et al. (1987). *IARC Scientific Publications, Number 88, Cancer incidence in five continents, Volume V*. Lyon, France: International Agency for Research on Cancer.

44. Parkin DM, Muir CS, Whelan SL, et al. (1992). *IARC Scientific Publications, Number 120, Cancer incidence in five continents, Volume VI*. Lyon, France: International Agency for Research on Cancer.

45. Parkin DM, Whelan SL, Ferlay J, et al. (1997). *IARC Scientific Publications, Number 143, Cancer incidence in five continents, Volume VII*. Lyon, France: International Agency for Research on Cancer.

46. Parkin DM, Whelan SL, Ferlay J, et al. (2003). *IARC Scientific Publications, Number 155, Cancer incidence in five continents, Volume VIII*. Lyon, France: International Agency for Research on Cancer.

47. Mathers CD, Fat DM, Inoue M, et al. (2005). Counting the dead and what they died from: an assessment of the global status of cause of death data. *Bull World Health Organ* 83: 171-177.

48. Eighteenth World Heath Assembly (1965). *Resolution WHA18.44. May 20 1965. Establishment of an International Agency for Research on Cancer*. Geneva: World Health Organization.

49. Institute of Medicine (U.S.), Sloan FA, Gelband H (2007). *Cancer control opportunities in low- and middle-income countries*. Washington, DC: National Academies Press.

50. Mathers CD and Loncar D (2006). Projections of global mortality and burden of disease from 2002 to 2030. *PLoS Med* 3: e442 doi:10.1371/journal.pmed.0030442.

51. WHO. *Quick cancer facts*. Available from: http://www.who.int/cancer/ Date Accessed: March 3, 2008.

52. World Health Organization and International Union Against Cancer (2005). *Global Action Against Cancer - Updated version*. Geneva: WHO, UICC.

53. Lopez AD, Mathers CD, Ezzati M, et al. (2006). Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. *Lancet* 367: 1747-1757.

54. McCredie M, Coates MS, Ford JM (1990). Cancer incidence in European migrants to New South Wales. *Ann Oncol* 1: 219-225.

55. Higginson J and Muir CS (1979). Environmental carcinogenesis: misconceptions and limitations to cancer control. *J Natl Cancer Inst* 63: 1291-1298.

56. Curado MP, Edwards B, Shin HR, et al. (2007). *IARC Scientific Publications, Number 160, Cancer incidence in five continents, Vol. IX*. Lyon, France: International Agency for Research on Cancer. Available from: http://www-dep.iarc.fr/

57. Doll R, Fraumeni JF, Muir CS (1994). *Trends in cancer incidence and mortality*. Plainview, N.Y.: Cold Spring Harbor Laboratory Press.

58. Haenszel W and Kurihara M (1968). Studies of Japanese migrants. I. Mortality from cancer and other diseases among Japanese in the United States. *J Natl Cancer Inst* 40: 43-68.

59. Cairns J (1978). *Cancer : science and society*. San Francisco: W.H. Freeman.

60. Boyle P (2004). Testicular cancer: the challenge for cancer control. *Lancet Oncol* 5: 56-61.

61. Boyle P, Soukop M, Scully C, et al. (1988). Improving prognosis of Hodgkin's disease in Scotland. *Eur J Cancer Clin Oncol* 24: 229-234.

62. Early Breast Cancer Trialists' Collaborative Group (1992). Systemic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy. 133 randomised trials involving 31,000 recurrences and 24,000 deaths among 75,000 women. Early Breast Cancer Trialists' Collaborative Group. *Lancet* 339: 71-85.

63. Cunningham D and Findlay M (1993). The chemotherapy of colon cancer can no longer be ignored. *Eur J Cancer* 29A: 2077-2079.

64. Boyle P, Veronesi U, Tubiana M, et al. (1995). European School of Oncology Advisory report to the European Commission for the «Europe Against Cancer Programme» European Code Against Cancer. *Eur J Cancer* 31A: 1395-1405.

65. Boyle P, d'Onofrio A, Maisonneuve P, et al. (2003). Measuring progress against cancer in Europe: has the 15% decline targeted for 2000 come about? *Ann Oncol* 14: 1312-1325.

66. Boyle P (2008). Favorable trends in cancer mortality in the European Union but no room for complacency. *Ann Oncol* 19: 605-606.

67. Levi F, Lucchini F, Negri E, et al. (2007). Continuing declines in cancer mortality in the European Union. *Ann Oncol* 18: 593-595.

68. Bosetti C, Bertuccio P, Levi F, et al. (2008). Cancer mortality in the European Union, 1970-2003, with a joinpoint analysis. *Ann Oncol* 19: 631-640.

69. Quinn MJ, d'Onofrio A, Moller B, et al. (2003). Cancer mortality trends in the EU and acceding countries up to 2015. *Ann Oncol* 14: 1148-1152.

70. Lingwood RJ, Boyle P, Milburn A, et al. (2008). The challenge of cancer control in Africa. *Nat Rev Cancer* 8: 398-403.

71. Barton MB, Frommer M, Shafiq J (2006). Role of radiotherapy in cancer control in low-income and middle-income countries. *Lancet Oncol* 7: 584-595.

72. Boyle P, Anderson BO, Andersson LC, et al. (2008). Need for global action for cancer control. *Ann Oncol* 19: 1519-1521.

73. Fuster V (2006). Cardiovascular disease and the UN millennium development goals: a serious concern. *Nat Clin Pract Cardiovasc Med* 3: 401.

74. Horton R (2005). The neglected epidemic of chronic disease. *Lancet* 366: 1514.

75. Horton R (2007). Chronic diseases: the case for urgent global action. *Lancet* 370: 1881-1882.

76. Fifty-eighth World Health Assembly (2005). *Resolution WHA58.22, May 25 2005. Cancer prevention and control*. Geneva: World Health Organization.

1.2 Cancer Nomenclature

Neoplasia (Greek for "new growth") is the abnormal and uncontrolled proliferation of cells in a tissue or organ. Most neoplasms proliferate to form distinct masses (tumours). Malignant neoplasms show a great degree of anaplasia and have the properties of invading neighbouring structures and an ability to spread through the lymphatic system and bloodstream to other organs. The term cancer is largely synonymous with neoplasm and is used as a general term for many diseases that are characterised by uncontrolled, abnormal growth of cells. Most frequent are carcinomas, malignant tumours that arise from epithelial cells in skin, the gastrointestinal tract and other internal organs. Sarcomas are derived from soft tissues (muscle, blood vessels, adipose tissue) and bone. Gliomas result from the transformation of glial cells in the central nervous system.

The WHO and IARC contribute significantly to cancer control worldwide by providing reliable cancer statistics that are a basis for the identification of cancer risks, time trends in cancer incidence and public health resource allocation. The basis of this must be a statistical classification of disease and pathology.

WHO Classification of Tumours

Cancer is typically diagnosed by pathologists on histological sections routinely stained with hematoxylin and eosin (H&E) as well as by immunohistochemistry. More recently, tumours have also been characterised by their genetic profiles, which complement histopathology and are increasingly used to predict prognosis and response to therapy.

To ensure an international standard for histopathological classification, the WHO publishes the book series WHO Classification of Tumours (WHO Blue Books). Since its initiation in 1957, the objectives of the WHO Classification have remained the same, i.e. to establish a classification and grading of human tumours that is accepted and used worldwide. IARC has been publishing the Blue Book series since 2000. Reflecting the recent rapid progress in genetics and our understanding of molecular mechanisms of cancer development, the 3rd edition (2000–2005) contains not only the histopathological classification, but includes genetics, genetic susceptibility, and concise sections on epidemiology, clinical signs and symptoms, imaging, prognosis and predictive factors. Publication of the 4th edition began in 2007, the first volume dealing with tumours of the central nervous system (Figures 1.2.1 and 1.2.2) [1].

Inclusion of new entities is a very important function of the WHO Classification. Entities are characterised by distinctive morphology, location, age distribution and biological behaviour, and not simply by an unusual histopathological pattern, whereas histological variants are defined as being reliably identified histologically and having some relevance for clinical outcome, but are still part of a previously defined entity. Once an entity or new variant is included in the WHO Classification, a morphology code of the International Classification of Diseases for Oncology (ICD-O) is assigned, which is used by cancer registries worldwide and forms the basis for the generation of histopathologically stratified data on cancer incidence. The cancer registry data provide essential data for the IARC book series *Cancer Incidence in Five Continents* (Figure 1.2.3) [2].

Tumour Grade and Stage

In the clinical setting, tumour grade and tumour stage are important additional factors that influence the choice of treatment, and allow a prediction of prognosis. Histological grade combines histological parameters, in particular the degree of dysplasia, that reflect the aggressiveness of a tumour. Grade is rated numerically (e.g. grade 1–4) or descriptively ("high-grade" or "low-grade"). The higher the numeric grade, the less differentiated the tumour cells are; a low-grade cancer is usually well-differentiated. The TNM classification system, developed and maintained by the International Union Against Cancer (UICC) is the most widely used tool for classifying the extent of cancer spread. This classification is based on the extent of the primary tumour (T), the absence or presence of regional lymph node metastasis (N), and the absence or presence of distant metastasis (M) [3].

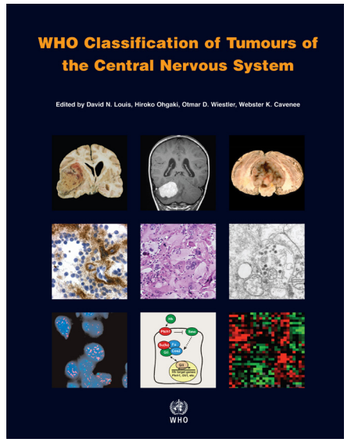
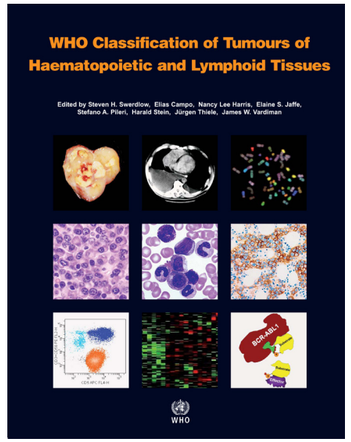


Fig. 1.2.1



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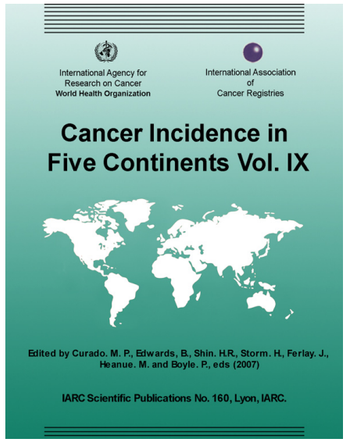


Fig. 1.2.3

REFERENCES

1. Louis DN, Ohgaki H, Wiestler OD, et al. eds (2007). WHO classification of tumours of the central nervous system. Lyon, France: International Agency for Research on Cancer.

2. Curado MP, Edwards B, Shin HR, et al. (2007). Cancer Incidence in Five Continents, Vol. IX. Lyon, France: International Agency for Research on Cancer.

3. Sobin LH, Wittekind C, eds. (2002). TNM classification of malignant tumours. New York: Wiley-Liss.

1.3 Worldwide Cancer Burden

Summary

- In 2008, there were 12.4 million new cancer cases and 7.6 million cancer deaths worldwide
- Lung cancer burden, in terms of incidence and mortality, is among the highest in the world
- More than half of cancer cases and 60% of deaths occur in the less-developed countries
- There are striking variations of cancer patterns by site from region to region
- Future cancer burden will be influenced by trends in the elderly population of both the less-developed and more-developed areas
- The role of prevention in cancer control programmes (tobacco control, vaccination, screening) will increase in the coming decades

Estimating the burden of cancer in terms of incidence (number of new cases occurring) and mortality (number of deaths) is necessary to establish priorities for cancer control. Overall in 2008, based on the most recently available international data [1,2,3], there were an estimated 12.4 million new cases and 7.6 million deaths. The most common cancers in the world in term of incidence were lung (1.52 million cases), breast (1.29 million) and colorectal (1.15 million). Because of its poor prognosis, lung cancer was also the most common cause of death (1.31 million), followed by stomach cancer (780 000 deaths) and liver cancer (699 000 deaths).

Figure 1.3.1 shows the magnitude of the most common cancers in terms of incidence and mortality, for men and women in the more-developed (Europe, North America, Australia/New Zealand and Japan) and the less-developed countries of the world. Overall, 53% of the total number of new cancer cases and 60% of the total number of deaths occur in the less-developed countries. In men, prostate cancer is now the most common form of cancer diagnosed in the more-developed regions recently (643 000 cases, 20.2% of the total of new cases), but only sixth in the less-developed countries (197 000 cases, 5.6%), whereas lung cancer ranks first (538 000 cases, 15.3%). In women breast cancer is by far the most frequent cancer worldwide, with an estimated 715 000 new cases diagnosed in the more developed regions (26.5% of the total) and 577 000 in less developed countries (18.8%).

Mortality reflects the fatality of the different cancers, and in men lung cancer remains the most common cause of death, with an estimated 455 000 deaths in the more developed regions (27% of the total number of deaths), and 475 000 in less developed countries (18.2%). Breast, lung and colorectal cancers represent 42.5% of the total deaths in women in more developed countries, while cancer of the uterine cervix ranks first in less developed countries, with an estimated 275 000 cancer deaths (13.9% of the total), followed by breast cancer (252 000 deaths, 12.7%) and stomach cancer (189 000 deaths, 9.6%). Figure 1.3.2 summarises these results and illustrates the striking variations among regions (as classified by the WHO) in the patterns of cancer occurence. Figure 1.3.3 shows the cancer incidence by site with the 20 registries with the highest and lowest rates in the Cancer Incidence in Five Continents Volume IX [4].

In 2008, the world population was estimated at around 6.7 billion, and it will reach about 8.3 billion by 2030 [5]. A 38% increase in the population of the less-developed countries is expected between 2008 and 2030, while the population growth of the more developed areas will be limited to 4%. Cancer affects mainly older age groups, and within the same period, the proportion of people over age 65 is projected to increase from 5.3% to 9.8% and from 14.6% to 22.6% in less developed and more developed areas respectively. We have already noted that there are slightly more cancer cases and deaths occurring in less-developed than in more developed countries, and since the biggest changes in the world's demography will take place in the developing areas, the future cancer burden will be more evident in these countries, and will be influenced by the elderly populations of both the more developed and less developed areas [6]. Table 1.3.1 shows the predicted number of new cases and deaths from cancer, based on demographic change and time trends. Without a change in current rates, cancer could kill more than 13 million people by 2030; with a 1% annual increase in the rate that number would be more than 17 million.

The role of prevention in cancer control programmes will increase in the coming decades: control of tobacco use, vaccination for human papillomavirus (HPV) and hepatitis B virus (HBV), and screening for breast and colorectal cancer and in less developed countries for cervical cancer remain significant challenges. If widely implemented, these measures could have a great impact in reducing the global burden of cancer.

Region	2008		2030[1]		2030[2]	
	Cases	Deaths	Cases	Deaths	Cases	Deaths
World	12.4	7.6	20.0	12.9	26.4	17.0
Africa (AFRO)	0.7	0.5	1.2	0.9	1.6	1.3
Europe (ERO)	3.4	1.8	4.1	2.6	5.5	3.4
East Mediterranean (EMRO)	0.5	0.3	0.9	0.6	1.2	0.9
Pan-America (PAHO)	2.6	1.3	4.8	2.3	6.4	3.1
South-East Asia (SEARO)	1.6	1.1	2.8	1.9	3.7	2.6
Western Pacific (WPRO)	3.7	2.6	6.1	4.4	8.1	5.9

Table 1.3.1 *Estimated (2008) and projected numbers (millions) of cancer cases and deaths, all cancers, both sexes, by development status or WHO region*
[1] no change in current rates
[2] with 1% annual increase in rates

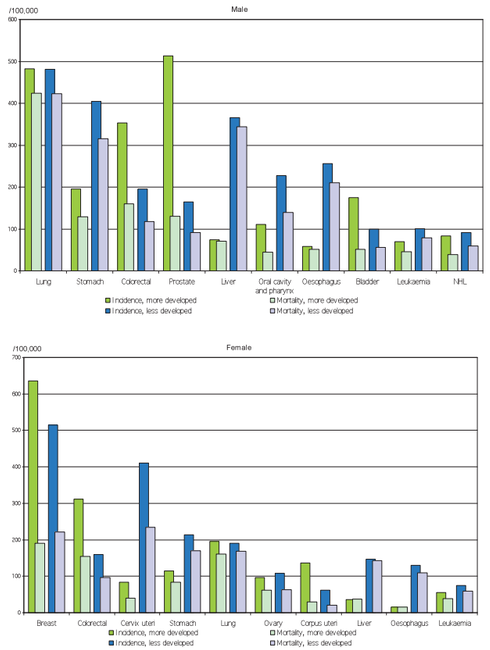


Fig. 1.3.1 *The incidence and mortality of the most common cancers in males and females in more-developed and less-developed countries*

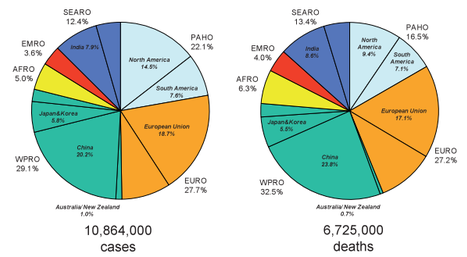


Fig. 1.3.2 *Incidence and mortality in the six WHO world areas.*
AFRO: Africa; EMRO: East Mediterranean; EURO: Europe; PAHO: PanAmerican; SEARO: South-East Asia; WPRO: Western Pacific

REFERENCES

1. Ferlay J, Bray F, Pisani P et al. (2004). GLOBOCAN 2002. Cancer Incidence, Mortality and Prevalence Worldwide. IARC Cancer Base No. 5 Version 2.0. Lyon: International Agency for Research on Cancer.

2. Ferlay J, Autier P, Boniol M, et al. (2007). Cancer Incidence and Mortality in Europe, 2006. Ann Oncol 16:481-488.

3. American Cancer Society (2008). Cancer Facts & Figures 2008. Atlanta: American Cancer Society.

4. Curado MP, Edwards B, Shin HR et al., eds (2007), Cancer Incidence in Five Continents, Vol. IX IARC Scientific Publications No. 160, Lyon, International Agency for Research on Cancer.

5. United Nations (2003). World Population Prospects, the 2002 revision. Population database. New York, NY: United Nations; Available at http://www.un.org/. Accessed December 22, 2004.

6. Parkin DM, Bray FI, Devessa SS (2001). Cancer burden in the year 2000. The global picture. Eur J Cancer 37: S4-S66.

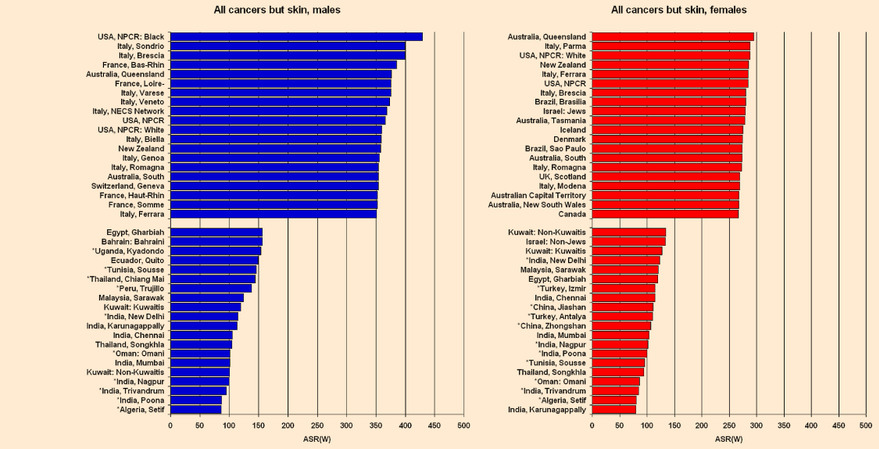
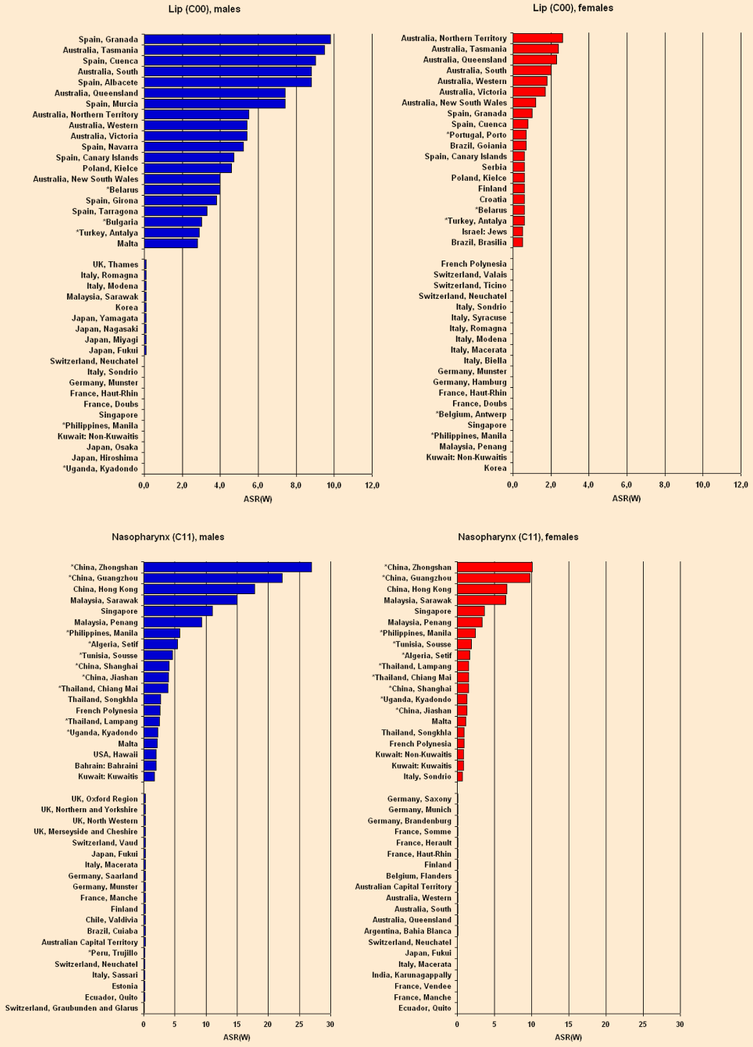


Fig. 1.3.3 *Cancer Incidence by site with the 20 registries with the highest and lowest rates*



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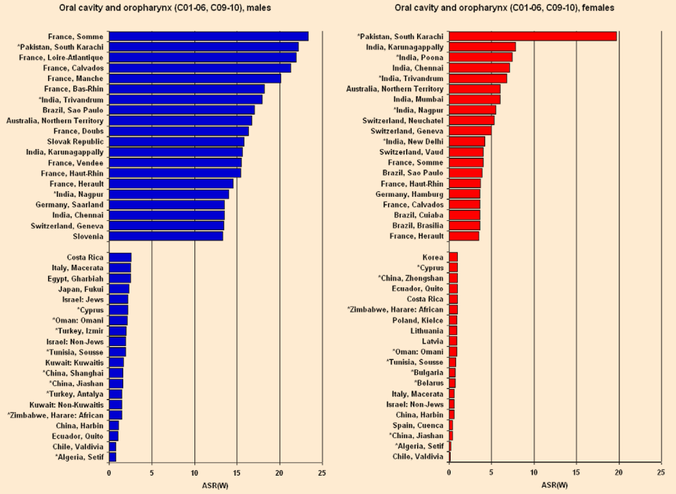

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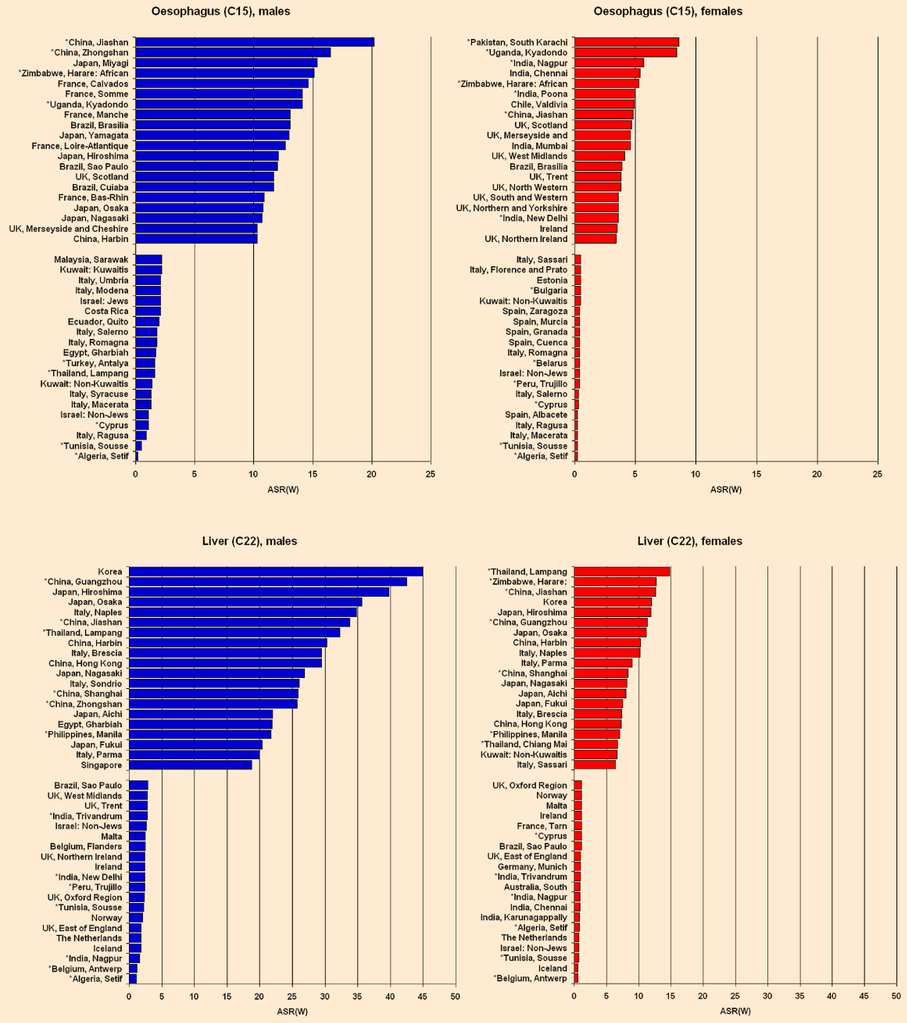

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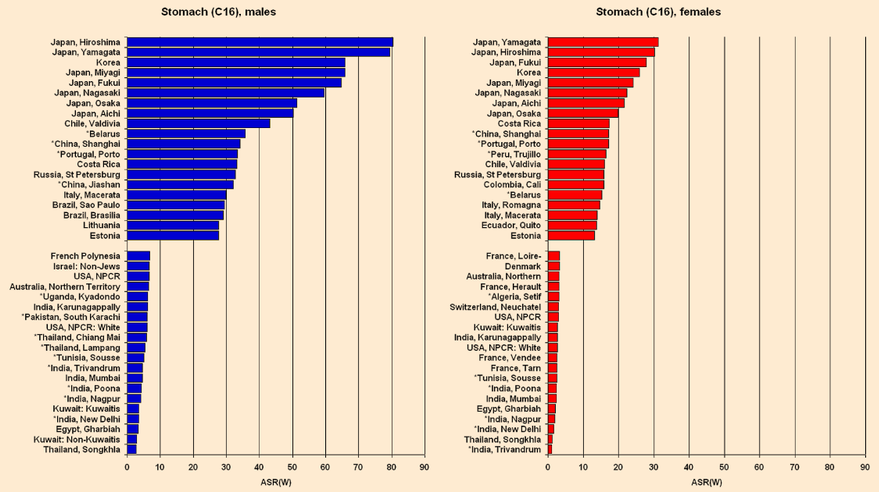

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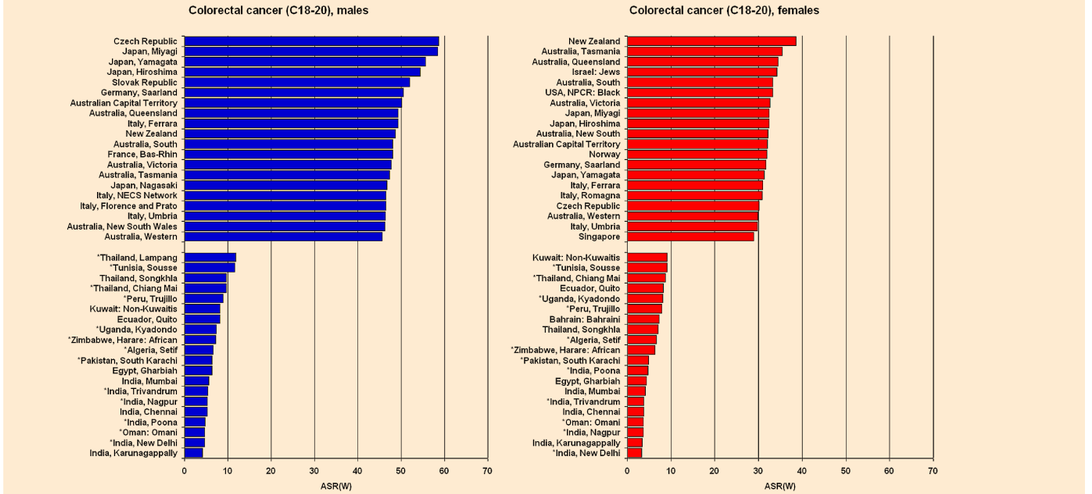

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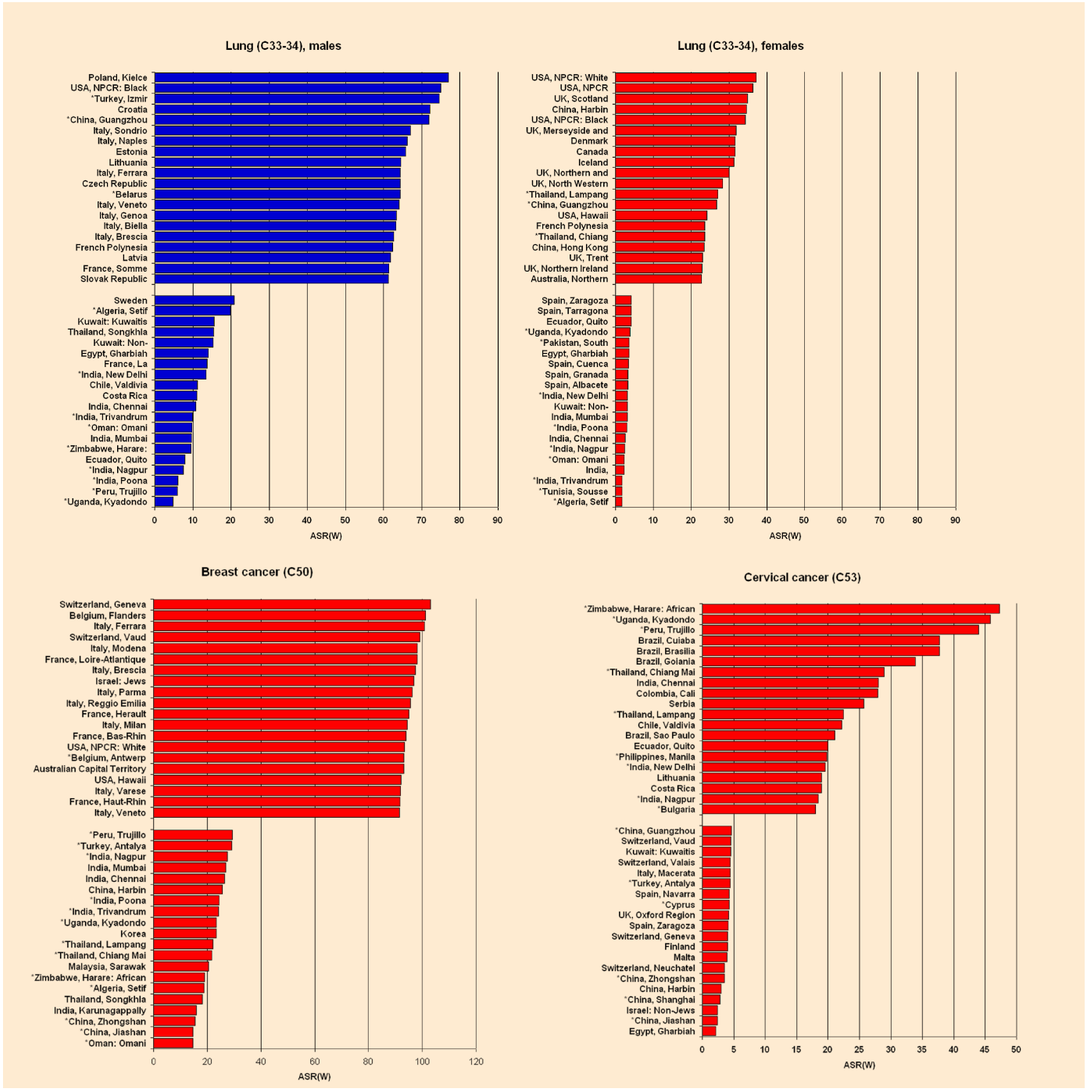

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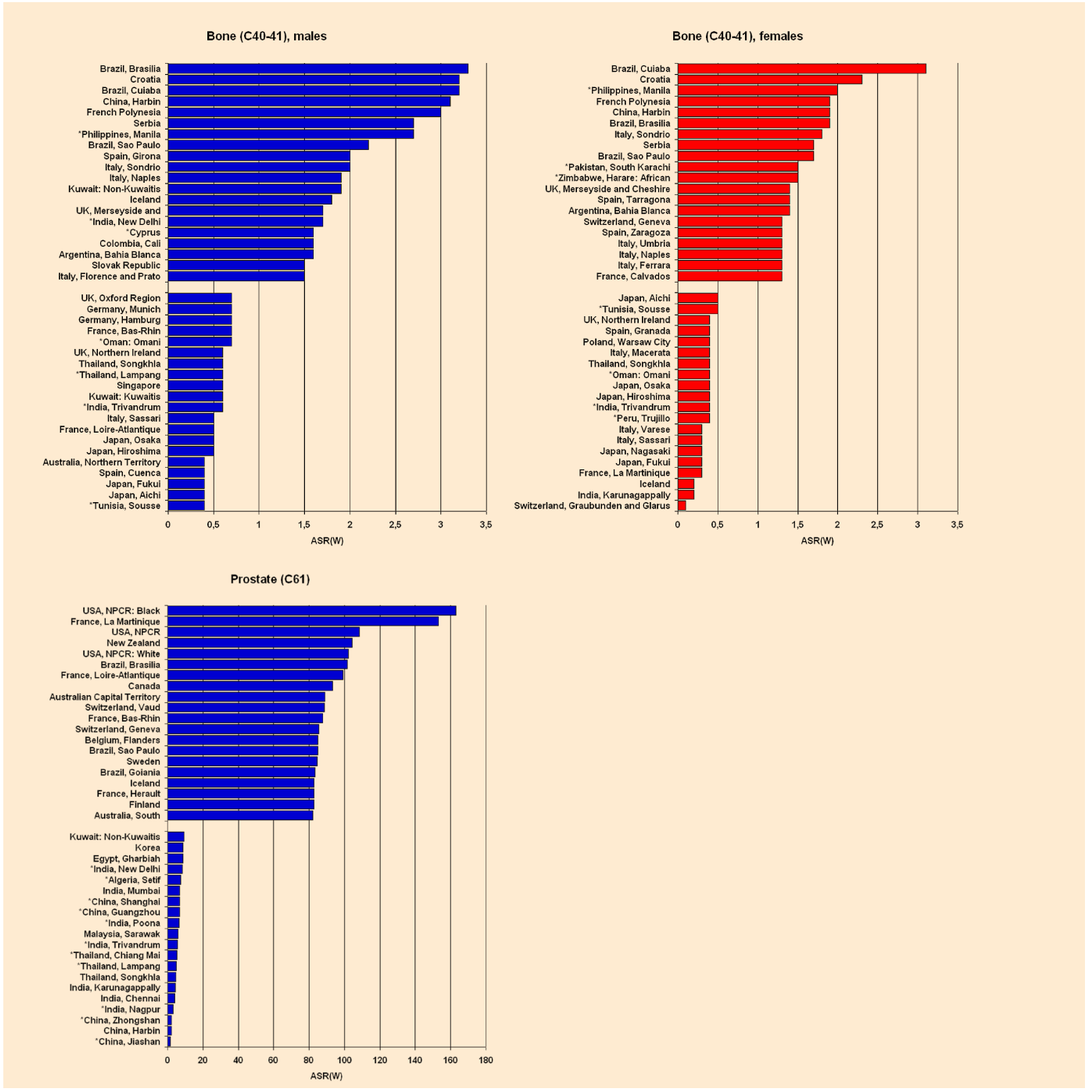

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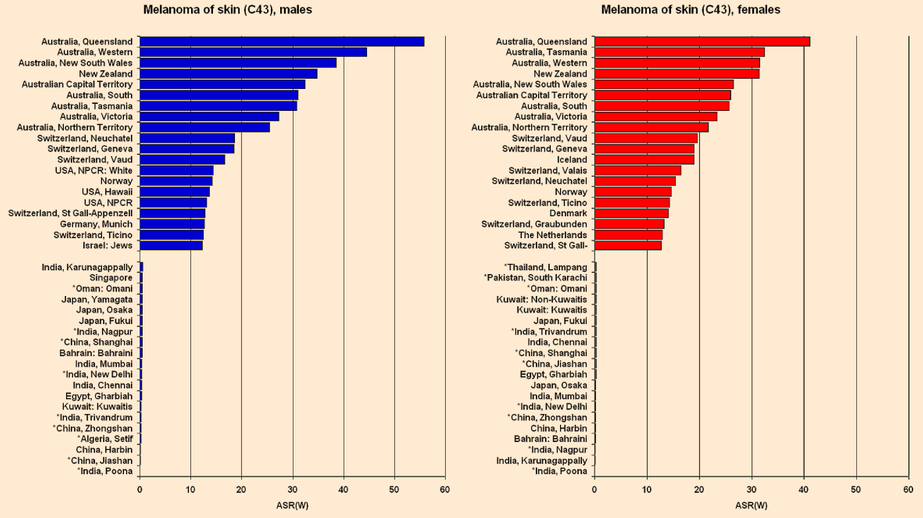

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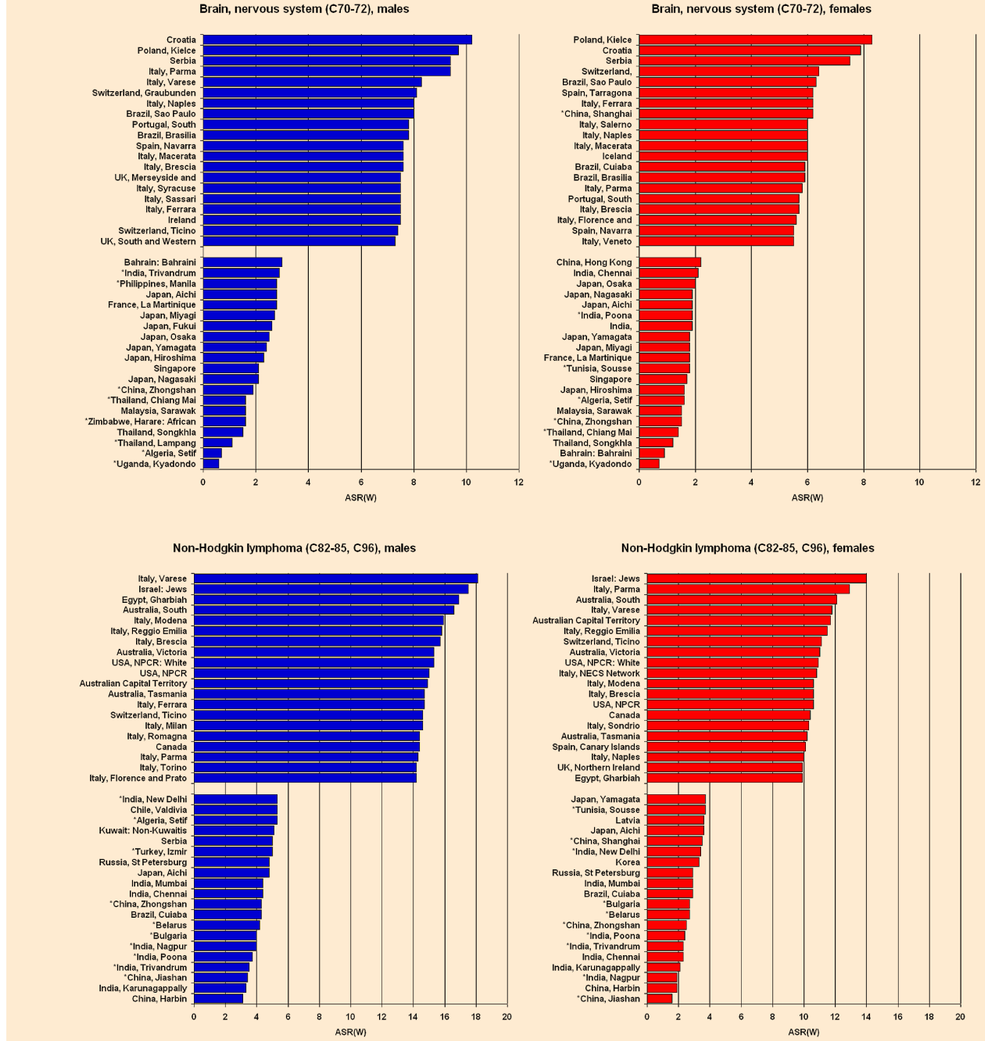

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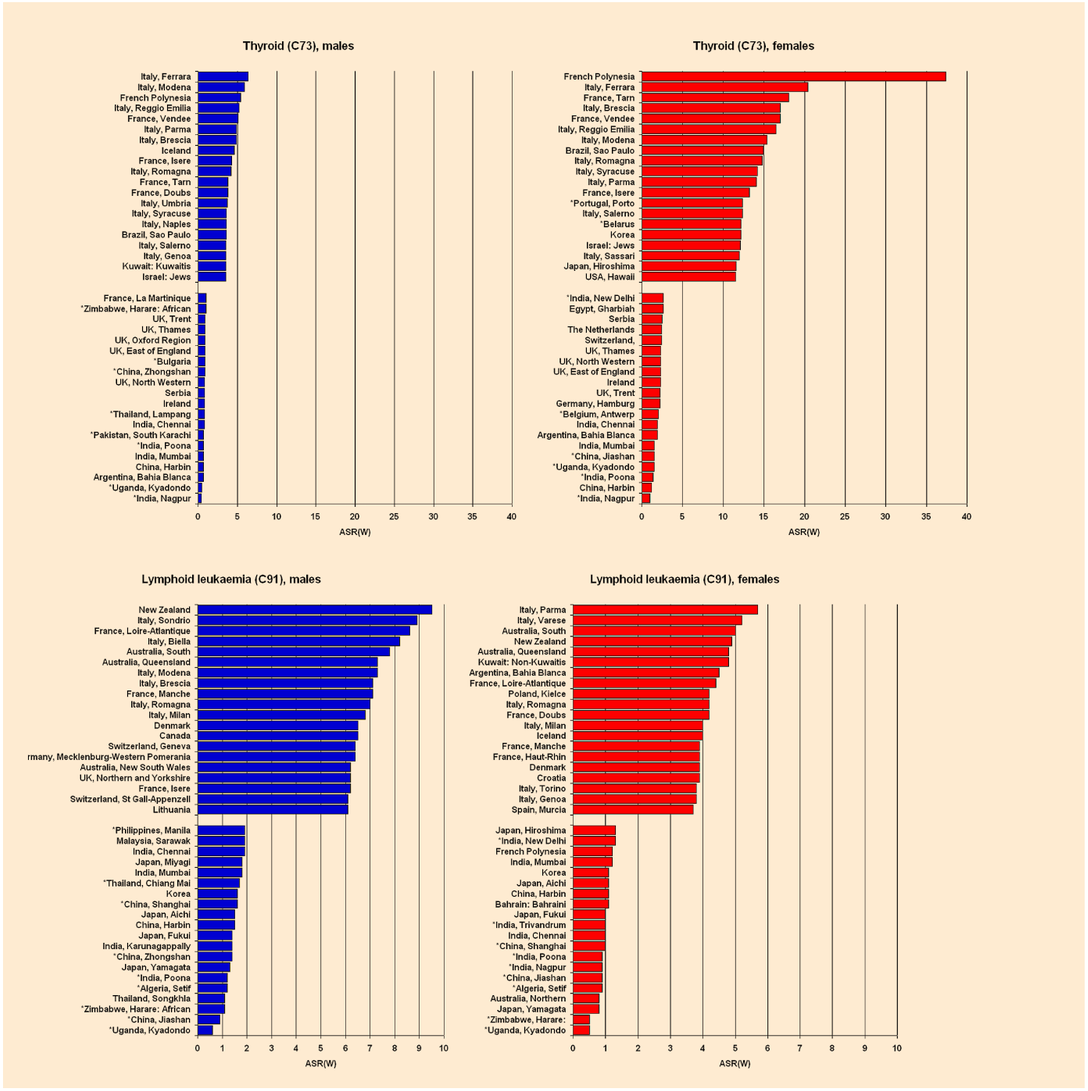

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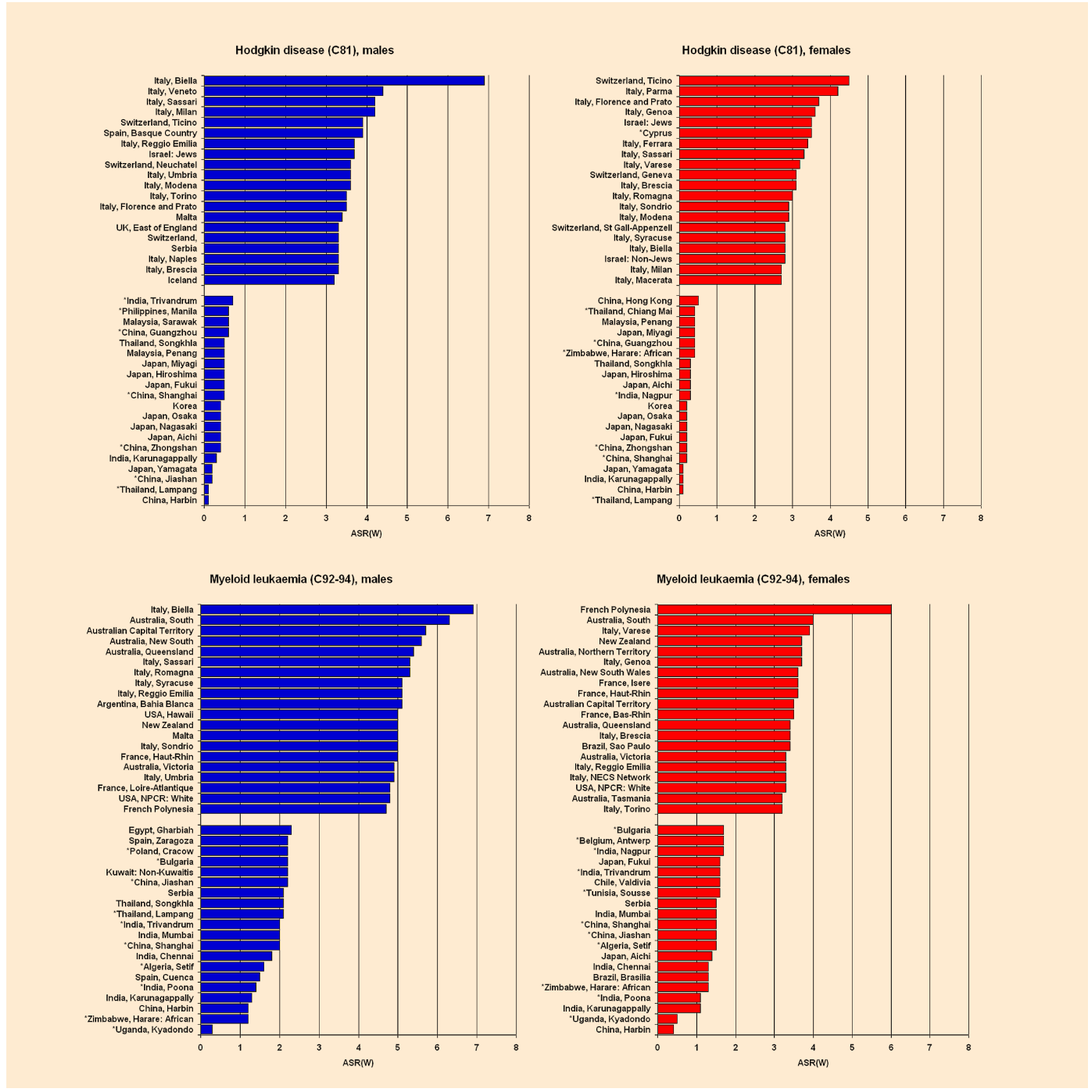

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1.4 Cancer Control in Low-Resource Environments

The burden of cancer in low-resource environments is growing, and threatens to exact a heavy toll in morbidity, mortality and economic cost in these countries in the next 20 years. The expected public health dimensions of the cancer pandemic in low-resource countries demand a widespread effective international response. The good news is that the majority of cancers in low-resource environments are preventable, and the efficacy of treatment can be improved with early detection. Currently there is enough knowledge to implement sound, evidence-based practices in cancer prevention, screening/early detection, treatment and palliation. The information at hand could prevent up to one third of new cancers and increase survival for another one third of cancers detected at an early stage. To achieve this, knowledge must be translated into action.

In the developed countries, great strides have been made over the past half century in translating knowledge into action but the same is not true in low-resource environments where cancer is generally low or absent on the health agenda. This is very unfortunate because the number of new cases of cancer in the world is predicted to increase to more than 27 million by 2030, with deaths increasing to 17 million; much of the burden of cancer incidence, morbidity and mortality will occur in low-resource countries.

However, despite the seemingly bleak outlook for cancer incidence in low-resource environments, there are many reasons for optimism. First, cancer is potentially the most preventable of the chronic illnesses [1]. Existing knowledge is sufficient to prevent at least one third of the 12 million cancer cases that occur annually. In addition, we already have the knowledge and tools needed to aggressively curb the cancer burden due to infections in low-resource environments. With the appropriate low-technology tools and resources for the application of these tools, an additional third of expected new cases can be prevented. For those with early stage cancer, there are effective strategies that can increase survival. For those with advanced and disseminated cancer, understanding of palliative care could also alleviate a great deal of suffering and improve the quality of life of cancer patients and their families.

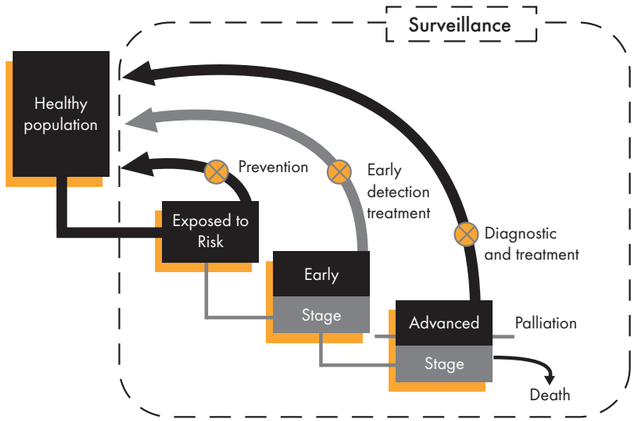


Fig. 1.4.1 *WHO's comprehensive approach to cancer control*

In most low-resource countries prevention remains suboptimal, but there are promising approaches such as the use of visual inspection methods with acetic acid (VIA) and the availability of a vaccine to prevent cervical cancer caused by human papilloma virus [2].

The WHO, in response to the looming pandemic, has intensified its fight against worldwide cancer with many promising avenues for sustainable change. In 2005, the World Health Assembly of the WHO (WHA 58) marked the urgency of global cancer incidence by the adoption of a sweeping resolution on cancer prevention and control [3]. This resolution provides the foundation for what is envisaged as a global strategy to accelerate the translation of knowledge into effective and efficient public health measures for cancer.

In low-resource environments, there is no doubt that this will be an enormous endeavour, requiring comprehensive policies and strategies to mobilise resources in prevention, early detection, diagnosis, treatment, rehabilitation and palliation [4]. These strategies will require substantial economic and human resources (as well as political will) that are non-existent at the moment. Importantly, in low-resource environments the success of cancer control will depend on the formation of equitable and enduring partnerships and the use of interventions that are culturally appropriate, economically feasible and evidence-based. Even in low-resource environments there is a large variation among countries in their ability to implement cancer control programmes; a unified cancer control strategy must consider the major differences in the implementation of cancer control activities.

The role of WHO in a unified cancer control strategy

To appreciate the role of WHO in a unified cancer control strategy, countries must look at the WHO's comprehensive approach to cancer control. This approach comprises 5 focus areas (Figure 1.4.1).

1. Surveillance

Ongoing surveillance is essential to: (1) identify the need for intervention according to the current and future cancer burden; (2) provide the evidentiary basis to formulate research plans and priorities; and (3) monitor the outcomes of preventive interventions, cancer treatment and palliation [5].

2. Primary Prevention

There are 3 step-wise interventional categories in the implementation of cancer control programmes. First is primary prevention, which means the elimination or reduction of exposure to recognised risk factors in susceptible populations. This approach potentially offers the most valuable method to improve public health, and is by far the most cost-effective and enduring intervention for reducing the cancer burden. Examples include curtailing the use of tobacco, controlling overweight and sedentary behaviour, reducing occupational exposures to carcinogenic chemicals or pollutants and diminishing the spread of cancer-associated infections such as hepatitis B virus (HBV) and human papilloma virus (HPV).

3. Secondary Prevention

The next component of WHO strategy is secondary prevention, or early detection, which entails timely diagnosis in symptomatic individuals and screening in at-risk asymptomatic persons.

Education to increase awareness of cancer signs and symptoms is an important part of this strategy. Early detection of cancer increases the chance that treatment is curative, especially for cancers of the cervix, breast, mouth, larynx, colon, rectum, testes and skin. For many of these cancers, individuals can be taught to recognise early warnings, such as a lump or lesion.

4. Diagnosis and Treatment

Diagnosis requires clinical assessment through use of modalities such as endoscopy, cytology, imaging, and histopathology. Appropriate services to combat cancer and return the patient to normal health include surgery, radiotherapy, chemotherapy or a combination of these.

Optimal treatment can improve cancer survival significantly. Unfortunately, diagnosis of cancer in low-resource environments is too frequently made in advanced stages [1].

5. Palliative care

WHO defines palliative care as an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and assessment and treatment of pain and other problems, physical, psychosocial and spiritual.

Palliative care:

- provides relief from pain and other distressing symptoms;
- affirms life and regards dying as a normal process;
- intends neither to hasten or postpone death;
- integrates the psychological and spiritual aspects of patient care;
- offers a support system to help patients live as actively as possible until death;
- offers a support system to help the family cope during the patients illness and in their own bereavement;
- uses a team approach to address the needs of patients and their families, including bereavement counselling if indicated;
- enhances quality of life, and may also positively influence the course of illness; and
- applies early in the course of illness, in conjunction with other therapies that are intended to prolong life, such as chemotherapy or radiation therapy, and includes those investigations needed to better understand and manage distressing clinical complications.

Surgical and radiological palliation and pain management are essential parts of the spectrum of cancer control and should be given high priority in every country. This is especially true in low-resource countries where late stage presentation is the rule, and the majority of cancer patients will remain uncured in the coming decades [5,6].

WHO initiatives toward a unified cancer control strategy

Over the years the WHO, in addition to producing publications on cancer control, has put forth several initiatives that can be considered milestones in the effort to put knowledge into action. These include a major international treaty on tobacco, global strategies on diet and physical activity, planning and implementing cervical cancer prevention and control programmes and several guidelines on national cancer control programmes.

1. Tobacco Treaty – The Framework Convention on Tobacco Control (WHO FCTC)

Tobacco consumption in low-resource environments is increasing. The devastation that will be caused by the increase in tobacco consumption is enormous. If no interventions are put in place, this will place a mammoth burden on healthcare systems in low-resource environments.

Tobacco is the single greatest preventable cause of cancer in the world, causing 80–90% of all lung cancers and 30% of all cancers in the developing countries. Under the current patterns of use, world tobacco-related deaths will continue to rise on a trajectory that will reach 500 million by 2050 [7]. Interventions that decrease the number of new smokers by half would lower that mortality to 340 million. While smoking rates have fallen in developed countries, tobacco multinationals have concerted their efforts toward promotion of new

markets in Asia, Central and Eastern Europe, and Latin America.

2. Global Strategy on diet and physical exercise

Most of the world's cancer burden is attributable to a few preventable risk factors. Diet is one of the modifiable risk factors for cancer that deserves worldwide attention and merits alliances comparable to those of the WHO FCTC. The WHO's Global Strategy on Diet and Physical Activity was adopted in 2004. The guiding principles of the resolution are four-fold: (1) improving the evidence for policy and guiding interventions according to the relationships between diet, activity, and disease; (2) advocating policy change; (3) increasing stakeholder involvement in implementation of a global strategy; and (4) formation of a strategic framework for action. Low-resource countries should adopt national food policies and develop ethical principles for marketing to children because these problems, while once considered problems of high-income nations, are now beginning to affect developing countries. This reflects a significant change in dietary habits and physical activity levels worldwide as a result of industrialisation, urbanisation, economic development and increasing food market globalisation. In addition, many countries still consume an excess of highly salted foods. A healthy diet of fresh fruit and vegetables can reduce risk for many cancers.

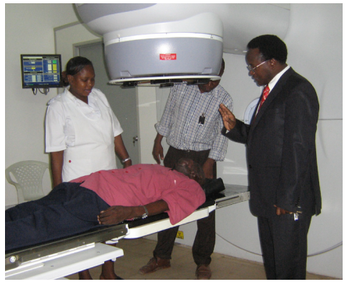


Fig. 1.4.2 *Professor Twalib N'goma in the Radiotherapy Department at the Ocean Road Cancer Institute in Dar es Salaam, Tanzania*

3. Comprehensive Cervical Cancer Control: A Guide for Essential Practice

Cervical cancer is one of the most important health problems for adult women in developing countries [8]. Cervical cancer is the second most common cancer among women worldwide.

There are 409 000 new cases diagnosed annually and 234 000 deaths in the developing world from cervical cancer [9]. The substantial burden of disease, together with the proven impact of effective screening and early treatment programmes, makes this an essential area for action [10].

Several notable resources from WHO have assisted in guiding the development and implementation of cervical cancer control programmes. An expert consultation initiated by WHO in 2001 resulted in the report *Cervical Cancer Screening in Developing Countries* [11]. This report documents guidelines on the importance of a position on cytology screening in middle-income countries with specific recommendations for improving efficacy and effectiveness of programmes in this type of setting. Additionally, it spurred development of a status report on use of visual examination with acetic acid and HPV screening for cervical cancer. The report analyzes level of evidence of their efficacy and effectiveness in different resource settings and highlights research issues that still need to be addressed for adequate policy development [11]. Guidance for the implementation of these policies is found in *Planning and Implementing Cervical Cancer Prevention and Control Programs: A Manual for Managers,* [12] which was developed to help management teams plan, implement, and monitor cervical cancer prevention and control services. This manual contributes to global efforts to improve women's health by promoting appropriate, affordable, and effective service delivery mechanisms for cervical cancer prevention and control. Detailed information on guidelines for clinical practice are available in the WHO publication *Comprehensive Cervical Cancer Control: A Guide for Essential Practice* [13].

Barriers to WHO initiatives in low-resource countries

1. Lack of recognition of cancer as a major public health issue

Cancer is often not a stated priority for health care expenditure in developing countries. Because infectious diseases typically dominate the healthcare agendas of such countries, cancer control efforts generally fall behind other priorities of the national health authorities. Due to low cancer awareness, although the majority of cancers are curable if detected and treated in the early stages, this is not the case in developing countries, because about 80% of all patients with cancer have advanced-stage disease at initial presentation.

Another factor is the lack of population-based data on cancer incidence and mortality. This problem aggravates the degree to which cancer is underappreciated as a significant healthcare challenge. The lack of local data and tendency to use data generated from western settings contributes to the low priority accorded to cancer, because ministries of health would that they do not have compelling evidence-based guidance on how cancer in their countries can best be addressed. Furthermore, because of differences in social and cultural factors, lifestyles, and available technology among other factors ,findings from studies performed in populations from developed countries may not have much relevance or applicability in developing countries. Another point is that although it is true that cancer has a low priority on the formal health care agenda of developing countries, resources nonetheless are spent on cancer when patients require care for advanced-stage disease. Such unplanned use of resources may not only be associated with poorer outcomes, but may also be more costly than planned, systematic use.

The good news is that since cancer is becoming an increasing public health problem as infectious diseases become better controlled and the population ages in developing countries, the WHO passed an important and sweeping cancer prevention and control resolution (WHA 58) that creates a mandate for member countries to address cancer care, including prevention, early detection, diagnosis, treatment and palliation of symptoms of cancer around the globe. This call for countries to address cancer control is a novel opportunity for ministers to act to address cancer in general as a core national health care issue with the expectation that assistance will be forthcoming.

2. Health care personnel and infrastructure shortages

Recruitment, training and retention of health care professionals constitute a very difficult problem in developing countries. Physicians, nurses and allied healthcare personnel are few in number and often most lacking in regions of greatest health care need. Funds are insufficient to fully equip hospitals and provide competitive salaries for appropriately trained health personnel. Developing countries are often unable to provide their professionals with an opportunity for career development and adequate remuneration. They lack the infrastructure required for professionals to carry out their work, leading to frustration and disenchantment with the system. Collectively, these factors make it difficult to attract new professionals and to retain those who have already been trained. Different developing countries will require different solutions for the same cancer problem, depending on their resources, their populations, the prevalence of disease and other factors. Thus, performing a situational analysis in developing countries is necessary before introducing cancer interventions. Situational analyses will allow researchers and health care ministries to identify ways in which the existing health care system can be used to improve cancer care in their countries.

3. Research viewed as a luxury in low-resource countries

There is an unfounded notion that research is a luxury in low-resource countries. This is not true. There are three categories of research (basic, epidemiological, interventional) that can be undertaken in developing countries. Currently most research in low-resource countries is epidemiological; some interventional research is starting while public health research is lacking. Health systems research assesses availability of manpower, training, and core equipment; the distribution and support of facilities; and the availability of funding for consumable supplies should be highly recommended in low-resource countries. It is also relevant to perform needs assessments in the general community and in the medical community, including asking the public and healthcare professionals, respectively, what their needs are and what problems they face. This type of research is efficient and allows the tailoring of programmes to a specific healthcare setting. Regarding the establishment of regional or national research programmes in low-resource countries to facilitate basic research, there is no doubt that the need exists and will grow over time with economic development. Basic research laboratories should be established, whether newly created or as an expansion of activities in existing institutions, because basic and clinical research provides for protocol-driven care in which intervention suitable to the population and resource level can be tested and adopted.

4. Loss of healthcare professionals by migration

In addition to the inherent manpower shortage, there is a problem of healthcare professionals migrating from rural to urban areas, transitioning from public to private health sectors, and emigrating from poorer to richer countries. The loss of trained health care professionals to other countries is often called the "brain drain", as professionals are actively pulled away by wealthy countries offering better opportunities. This loss could also be termed "brain flight" in that professionals are sometimes fleeing from a system that cannot offer them a viable career commensurate with their training and potential for professional growth. Thus, both low- and high-resource countries play a role in this migration phenomenon.

5. Social and cultural barriers to cancer care

In some low-resource countries non-economic barriers impede early detection and effective management of cancer. These include a host of cultural and ethnic beliefs and taboos, which can vary between different regions of the same country, religions and cultures. Failure to recognise these internal obstacles can doom the success of any cancer care programme, even when adequate resources are provided. If patients lack trust in their health care system, believe that cancer cannot be cured, or face discrimination or loss within their community by virtue of having a cancer diagnosis, they will predictably fail to use cancer services, no matter how accessible and affordable they may be. Patients will commonly turn to alternative health care strategies and traditional healers, believing them to have equal or superior ability to address difficult health problems. If cancer patients avoid seeking care until their disease is undeniably extensive, they create a self-fulfilling prophecy by virtue of the fact that the disease is truly incurable at that point. Moreover, advanced cancer requires aggressive treatment that results in side effects further adding to the fears and barriers that keep patients from seeking care. In the worst-case scenario, the public comes to believe that the treatment, rather than the cancer, causes death. These beliefs, which are difficult to overcome once established in the social network, can undermine, if not shut, down any ministry efforts toward early detection programs. Because the social stigmata of cancer can be so powerful, social barriers must be fully understood before any improved strategy is implemented in low-resource countries.

Experience from Tanzania shows that it may not be enough to simply establish a system and expect the public to use it. It may also be necessary to provide the public with the rationale for why they would want to use the system, especially in societies where there are substantial barriers to seeking care for cancer, such as lack of awareness, fatalism, stigma and fear. Societal barriers can be overcome by educating the public

and including a message of empowerment for patients to take charge of their own health.

Several parties can help overcome social barriers to cancer care. A potentially very effective way of promoting public participation is by involving the public itself or trusted community religious leaders to give the public a sense of ownership.

6. Poor resource allocation in cancer services in low-resource countries

Setting priorities for health care in general, and cancer care specifically for, is particularly difficult in limited-resource environments in light of the meagre resources set aside for health services. By creating evidence-based guidelines that stratify health care interventions into specific levels and through programmatic proposals based on cost-neutral implementation strategies, ministries of health can be offered realistic options for planning the delivery of cancer services within their public health system.

7. Lack of collaboration with other sectors and organisations

Improving a healthcare system so that it can deliver better cancer care can be accomplished if multiple sectors and organisations act in collaboration. A good example is that of the IAEA/PACT programme. The Programme of Action for Cancer Therapy (PACT) was created within the International Atomic Energy Agency (IAEA) in 2004 to build on the Agency's experience in radiation medicine and technology, with a mission of enabling developing countries to introduce, expand or improve their cancer care capacity and services in a sustainable manner. PACT does this by integrating radiotherapy into a comprehensive cancer control programme that maximises therapeutic effectiveness and impact. PACT integrates and aligns cancer prevention, screening and early detection, treatment and palliative care activities. Based on the WHO guidelines, PACT also addresses other challenges, such as long-term support for the continuing education and training of cancer care professionals in developing countries.

8. Limited use of information technology and other creative approaches

Overcoming cancer care constraints and obstacles in low-resource countries requires novel thinking and creative approaches. This is important because low-resource countries have limited availability of trained human resources and adequate facilities for prompt cancer diagnosis. The use of commonly available communication technology to transmit images to facilities in developed countries, i.e. diagnosis using telemedicine, would be very helpful in low-resource countries.

Conclusion

Low-resource countries face numerous challenges in designing and implementing programmes to improve cancer care. Although financial constraints are one obvious barrier to improving cancer outcomes, low-resource countries face a variety of other barriers, such as lack of scientific and epidemiological information to guide resource planning, shortage of trained professionals to provide necessary clinical care, competing health care crises, political insecurity or wars, or combinations thereof that divert attention from long-term healthcare issues, and social/cultural factors that obstruct the timely and effective delivery of care.

In particular, efforts aimed at early cancer detection are impeded by public misconceptions about cancer that make patients reluctant or unwilling to seek care when they notice early symptoms.

The World Health Organization has provided the framework for cancer control and improving outcomes for patients with cancer in low-resource countries and has also stressed the importance of alliances and working together with other organizations working in the cancer field. The International Atomic Energy Agency has established a Programme of Action for Cancer Therapy (PACT) and so far has six PACT model demonstration sites project in Tanzania, Sri Lanka, Vietnam, Albania, Nicaragua and Yemen.

REFERENCES

1. Sener SF and Grey N (2005). The global burden of cancer. *J Surg Oncol* 92: 1-3.

2. Franco EL and Harper DM (2005). Vaccination against human papillomavirus infection: a new paradigm in cervical cancer control. *Vaccine* 23: 2388-2394.

3. WHO Secretariat (2005). *Cancer Prevention and Control. Report by the Secretariat to the 58th World Health Assembly.* Available from: http://www.who.int/gb/ebwha/pdf_files/WHA58/A58_16-en.pdf Date Accessed: November 15, 2008.

4. Ullrich A, Waxman A, Luiza da Costa e Silva V, et al. (2004). Cancer prevention in the political arena: the WHO perspective. *Ann Oncol* 15 Suppl 4: s249-s256.

5. WHO (2002). *National cancer control programmes : policies and managerial guidelines.* Geneva: World Health Organization.

6. Sepulveda C, Habiyambere V, Amandua J, et al. (2003). Quality care at the end of life in Africa. *BMJ* 327: 209-213.

7. Jha P, Chaloupka FJ (2000). *Tobacco control in developing countries.* Oxford: Oxford University Press.

8. Sankaranarayanan R, Budukh AM, Rajkumar R (2001). Effective screening programmes for cervical cancer in low- and middle-income developing countries. *Bull World Health Organ* 79: 954-962.

9. Ferlay J, Bray F, Pisani P, et al. (2004). GLOBOCAN 2002: Cancer Incidence, Mortality and Prevalence Worldwide. *IARC CancerBase* No. 5 Version 2.0. Lyon, France: International Agency for Research on Cancer.

10. Bradley J, Barone M, Mahe C, et al. (2005). Delivering cervical cancer prevention services in low-resource settings. *Int J Gynaecol Obstet* 89 Suppl 2: s21-s29.

11. WHO (2002). *Cervical cancer screening in developing countries report of a WHO consultation.* Geneva: World Health Organization.

12. Alliance for Cervical Cancer Prevention (ACCP) (2004). *Planning and implementing cervical cancer prevention and control programs : a manual for managers.* Seattle, WA: ACCP.

13. WHO (2006). *Comprehensive cervical cancer control: A guide to essential practice.* Geneva: World Health Organization.

1.5 Principles of Cancer Therapy: Medical Oncology

Summary

> There are 20–30 cytotoxic drugs commonly used in the treatment of malignant disease

> These drugs are often administered in combination, using multiple mechanisms to induce cancer cell death

> Cytotoxic drugs can be associated with a range of side effects (neutropenia, oral ulceration, diarrhoea, hair loss, and nerve and kidney damage)

> Chemotherapy has significantly improved survival of breast, colorectal, testicular and ovarian cancer, sarcoma and a range of haematological malignancies

> Molecular biological insights have given us a range of new targets based on growth factors and their receptors which have already begun to yield new drugs

One of the most striking innovations in cancer therapy over the past decade has been the widespread realisation that cancer care is better delivered by a consultant team made up of the requisite disciplines, cooperating to construct a joint treatment plan. Improvements in the quality and standard of pathology services, driven by an internationally-agreed reporting format, which describes all the relevant morphological prognostic features coupled to high-fidelity imaging modalities (computed tomography, magnetic resonance imaging and positron emission tomography scanners), provide an ever-refined platform upon which to judge the stage of the cancer and offer the most rational treatment option. In the UK, all new cancer patients have their case presented and discussed in the multidisciplinary forum (MDT), a formal meeting subject to peer review, which minutes and implements all treatment decisions made [1]. The advantages of the MDT include the following:

- Improvements in the consistency and quality of clinical decision-making
- Creation of a forum that promulgates clinical trial recruitment
- A focus for audit, cancer registration and population studies
- A vehicle through which the latest trial results can be incorporated into current care
- A mechanism for delivering service improvement around patient access, waiting times, etc.
- An educational opportunity for students and postgraduate trainees

The therapeutic mainstays of cancer remain surgery, radiotherapy and chemotherapy, the relative contribution of each being mandated by the natural history of the specific tumour.

Principles of chemotherapy

The process of metastasis often puts the cancer beyond the potential for surgical extirpation or local ablation by radiotherapy, defining the need for a truly systemic drug based approach to cancer treatment. The history of antineoplastic drug treatment can be usefully, if rather falsely, divided into two discrete phases: drug-development pathways based on enlightened empiricism and more recently, rational drug design linked to a clear mechanism of action.

The early tumour model systems, predominantly murine cell lines which could be cultivated in vitro and in vivo, which were used to screen large chemical libraries for evidence of anti-cancer activity, had a high proliferation rate, short doubling times and a large proportion of cycling cells. This predisposed the screens to selecting inhibitors of DNA synthesis and these features led to the early taxonomies describing broad classes of cytotoxic drugs [2].

Antimetabolites are chemicals which by virtue of structural similarity to an existing metabolite, vital for the cancer cell's economy, can interfere with its utilisation, deplete its intracellular stores and promote cell death. One of the earliest examples of this class is methotrexate, an inhibitor of the enzyme dihydrofolate reductase (DHFR) which reduces dihydro to tetrahydrofolate a cofactor required for methyl transfer, e.g. in synthesis of the DNA building block thymidine (Figure 1.5.1).

The pyrimidine anti-metabolites include 5-fluorouracil, which is metabolised by cancer cells to 5-flurodeoxyuridine monophosphate, which inhibits the enzyme thymidylate synthase [3], a key component of the DNA synthetic pathway, and cytosine arabinoside and gemcitabine, which deplete intracellular pools of deoxycytidine. Similarly, the purine antimetabolites, thioguanine and mercaptopurine inhibit enzymes involved in synthesis of guanine and tend to be used in haematological malignancies.

DNA adductors. These drugs are activated to more chemically reactive species that can bind to DNA, distorting it by forming monofunctional adducts that interfere with DNA synthesis or bifunctional crosslinks that bind the two strands of the double helix together, preventing access of the various polymerases required to reduplicate DNA. This class encompasses the alkylating agents (cyclophosphamide nitrosoureas), platinum analogues (cisplatin, Carboplatin and Oxaliplatin) and mitomycin C.

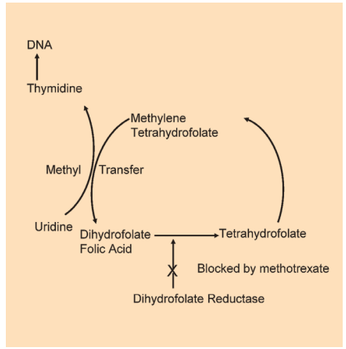


Fig. 1.5.1 *Mechanism of action of methotrexate*

Mitotic inhibitors. After the cell has doubled the amount of its DNA during the S-phase of the cell cycle, it eventually enters mitosis, when the chromosomes are pulled apart so that each daughter cell receives a full chromosomal complement. There is a complex cellular "winch", the mitotic spindle, that requires the cooperation of many proteins, chiefly tubulin, to correctly align and separate these newly synthesised chromosomes. Several anticancer agents interfere with this carefully choreographed process, by either preventing construction of the tubulin scaffold necessary for mitotic separation or indeed from inhibiting its dissolution. These are the taxanes (taxol and taxotere), the vinca alkaloids (vincristine and vinblastine) and the emerging class of epothilones.

Prevention of DNA unwinding. Doxorubicin [4] (an anti-tumour antibiotic) and etoposide (both of which are topoisomerase II inhibitors) and irinotecan and topotecan (topoisomerase I inhibitors) bind to and inhibit the enzymes responsible for the complex unwinding of the double helix required for DNA synthesis, pushing the cancer cells into an apoptotic death.

Hormone receptor antagonists

The growth and proliferation of breast and prostate cancers can be driven by their respective classes of steroid hormones estrogens and androgens by binding to their cognate receptors. One of the great therapeutic successes in cancer treatment was the development of tamoxifen, an estrogen receptor (ER) antagonist that is well tolerated and effective in patients with ER-positive breast cancer. More recent drugs like arimedex reduce production of estrogen at multiple sites within the body and have been shown to be effective breast cancer treatments, whilst androgen receptor blockers like flutamide have a useful role in the management of prostate cancer. Similarly, luteinising hormone releasing hormone (LHRH) agonists can be used to prevent the release of LHRH, by the pituitary gland, reduce production of testosterone and deprive prostate cancer cells of the androgen they need to drive proliferation.

Chemotherapy toxicity

Although these agents have disparate mechanisms of action, they tend to be more selectively cytotoxic to rapidly proliferating cell compartments, causing a number of common toxicities (e.g. bone marrow suppression leading to neutropenia, anaemia and thrombocytopenia; hair follicle cell damage leading to alopecia; induction of apoptosis (programmed cell death) of gastrointestinal crypt cells leading to diarrhoea and oral ulceration [mucositis]). There are specific toxicities associated with individual drug classes; e.g. the anthracyclines can cause cumulative damage to the heart; several drugs (cisplatin, taxanes, vinca alkaloids) damage peripheral nerves leading to sensori-motor neuropathy; cisplatin can cause renal damage; bleomycin, methotrexate and cyclophosphamide can cause pulmonary fibrosis. Thus these are potentially toxic drugs which must be prescribed by clinicians who have been sufficiently well trained in their delivery. The narrow safety margin for conventional cytotoxic drugs is magnified by the fact that most cancer patients are elderly, may suffer from co-morbidity that could sensitise them to the side effects of chemotherapy (e.g. a diabetic patient with poor renal function would need dose reductions in cytotoxic drugs like capecitabine) or may be receiving other drugs that could interact with chemotherapy and worsen toxicity (e.g. aspirin and methotrexate). Rather than Descartes' famous dictum "Cogito ergo sum", the medical oncologist, highly trained to deliver these complex agents, could have his or her professional standing described as "veneno ergo sum".

Combination therapy

The majority of cytotoxic drugs are given in combination, doublets or triplets (two or three different drugs combined) based on the notion that it is likely to induce greater degrees of cell kill by using drugs with a different mechanism of action and hopefully non-overlapping toxicity. The idea would be to use both drugs at their optimal individual doses, but in clinical practice, it is more likely that the drugs need to be dose-reduced in order to be accommodated in a multi-drug regime. Clinical trials have also explored alternating treatment between different chemotherapy regimes in order to try to prevent the outgrowth of resistant disease (with some success in breast cancer), and other studies have explored the duration of treatment, finding for example for patients with advanced colorectal cancer that there is improved quality of life for patients who have "chemotherapy holidays" of 2–3 months compared to continuous chemotherapy until the cancer progresses, without having a negative impact on the length of time patients survive [5].

Markers of effectiveness

It is interesting to consider how the effectiveness of anticancer agents is assessed. Clearly, the long-term aim is to increase overall survival for cancer patients, but in clinical trials it has proven necessary to develop a number of markers of efficacy like response rate—using modern imaging techniques like CT, PET and MRI scans to measure tumour volume prior to and at intervals during treatment to monitor tumour shrinkage or growth—and related markers like the duration of the response or the length of progression-free survival. These are useful to measure in clinical trials of new agents, as progression-free survival often correlates with overall survival, but mean that the clinical investigators do not have to wait as long to pronounce a drug effective or ineffective. Of course, as with all drug therapy, there needs to be a balance between the potential benefits (buying an extra couple of months of life) and detriments of toxicity and reduced quality of life whilst on chemotherapy, especially for those patients at the end of life. There have been steady advances in the treatment of cancer with chemotherapy and there are now tumour classes which can be cured, even when presenting at an advanced stage [6] e.g. testicular and germ cell ovarian cancers, some pediatric cancers, lymphomas and leukaemias.. The majority of common solid cancers (Table.1.5.1) can be palliated with chemotherapy, associated with significant prolongation of survival, but not cure e.g. the average survival

for cancer patients with advanced colorectal cancer without treatment is approximately six months, but rises to 20–24 months for patients who receive sequential chemotherapy [7]. Adjuvant therapy (six months of chemotherapy following surgical resection of the primary cancer) has increased the cure rate for both breast and colorectal cancer by around 10% [8]. Thus a history of steady progress rather than of the "breakthroughs" which we see so heavily promulgated in the media, but which are now reflected, for breast and bowel cancer, in improvements in population-based national cancer survival statistics.

Novel agents

The past decade has seen a remarkable increase in the translation of basic scientific knowledge into novel treatments, particularly in the field of growth factor signalling [9]. This is an evolving and increasingly complex area of science but the broad principles can be illustrated with the simple schematic in Figure 1.5.2.

A peptide growth factor, e.g. Epidermal Growth Factor (EGF), binds to its cell membrane receptor, changing the conformation of the receptor which allows it phosphorylate (tyrosine kinase activity) a host of intracellular proteins, which in turn activate ras, one of the key drivers of proliferation, which activates a cascade of kinases including B-raf, mek and erk, which signal into the nucleus, instructing the cancer cell to proliferate. Each of the proteins mentioned in this hugely simplified signal transduction pathway is a target for therapeutic intervention, blocking the pathway at a control point, reducing the rate of proliferation of the tumour cells and increasing the possibility of apoptotic cell death.

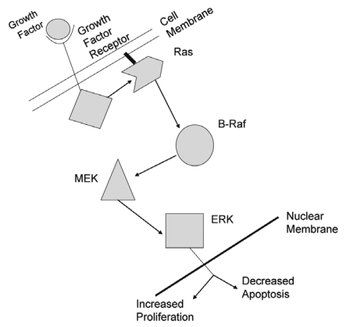


Fig. 1.5.2 *Growth factor – receptor signal transduction cascades offer multiple potential targets for anticancer drug development*

The EGF receptor is a validated target, with a number of licensed agents that disrupt its activity (e.g. the monoclonal antibody cetuximab binds to and inhibits the external surface of the receptor, preventing EGF from engaging its own receptor; lapatinib acts within the cell, inhibiting the tyrosine kinase function of the receptor, preventing onward passage of the signal following EGF binding and receptor activation) already firmly established in the clinic for the treatment of breast and colorectal cancer. The other downstream effectors (B-raf, mek and erk) are all druggable targets that have novel inhibitors in early phase clinical trials.

Inhibition of angiogenesis

Micrometastases can grow to a size of 1–2 mm in diameter, but to advance further, require establishment of their own blood supply. The tumours signal their lack of oxygen by releasing vascular endothelial growth factor (VEGF) which stimulates the growth and invasion of new blood vessels into the tumour nodule, greatly accelerating its proliferative capacity (Figure 1.5.3). The most successful means of blocking angiogenesis has come from the development of the monoclonal antibody bevacizumab, which binds to and inactivates VEGF. This antibody has been assessed in a number of large, well-designed clinical trials and prolongs survival (2–4 months) in patients with advanced colorectal, breast and lung cancer [10]. The antibody is well tolerated (it causes hypertension, proteinuria and rarely, thrombosis) but

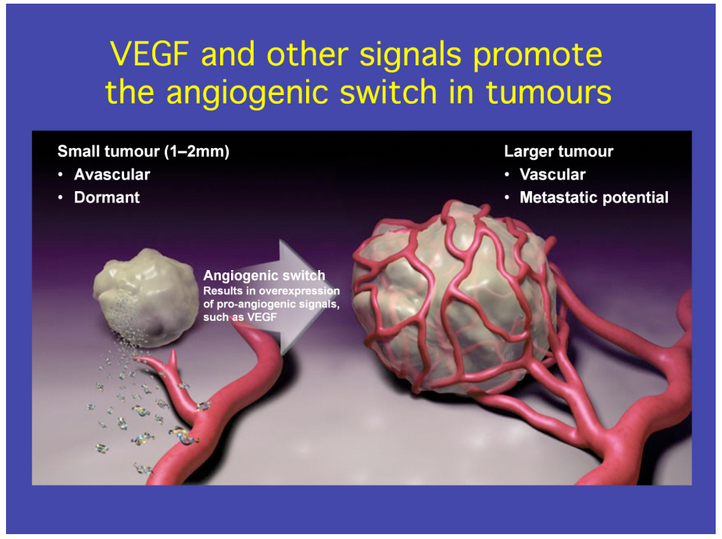


Fig. 1.5.3 *Angiogenesis. Adapted from Bergers G et al (2002) Nature Reviews: Cancer 3(6): 401-410*

expensive, costing up to $100 000 per year for individual patients, putting it currently beyond the cost-effectiveness model employed by the UK's National Institute for Clinical Excellence.

These innovative cancer medicines pose an enormous challenge to the oncology community given the profusion of new targets, novel agents and the potential they have to be combined with conventional chemotherapy and with other transduction inhibitors. It will require a huge number of empirical clinical trials, or a change in trial paradigm in which we try to select patients with tumour-associated biomarkers which would predict a higher-than-average likelihood of response. If we can use tumour biology to identify markers of chemosensitivity, then these can be used to enrich the population of patients we treat, then we should be able to refine and speed up recruitment to clinical trials. We are entering a period when sophisticated molecular tools—e.g. RNA signatures, specific DNA mutations, and patterns of phosphorylation of specific proteins—will give us the technical capacity to deliver on the potential of personalised medicine, saving patients from the needless toxicity of inactive drugs, and allow healthcare systems the possibility of targeting expensive new cancer drugs to the subpopulation of patients who will benefit most [11].

Medical oncology in the developing world

As has been emphasised elsewhere (Chapter 1.1), the increasing incidence of cancer in the developing world presents an extraordinary challenge to the healthcare systems of these emergent nations. Whilst realising that there are many competing priorities (cancer screening early detection and prevention, palliative care etc.), this does not detract from the requirement

Category	Tumour type
1	Childhood cancer; leukaemia; lymphoma; testicular cancer (teratoma and seminoma); germ cell tumours of ovary; choriocarcinoma
2	Early breast and colorectal cancer; sarcoma
3	Advanced breast, colorectal, lung, gastric, ovarian, hepatocellular, pancreatic and renal cancer, myeloma
4	Breast and rectal cancer; sarcoma
5	Melanoma; brain tumours

Table 1.5.1 *Chemotherapy efficacy in different cancer types by category*
Category 1: Tumours for which there is evidence that the use of a single or a combination of drugs used alone or with other therapeutic modalities will result in cure as defined by a normal lifespan in some and prolongation of survival in most patients.
Category 2: Tumours where the average survival is prolonged when chemotherapy is used as an adjuvant to local surgery or radiotherapy in the early stages of disease.
Category 3: Tumours where there is evidence that a single drug or a combination will produce clinically useful responses in more than 20% of patients. Prolongation of survival occurs in most responding patients but may be of short duration.
Category 4: Tumours where local control may be improved by using chemotherapy before, during or after surgery and radiotherapy.
Category 5: Tumours for which there are currently no effective drugs. Objective responses occur in less than 20% of patients and there is no evidence of survival benefit in randomised controlled trials when compared to best supportive care.

Alkylating drugs	Cytotoxic antibiotics	Antimetabolites and related therapy	Vinca alkaloids and etoposide	Other antineoplastic drugs
Cyclophosphamide	Bleomycin	Cytarabine	Vinblastine and vincristine	Asparaginase
Chlorambucil	Doxorubicin	Fluorouracil	Etoposide	Cisplatin
	Dactinomycin	Mercaptopurine		Dacarbazine
	Daunorubicin	Methotrexate		Procarbazine
		Calcium folinate		

Table 1.5.2 *WHO drug list*

to treat patients who present with established cancer. These nations suffer from a relative paucity of treatment facilities, few accredited oncologists and limited access to the appropriate drugs, coupled to the fact that patients tend to present with advanced disease. Given the background of intercurrent illness (infection, AIDS) and malnutrition, dose adaptation from conventional cytotoxic drug regimes is often required. There is a large survival gap comparing outcomes between high-resource and low-resource nations, especially when comparing the potentially chemocurable cancers. Survival rates for childhood cancers can be more than twenty times better in developed healthcare systems. As previously described, research has yielded steady improvements in outcome from novel agents, but at a hugely increased cost. This must be set against a context of the per-capita total healthcare expenditure of approximately $8 per annum in Kenya [12]. It would seem rational to create a priorities list of essential anticancer drugs, striking a balance between efficacy, tolerability and cost. The WHO has published a cancer formulary, identifying drugs that are generic, relatively cheap and moderately effective. As national cancer plans are developed by individual countries, priority should be given to those tumours which may be curable, perhaps focusing on paediatric cancers and on prevalent tumours where chemotherapy can offer useful palliation and prolongation of life, e.g. breast and cervical cancer, by far the two most common cancers of women in Africa, accounting for about 60% of disease burden.

REFERENCES

1. Kerr D, Bevan H, Gowland B, et al. (2002). Redesigning cancer care. *BMJ* 324: 164-166.

2. Graham MA, Riley RJ, Kerr DJ (1991). Drug metabolism in carcinogenesis and cancer chemotherapy. *Pharmacol Ther* 51: 275-289.

3. Goldberg JA, Kerr DJ, Willmott N, et al. (1988). Pharmacokinetics and pharmacodynamics of locoregional 5-fluorouracil (5FU) in advanced colorectal liver metastases. *Br J Cancer* 57: 186-189.

4. Kerr DJ, Wheldon TE, Kerr AM, et al. (1986). The effect of adriamycin and 4'-deoxydoxorubicin on cell survival of human lung tumour cells grown in monolayer and as spheroids. *Br J Cancer* 54: 423-429.

5. Maughan TS, James RD, Kerr DJ, et al. (2003). Comparison of intermittent and continuous palliative chemotherapy for advanced colorectal cancer: a multicentre randomised trial. *Lancet* 361: 457-464.

6. Graham J, Harding M, Mill L, et al. (1988). Results of treatment of non seminomatous germ cell tumours; 122 consecutive cases in the West of Scotland, 1981-1985. *Br J Cancer* 57: 182-185.

7. Midgley R and Kerr D (1999). Colorectal cancer. *Lancet* 353: 391-399.

8. Quasar Collaborative Group, Gray R, Barnwell J, et al. (2007). Adjuvant chemotherapy versus observation in patients with colorectal cancer: a randomised study. *Lancet* 370: 2020-2029.

9. Nair P (2005). Epidermal growth factor receptor family and its role in cancer progression. *Current Sci* 88: 890-899.

10. Kerr DJ (2004). Targeting angiogenesis in cancer: clinical development of bevacizumab. *Nat Clin Pract Oncol* 1: 39-43.

11. Chan R and Kerr DJ (2004). Can we individualize chemotherapy for colorectal cancer? *Ann Oncol* 15: 996-999.

12. Lingwood RJ, Boyle P, Milburn A, et al. (2008). The challenge of cancer control in Africa. *Nat Rev Cancer* 8: 398-403.

CANCER INSTITUTE PROFILE:
Cancer Australia

Cancer Australia is a national agency established by the Australian Government in 2006 to help reduce the impact of cancer on all Australians. Cancer Australia also aims to lessen differences in outcomes for people with cancer whose survival rates or cancer experiences are poorer, including Australia's indigenous people, people living in rural and regional areas and people from culturally and linguistically diverse backgrounds. It works directly, and in partnership with consumers, health professionals, cancer organisations, researchers and governments, to improve cancer outcomes.

Cancer Australia's initial priorities are to:

- enhance support and information for people affected by cancer,
- increase coordination and funding of cancer research and support clinical trials,
- improve cancer services and the availability and use of cancer data,
- support professional development of the cancer care workforce,
- review national cancer control and cancer research activity and identify action to improve cancer outcomes in Australia, and
- establish and manage the National Centre for Gynaecological Cancers.

CEO: Professor David Currow

Tel: +61 2 6200 1700
Fax: + 61 2 6200 1799
email: enquiries@canceraustralia.gov.au
website: www.canceraustralia.gov.au

1.6 Basics of Cancer Surgery

History

The first reported use of surgery to treat cancer was in ancient Egypt circa 1600 BCE, though Hippocrates (400 BCE) later advised against it, and his advice influenced the attitude of the Christian church throughout the Middle Ages. Since then, surgery has become a potent tool in the management of cancer. Epochal events in the surgical management of cancers include the development of surgical methods for primary treatment of cancers of the larynx, oesophagus and stomach by Albert Theodore Billroth, breast by William Stewart Halstead, thyroid by Emil Theodore Kocher and prostate by Charles Huggins [1]. In contrast with those early days, surgery is now used within the context of multidisciplinary management of cancer patients, where it plays a role as one of the components of modern cancer management.

Surgery for cancer screening and prevention

Surgery has a well-defined role in the prevention of cancers. Apart from clinical conditions that are treatable by surgery, which can undergo malignant transformation if left untreated for a long time (for example scar carcinomas associated with burns, chronic skin ulcers and chronic infections like pulmonary tuberculosis), surgery can be used for the treatment of precancerous lesions or for removal of normal organs which are at an elevated risk of developing cancers.

Fig. 1.6.1 *Professor Clément Adebamowo, Professor of Surgery at the University of Ibadan, Nigeria*

Well-identified precancerous lesions where surgical intervention is beneficial include Medullary Thyroid Carcinoma (MTC) when it occurs as part of Multiple Endocrine Neoplasia Syndrome (MENS) Types 2A and 2B. MENS arises as a result of autosomal dominant germline mutations in *RET* proto-oncogene, and all carriers of the mutations develop MTC. To prevent MTC, prophylactic total thyroidectomy is done before 5 years of age in MENS 2A and during the first year of life in MENS 2B [2]. Germline mutations in BRCA1 and BRCA2, present in between 1 in 150 to 1 in 800 North Americans, is associated with about an 80% lifetime risk of breast cancer and between 23–54% lifetime risk of ovarian cancer. Prophylactic mastectomy and surgical oophorectomy are among established methods of reducing this risk [3]. Several high-penetrance genetic risk factors for colorectal cancer have been identified, and their presence is an indication for increased frequency of screening and in some cases prophylactic resection of the colon and rectum [4,5]. Surgical intervention in intraepithelial neoplasms (IEN) involving organs such as the oral cavity, urinary bladder, breast, uterine cervix and oesophagus also lead to substantial reduction in invasive cancer risk [6].

Surgeons have access to other individuals at high risk for malignancies. With the marked improvements in outcome for treatment of cancers, there is an increasing number of cancer survivors who are at elevated risk of developing new cancers in residual tissues, as a result of genetic predispositions or due to mutagenic effects of chemotherapeutic or radiotherapeutic treatments [7]. Other high-risk populations that may be seen with precancerous lesions and opportunities for cancer prevention include people with albinism, who are at risk for a range of skin lesions including cancer [8].

Apart from these active surgical interventions, surgeons also have an important role to play in referring patients for genetic counselling and testing, and counselling patients on smoking, weight control, healthy diet, physical activity and other behavioural risk factors [9]. Given the high prevalence of obesity worldwide [10], the role of high dietary calorie intake in cancer etiology [11] and the increasing role of bariatric surgery in weight management, surgical management of obesity [12] may soon become an important cancer prevention intervention.

Surgery for cancer diagnosis

The role of the surgeon in cancer diagnosis is very important because this is often the first step for many patients, and the choices made by the surgeon may have significant and far-reaching effects on the treatment and outcome for the individual patient. Careful history-taking and clinical examination remains the bedrock upon which a sound diagnosis is based. This includes evaluation of the presence of risk factors, clinical stage of disease, presence of co-morbid factors, family history of cancer, psycho-social status of the patient and the patient's expectation from treatment. Clinical interaction also provides an opportunity for the clinician to educate the patient about the disease and treatment options, ascertain the patient's treatment preferences and let the patient know follow-up requirements. It is often the surgeon's duty to obtain a tissue sample for diagnosis. In order to do this and obtain tissue that will help the pathologist contribute to the management of the patient, the surgeon must select the appropriate biopsy method, decide on need for ancillary imaging facilities, ensure that the tissue is properly fixed and gets to the pathologist on time, and that the results are obtained promptly from the pathologist. The work of communicating with the patient about the illness starts with the clinical evaluation and continues with explanation of the tissue diagnosis and need for additional tests as may be required.

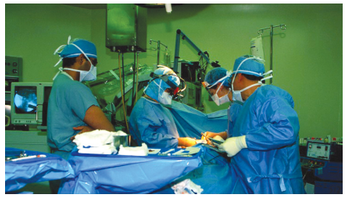


Fig. 1.6.2 *A surgical intervention*

Surgery for cancer staging

Surgery plays an important role in the clinical staging of cancer. Staging is important in order to objectively document the extent of disease, choose appropriate treatment for stage, follow-up the patient's response to treatment, prognosticate, enhance ability to compare treatment outcomes across health systems and facilitate research. The most widely used staging system is the TNM system, but a few other cancers like lymphomas use a different classification system that reflects the natural history of those diseases and guides planning of their treatment [13].

Surgery for cancer treatment

Modern cancer treatment involves a multidisciplinary approach that includes other treatment options and is based on knowledge of the molecular biology of cancer. Optimisation of cancer treatment depends on careful orchestration of the different treatment modalities in order to provide patients with maximal benefit. In deploying surgery for the treatment of cancer, the surgeon must make a careful preoperative evaluation of the patient, weigh the risks and benefits of surgery, identify and correct underlying health problems and take account of co-morbid factors. The choice of surgical intervention depends on the nature and stage of disease. Standard indications exist for choosing limb- or body part-preserving surgeries over more extirpative procedures. The trend is towards use of less mutilating procedures except where indicated. Surgical intervention may also be needed to provide vascular access for chemotherapy [14], for cytoreductive surgery as an adjunct to other treatments [15], for the treatment of complications of cancer treatment and for the treatment of metastases.

Surgery for rehabilitation

After primary treatment for cancer, surgery plays a role in the rehabilitation of patients. Cosmetic surgery to fashion body parts, enhance form, function or cosmesis is important and is an integral part of surgical interventions designed to improve the quality of life. Other surgical interventions for improvement in quality of life include bypass surgery in hollow viscus obstruction even when the primary tumour is inoperable or not surgically curable, surgical creation and care of ostomies, provision of psychological support and other interventions designed to maintain and improve quality of life.

Surgery for palliative care

Surgical palliation is designed to relieve symptoms for patients beyond cure when non-surgical measures are not feasible, not effective or not expedient. It encompasses all treatment options that are designed to enhance quality of life rather than eliminating disease [16]. The provision of comfort and control of cancer-related symptoms can optimise the remaining life of a patient, increase functioning and enable self-care [16]. Active surgical procedures designed for palliative care include nerve plexus blocks, epidural and pudendal blocks for the management of pain, enteral and parenteral nutrition, wound or ulcer care, intubation for bypass of hollow viscus obstruction, tracheostomy for airways obstruction, management of renal failure and management of rectal or urinary incontinence.

Surgery for cancer emergencies

Certain presentations of cancers require emergency intervention in order to save the life of the patient, relieve pain or prevent organ deterioration and failure. Examples of such situations include perforation of hollow viscera which may occur on account of progression of cancer or as a complication of chemotherapeutic treatment, for example, in gastrointestinal lymphoma. Cancers can also perforate and cause acute peritonitis or chronic abscesses. Major haemorrhage may arise from cancers and this can be due to growth of cancers into and erosion of major vascular structures; capillary haemorrhage from ulcerated cancer, and tumour rupture [17]. Other oncological emergencies include progressive spinal cord compression after corticosteroids and radiation therapy; relief of respiratory distress secondary to pleural effusion and surgical extirpation of localised carcinoids.

Factors that influence outcome of treatment

Outcome of surgical treatment depends on healthcare personnel (including surgeons) related factors, patient-related factors and healthcare environment and infrastructure-related factors. Health care personnel-related factors include surgical skills, volume of surgery, specialisation, adequacy of support staff, etc., which all have a direct influence on outcome of surgical intervention. Patient-related factors include the patient's psycho-social state; diligence in following complex treatment plans; compliance with follow-up regime and symptom surveillance for early detection of complications, recurrence and metastasis; nutrition and physical activity; post-operative emotional state; and co-morbidities. Infrastructure-related factors that can also influence the outcome of surgical treatment of cancers include the adequacy and level of sophistication of treatment resources and outreach to the individual patient.

Future of surgery in cancer management

Despite advances in other treatment modalities, surgery will continue to play an important role in the multidisciplinary treatment of cancer. Further clarification of the genetic risk

of cancer and identification of populations at risk may increase the role of surgery in prevention. Future advances include expanded use of laparoscopic and other minimally invasive techniques, robotic surgery, image-guided interventions and telemedicine. In developing countries, surgical services, though grossly inadequate, remain the most widely used treatment for solid tumours [18]. Efforts at improving availability and consideration of alternative models for delivery of surgical treatment for cancer patients are needed [19].

REFERENCES

1. Kufe DW, Pollock RE, Weichselbaum RR, et al., eds. (2003). *Cancer Medicine* 6. Hamilton, Ontario: BC Decker.

2. Ogilvie JB and Kebebew E (2006). Indication and timing of thyroid surgery for patients with hereditary medullary thyroid cancer syndromes. *J Natl Compr Canc Netw* 4: 139-147.

3. Narod SA and Offit K (2005). Prevention and management of hereditary breast cancer. *J Clin Oncol* 23: 1656-1663.

4. Adebamowo CA, Adeyi O, Pyatt R, et al. (2000). Case report on hereditary non-polyposis colon cancer (HNPCC) in Nigeria. *Afr J Med Med Sci* 29: 71-73.

5. de la Chapelle A (2004). Genetic predisposition to colorectal cancer. *Nat Rev Cancer* 4: 769-780.

6. Bertagnolli MM (2005). Surgical prevention of cancer. *J Clin Oncol* 23: 324-332.

7. Aziz NM (2002). Cancer survivorship research: challenge and opportunity. *J Nutr* 132: 3494S-3503S.

8. Hong ES, Zeeb H, Repacholi MH (2006). Albinism in Africa as a public health issue. *BMC Public Health* 6: 212.

9. Emery J, Lucassen A, Murphy M (2001). Common hereditary cancers and implications for primary care. *Lancet* 358: 56-63.

10. Hedley AA, Ogden CL, Johnson CL, et al. (2004). Prevalence of overweight and obesity among US children, adolescents, and adults, 1999-2002. *JAMA* 291: 2847-2850.

11. Popkin BM (2007). Understanding global nutrition dynamics as a step towards controlling cancer incidence. *Nat Rev Cancer* 7: 61-67.

12. Gasteyger C (2007). Bariatric surgery for morbid obesity. *N Engl J Med* 357: 1158-1159.

13. UICC International Union Against Cancer (2008). *TNM classification of malignant tumours*. Available from: http://www.uicc.org/tnm Date Accessed: November 15, 2008.

14. Tilney NL, Kirkman RL, Whittemore AD, et al. (1986). Vascular access for dialysis and cancer chemotherapy. *Adv Surg* 19: 221-270.

15. Al-Shammaa HA, Li Y, Yonemura Y (2008). Current status and future strategies of cytoreductive surgery plus intraperitoneal hyperthermic chemotherapy for peritoneal carcinomatosis. *World J Gastroenterol* 14: 1159-1166.

16. Desai MJ, Kim A, Fall PC, et al. (2007). Optimizing quality of life through palliative care. *J Am Osteopath Assoc* 107: ES9-14.

17. Adebamowo CA (2000). Topical formalin for management of bleeding malignant ulcers. *World J Surg* 24: 518-520.

18. Ozgediz D and Riviello R (2008). The "other" neglected diseases in global public health: surgical conditions in sub-Saharan Africa. *PLoS Med* 5: e121. DOI:10.1371/journal.pmed.0050121

19. Ajayi OO and Adebamowo CA (1999). Surgery in Nigeria. *Arch Surg* 134: 206-211.

CANCER INSTITUTE PROFILE: National Cancer Center of Korea (NCC)

Founded as a government-funded institution in 2001, the National Cancer Center of Korea (NCC) strives to reduce cancer incidence and mortality in Korea through research, patient care, support for the national cancer control programs, and education and training for cancer specialists. NCC is composed of three main components: Research Institute (RI), Affiliated Hospital (Hospital) and National Cancer Control Research Institute (NCCRI).

The RI conducts its own research and supports the Korean cancer community's research activities through its intramural and extramural programs focused on translational research.

The hospital has 6 organ-specific centres. Staffed by medical, surgical, radiation oncologists and oncology nurses, each centre always provides patients with quality cancer care services.

NCCRI plays a think-tank role, assisting the government in formulating, implementing and evaluating the government's cancer control programmes.

Currently, more than 1000 employees, including 250 medical doctors and researchers, are involved in the NCC's activities.

website: www.ncc.re.kr/index.jsp

1.7 Radiotherapy

Summary

> Radiotherapy has been developing as a clinically essential part of the armamentarium against cancer since the last decade of the nineteenth century, when Röntgen invented a means of generating X-rays

> A little over 50% of all patients who develop cancer will require radiotherapy at some time during their illness. This percentage will vary from one tumour type to another

> The basic essentials then of a modern radiotherapy department would be sufficient linear accelerators to deliver the treatment capacity requirements for the region served. However, radiotherapy is one of the least expensive cancer treatments per patient and one of the most effective in terms of cure and overall survival

> Radiotherapy has seen a technology avalanche in the last twenty years that has offered the same level of exciting prospects that the quantum leap from kilovoltage to megavoltage equipment encouraged sixty years ago

> Radiotherapy is part of the multimodality and multidisciplinary management of patients with cancer. It is essential for good cancer care: chemotherapy and surgery cannot effectively replace it. Where it is not available 50% of cancer patients are being denied appropriate care.

Radiotherapy has been developing as a clinically essential part of the armamentarium against cancer since the last decade of the nineteenth century, when Röntgen invented a means of generating X-rays. The scientific basis has been explored and explained through radiobiology and its associated sciences. The clinical foundation of radiotherapy has expanded through high-quality clinical trials. The economic and social justification for radiotherapy is defined by numerous cancer service and public health reviews.

A little over 50% of all patients who develop cancer will require radiotherapy at some time during their illness [1]. This percentage will vary from one tumour type to another. About 70–83% of breast cancer patients would be expected to undergo radiotherapy [2] while only 1% of patients with colonic cancer will require such intervention [2]. Service needs depend, therefore, on the disease profile in a community. It is also affected by the extent of disease at presentation. Where the disease burden is such that the norm at presentation is more locally advanced disease, indications for a given treatment intent and duration will differ from situations where early presentation, for example through screening, is more common.

Radiotherapy may be applied with different intents which vary with the disease type and its extent. Palliative radiotherapy, delivered often in a few (one to five or ten) radiation exposures (or fractions) and using simple, often single-field techniques, will be offered to improve quality of life and reduce symptoms in advanced or metastatic disease. It is particularly effective in the palliation of bone metastases pain, dyspnoea from obstructive lung tumours, dysphagia from obstructive oesophageal cancer, bleeding from advanced pelvic malignancies, headache and symptoms of raised intracranial pressure from brain secondaries, superior vena caval obstruction and early presentation of malignant spinal cord compression.

Radical and generally high-dose radiotherapy may be required either as sole treatment or as an adjunct to surgery (usually post-operative) for early-stage malignancies. Typically such courses of treatment last several weeks with radiotherapy delivered daily and using multi-field complex techniques.

Such adjuvant treatments are routinely used in breast cancer after breast-conserving surgery or in selected patients after mastectomy to reduce local recurrence risk by two thirds, with the prospect of reducing breast cancer mortality by one sixth and improving overall survival. Radical radiotherapy alone may be delivered for early laryngeal cancer with the intent to cure while preserving function and the voice.

Essential components of a radiotherapy service

While radiotherapy has been prescribed since the early days of the X-ray era in medicine, the first major developments leading to improved effectiveness and reduced morbidity were introduced in the 1950s. The introduction then of machines capable of delivering high-energy–megavoltage–X-rays (rather than kilovoltage beams) or gamma-rays, the former from linear accelerators and the latter from equipment such as the cobalt therapy machine utilising high activity radioactive sources, was critical to the further development of modern radiotherapy. High-energy ionising radiation beams spare the surface tissue, thereby removing one limitation to delivering an adequate radiation dose deep in the body at a tumour: the skin surface was no longer the area of maximum dose and the acute radiation skin reaction no longer limited the patient's tolerance.

With mega-voltage machines, radiation beams were delivered from equipment that no longer required leaded cones to direct and confine the beam. Treatment machines could, therefore, be mounted on 360° gantries allowing treatment utilising multiple beams, each of which could be shaped into rectangular fields from a small size (about 4x4cm) up to very large sizes. Rectangular beams could be shaped by the placement of custom-made lead blocks into the beam. More normal tissue could, thereby, be spared.

Such principles remain the basis of modern radiotherapy while the technological improvements in equipment in the last two decades have refined the processes and significantly increased the possibilities. Now beams can be made smaller by utilising special beam modifiers that allow stereotactic beam arrangements in, for example, the brain. Beam shapes can be varied using multi-leaf collimators consisting no longer of two sets of thick steel shutters set at right angles (to give rectangular shapes) but of, for example, 120 single sliding steel "leaves", each 0.5cm thick and capable of independent placement in the beam.

Beam energies can be varied to give different degrees of dose penetration. While X-rays and (less so) gamma-rays are still used, high-energy electrons can also be delivered to treat more superficial tumours of variable depth while sparing deeper tissues.

This sophistication of treatment delivery has required a similar improvement in systems to keep patients immobilised for the few minutes of treatment and to image the treatment areas before treatment is embarked upon, before individual treatment exposures are delivered and after radiation exposure. In the latter half of the twentieth century, much of the planning of an individual patient's treatment depended on clinical skills, palpation, direct visualisation and plain, often orthogonal, X-ray films. From the 1970s, image intensifiers mounted on gantries of the same specification and accuracy as a linear accelerator–radiotherapy simulators–provided more accurate treatment field placement. In recent years, with the introduction of digital imaging processes and cross-sectional imaging, these simulators have developed basic CT capability to further improve treatment field planning.

More recently still, CT scanners have been used to provide cross-sectional images that can be incorporated into the computers used to determine radiation dose distribution from optimal field arrangements. Now it is commonplace to have specific CT scanners designed for radiotherapy field simulation–CT simulators–in radiation oncology departments, dedicated to radiotherapy planning and often replacing simulators.

The basic essentials then of a modern radiotherapy department would be sufficient linear accelerators to deliver the treatment capacity requirements for the region served. Where electrical supply is more erratic and unreliable, an adequate option is a cobalt therapy megavoltage unit. The linear accelerators must be of a specification to deliver safe treatments efficiently. Multi-leaf collimation, while highly desirable for field shaping, is not absolutely essential but more efficient and safer for use than customised blocks.

In addition, an accurate imaging process–a diagnostic level CT scanner or a CT specified simulator or CT-simulator–is required. A computerised planning system provides the other essential component.

These demand an initial high capital outlay. However, radiotherapy is one of the least expensive cancer treatments per patient [3] and one of the most effective in terms of cure and overall survival. It accounts in the UK for less than 10% of the cancer budget, while chemotherapy will cost more than 15% and surgery more than 30%, as does emergency unscheduled care for cancer patients [4].

Apart from equipment needs, any radiotherapy department requires a multi-professional team of oncologists, physicists, dosimetrists, radiation therapy technicians or radiographers, nurses and clerical and administrative staff. A comprehensive cancer care service also needs allied health staff in psychology, speech and language therapy, nutrition, occupational therapy and physiotherapy. Each group requires adequate prequalification training and subsequent and on-going professional development.

Quality and safety

Improvements in radiotherapy technology and equipment have facilitated improvements in care and generally resulted in a reduction in radiation-induced morbidity. Radiotherapy can be offered to more patients with a broader range of performance status for not just a wider range of tumours but also a broader spectrum of stage. While some innovations were developed to improve safety, such as the automatic and digital transfer of radiation beam data from computer planning systems to the record and verification systems that manage and control the treatment units, others have demanded increased quality checks.

An essential component for any radiotherapy centre is, therefore, a robust multi-professional quality and safety protocol and review process as described in the recent multi-professional report *Towards Safer Radiotherapy* [5].

Recent radiotherapy developments

Radiobiologically it has been understood for over fifty years that hypoxic cells are more resistant to X-, gamma- and beta-(electron) rays. Various approaches have been investigated to overcome this problem. To date irradiation in hyperbaric oxygen, concurrent treatment with hypoxic cell sensitisers and the use of high

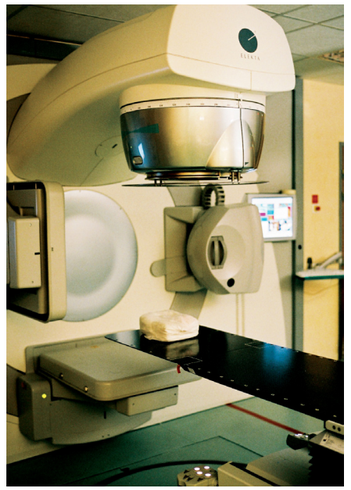


Fig. 1.7.1 *Radiotherapy is part of the multimodal and multidisciplinary management of patients with cancer*

linear energy transfer (LET) radiation such as neutron therapy have either proved ineffective, too toxic or logistically too complex.

The effect of radiation may be increased by the use of concomitant chemotherapy as used increasingly in oesophageal, head and neck, cervix and rectal cancers. Concomitant radiation and targeted therapies–such as cetuximab in head and neck cancer–is also being used in selected patients.

Altered fractionation of radiotherapy has been explored for a number of tumours. In head and neck cancer, twice-daily treatment has been found more effective than daily treatment. For non-small cell lung cancer Continuous Hyperfractionated Accelerated RadioTherapy (CHART) given in three fractions per day over twelve consecutive days (no weekend break) has been shown to be superior to single daily (Mon–Fri) treatments over six weeks. Acute toxicity with these combinations and other alterations from standard therapy may be more severe.

Stereotacticly aimed and delivered small beams have been used for both malignant and benign intracranial lesions for many years. Arterio-venous malformations may be thrombosed with single high-dose treatments, known as stereotactic radio*surgery*. If a fractionated course is given it is stereotactic radio*therapy*.

These stereotactic techniques are being explored in extracranial sites such as head and neck and also lung (for small peripheral lesions) and intra-abdominally for liver metastases. These require significant modification of a linear accelerator and special immobilisation techniques. It is also essential where organ and hence tumour movement is marked with respiratory movements to deliver the radiation beam only in specific parts of the respiratory cycle. Respiratory gating is now available as an add-on to modern linear accelerators. Systems to confirm tumour position radiologically before and during treatment are also essential, and modern linear accelerators can be equipped with on-board kilovoltage or cone-beam CT imaging devices.

In addition there are megavoltage treatment units with built in CT scanner capability (Tomotherapy™) or which have high precision stereotactic treatment capability (Cyberknife™).

In the last decade the value of heavy particle irradiation with protons or heavy ions has been investigated following the development of particle generators delivering manipulateable and often multiple beams. These therapies have a proven role in the management of some orbital tumours and, for example, base of skull sarcomas. Due to very high cost few such installations exist, but as the cost is falling and as the clinical role is becoming further defined, national services are being proposed.

Overview

Radiotherapy has seen a technology avalanche in the last twenty years that has offered the same level of exciting prospects that the quantum leap from kilovoltage to megavoltage equipment encouraged sixty years ago.

Equipment costs have risen, as has demand on staff and the need for improved quality assurance and safety. However, as the range of treatments has correspondingly increased, toxicity has decreased. Thus, what were common side effects, such as 3–4% incidence of acute pneumonitis and unacceptable levels of radionecrotic fractures of rib and even the low but dreadful incidence of radiation-induced brachial plexopathy from breast radiotherapy technique and noted too often until the 1980s, are now rarities.

While the cost of radiotherapy has slowly risen over the last twenty years, those costs remain lower per episode of care than for other modalities, the mean cost for "standard treatment" delivering 21 fractions being estimated at €3239 across three European and one Canadian studies [3].

However, while radiotherapy technology has changed beyond recognition and hence requires a greater initial capital outlay, high quality radiotherapy demands no more than a functioning megavoltage unit–cobalt or linear accelerator–with facilities for adequate beam shaping, a process to image the area of interest to determine field placement, a basic planning computer system and, of course, trained and dedicated medical, physics and technology staff committed to safety. High quality but basic and hence low-cost equipment is now being produced by major equipment manufacturers for lower-resource nations. These developments may allow the introduction of low-cost sustainable radiotherapy services where none or few exist currently.

Radiotherapy is part of the multimodality and multidisciplinary management of patients with cancer. It is essential for good cancer care: chemotherapy and surgery cannot effectively replace it. Where it is not available 50% of cancer patients are being denied appropriate care.

REFERENCES

1. Delaney GP, Jacob S, Featherstone C, et al. (2003). *Radiotherapy in Cancer Care: estimating optimal utilisation from a review of evidence based clinical guidelines*. Sydney, Australia: Collaboration for Cancer Outcomes Research and Evaluation (CCORE).

2. Scottish Executive Health Department. *Cancer in Scotland. Radiotherapy Activity Planning for Scotland 2011 – 2015*. Available from: http://www.scotland.gov.uk/Publications/2006/01/24131719/0 Date Accessed: November 18, 2008.

3. Ploquin NP and Dunscombe PB (2008). The cost of radiation therapy. *Radiother Oncol* 86: 217-223.

4. Richardson M. Lead clinician for cancer, NHS England (2008). Oral Presentation.

5. British Institute of Radiology, Institute of Physics and Engineering in Medicine, National Patient Safety Agency, et al. (2008). *Towards safer radiotherapy*. London: The Royal College of Radiologists.

1.8 Principles of Supportive and Palliative Care

Summary

> Every cancer service requires an active and resourced Supportive and Palliative Care Service (spanning university teaching hospitals to community care) that is engaged in a timely way for patients and their families

> Supportive and Palliative Care Services should be developed in parallel with cancer services (in high-resource and low-resource countries)

> Opioids, together with other key medications for symptom control, need to be more systematically available around the world

> People with advanced cancer should have access to supportive and palliative care services long before their terminal phase. 'Terminal care' represents a small fraction of the illness trajectory for which supportive and palliative cancer care services should be available

'If you treat the disease, it is win or lose. If you treat the person you will always win.'

Patch Adams

Impact of cancer around the world

Cancer continues to be a major cause of human suffering everywhere. The diagnosis of cancer is strongly associated with premature death in the mind of the community. Despite continuing significant advances in understanding modifiable risk factors, prevention programmes, early detection of some cancers or pre-cancerous conditions and rapid advances in the treatment of many previously universally fatal cancers, for many people around the world, cancer will cause premature death. For others, active cancer will be present at the time of their death although not directly causing it, and for a third group of people, cancer will have been diagnosed and treated at some earlier time in life sometimes with long-term consequences.

Premature death from cancer affects all age groups. Very poor five-year survival persists for many cancers, including lung and unknown primary, even in high-resource countries.

In low-resource countries, cancers associated with infectious diseases (cervical cancer, hepatocellular carcinomas, nasopharyngeal carcinoma) continue to cause premature mortality that has significant consequences for families and the communities in which they live. The increasing contribution to premature death because of lifestyle factors such as tobacco use has not peaked in many countries.

In parallel with therapies designed to improve cure or survival rates is a process of optimising a person's function while having therapy and subsequently in line with the resources available [1]. Such care needs to be planned in a national framework that reflects the resources, practices and beliefs of the country [2]. Wherever people are in their disease trajectory, there is a need to address symptom control. This happens in tandem with disease modifying therapy [3].

Like any area of clinical practice, much of the work of palliative and supportive care needs to be achieved by a wide range of health professionals. For a number of people, involvement of health professionals with specific training in supportive and palliative care is needed to meet the complexity of their needs, take forward an agenda of research to refine clinical practice and service provision, and educate existing practitioners (for whom supportive and palliative care was not part of their training) and those still in training.

Definitions

There are three populations covered in these definitions. *Supportive care* sits in parallel with therapy to modify the course of cancer irrespective of the possible outcomes (cure, living with cancer in the long term or premature death because of cancer) and includes symptom control, psychosocial support and rehabilitation.

A sub-set of supportive care is *palliative care,* where it is anticipated that life will be shortened as a result of cancer. Having disease-modifying therapy is still open to patients in this context, but with advanced disease, cancer should be considered a systemic disease, with systemic problems mostly causing death.

A subset of palliative care is *terminal care* – the last few hours or days of life as the person's body closes down. This final common pathway for many people is an almost seamless extension of their inexorable systemic decline: increasing fatigue, weight loss and anorexia. Care in this setting should reflect goals that are entirely built around the comfort of the dying person, as at this time nothing can change the course of the disease.

Given these three definitions, it can be seen that the skill base of supportive care and palliative care draws from the same body of specialist knowledge.

Every health professional should be able to provide care and support to people with cancer, and to have a working understanding of symptom control, psychosocial care and how to optimise a person's function. Such processes need to take account of the physical, social, emotional, existential, sexual and financial issues involved. Most of the issues encountered in people with advanced cancer span several such domains, and the solutions therefore are also likely to span several domains.

There are a group of people with cancer whose needs are more complex, and their care demands the involvement of healthcare professionals whose substantive work is in supportive and palliative care. Specialised supportive and palliative care services are configured within the broader provision of health around the world in different ways.

The definition of *comprehensive cancer care* cannot be derived in isolation of the contribution of supportive and palliative services. To exclude supportive and palliative care from comprehensive cancer care limits the definition to trying to modify the clinical course of the cancer, not of treating the patient. Disease-modifying treatment is only one aspect of any cancer care plan. How can one possibly have a comprehensive cancer centre without supportive and palliative care? By doing this, one is making no provision for the one in two people who will die prematurely because of their cancer.

Specialized supportive and palliative care services are a catalyst for research (improving care and improving models of health service provision) and educational programmes (for existing practitioners who may not have been exposed to supportive and palliative care as they trained, for the next generation of health practitioners for inclusion in their curricula, and for the community more broadly in expectations for good palliative care).

The threshold for the involvement of a broader team of health professionals is based on the needs of the person with cancer, their family and other caregivers and the needs and skills of the health care professionals serving them. Referral is *not* defined by prognosis, but ensuring that needs have been systematically evaluated and, where possible, addressed. Such a model also acknowledges that many people do not need to access specialist services: the current care of family and health professionals is meeting their needs.

Informed decisions include all the reasonable options, including not having any therapy aimed at changing the course of the disease at any given time. For most of the palliative care phase, there will be decisions that need to reflect the patient's input. These decisions will arise because the course of the illness (either as a direct result of the cancer, the treatment of cancer or inter-current co-morbid disease) can potentially be modified. Equally, there comes a time when changes in the course of the illness are no longer possible.

Why do we need specifically identified supportive and palliative care services? Its breadth includes the direct effects of the cancer and the short- and long-term effects of its treatment, co-morbid illnesses that can be affected by the systemic challenge to the body of cancer. Alongside the physical effects are the psychological and existential effects of a diagnosis synonymous with death around the world. Even for those people with a cancer that will cause no further problems in the person's lifespan, there is still the real challenge to one's mortality.

Every health professional can contribute to improving care across the whole trajectory of cancer. Prolonged doctor-patient or nurse-patient relationships may *lessen* the likelihood of discussing highly relevant but sensitive topics as patients try and protect their health practitioners [4]. The practitioner who claims 'to do my own palliative care' may be compromising discussions about key issues to people as death approaches.

Measures of supportive and palliative care

Across the whole course of cancer, in parallel with disease control, there needs to be agreement on the metrics to measure the impact of supportive and palliative care. This allows assimilation of supportive and palliative care into a comprehensive cancer care.

How does the impact of cancer define the needs for palliative and supportive care around the world? The metrics for measuring cancer translate directly to measuring the needs for supportive and palliative care: incidence defines the population who need supportive care; prevalence defines the population at risk of ongoing problems as a result of cancer or its treatment; mortality rates define the population who need to be assessed for referral to specialist palliative care services and life years lost define, in part, bereavement support needed.

Although often framed around quality of life, or more specifically health-related quality of life, the goals of care are to optimise function and comfort in domains that cover the full spectrum of human endeavour (physical, social, sexual (including change in body image as the result of the cancer or its treatment), financial, existential, and emotional aspects of a person's life). This does not limit involvement of supportive and palliative care services to uncontrolled physical symptoms, although that is most often the catalyst to referral [5]. It means that each domain needs comprehensive assessment in order to ensure that, wherever possible, unmet needs are addressed. Such attention to detail requires specific resources, skills and continuing professional development.

Outcomes from supportive and palliative care need to be measured across time, not limited to only the terminal phase of care. This includes outcomes for the person with cancer [6] and their caregivers, while in the role and after they have relinquished the role. Caregiver outcomes can be seen to relate to metrics associated with widely reported health outcomes – survival, impaired health states, health service utilisation, mental health and physical functioning.

The evidence base for supportive and palliative care

What is the evidence base of net benefit (benefit and burden) from the specific involvement of specialist supportive and palliative care services for people with more complex needs from cancer? There are four levels at which such a conversation could occur:

– The person with cancer;
– Family caregivers;
– Health service providers; and
– Whole populations.

No single systematic review has brought together the many aspects of care across time covered by supportive and palliative care services. The net impact of supportive and palliative care services is a cumulative effect from each aspect of assessment and care.

At a community level, end-of-life care is valued consistently as an integral part of quality health care [7]. Such care demands adequate resources, a trained workforce and application of the increasing evidence base in practice [8].

What are the issues that are important for people with advanced cancer? Issues as time becomes finite include excellent symptom control, planning for future care, resolving problematic relationships, having a legacy (the things by which we will be remembered and valued) and being able to finalise one's personal affairs [9]. The ability to be cared for in the environment of choice may include one's home or, at times by choice, an inpatient setting [10].

Benefits from specialised palliative care service involvement for patients with advanced cancer that have been identified include:

- the "quality of dying" and comfort in the last two weeks of life; [11,12]
- pain assessment; [13]
- management of people dying in nursing homes; [14]
- symptomatic management in people admitted to hospital; [15]
- met needs; [16] and
- satisfaction with care [17-19].

For caregivers, data from around the world support that specialised palliative care service involvement has been shown to:

- improve satisfaction with care; [16,18]
- be associated with fewer identified unmet needs for day-to-day caregivers; [20,21]
- improve adjustment when caregivers relinquish the role [20].
- help reduce caregiver anxiety [19]; and
- be associated with improved caregiver survival having relinquished the role [22].

For health funders, the involvement of specialised palliative care services for appropriate patients leads to:

- reduced inpatient bed days [17,23];
- reduce number of hospital admissions [24];
- decreased costs when compared to conventional care [17,25]; and
- potentially influence the likelihood that place of death is that of the patient's choosing [26].

Importantly, there is often a perception that referral to a hospice/palliative care service will compromise care in a way that may shorten prognosis. Although this could not be tested with randomised controlled trials, it is noteworthy that in at least one large population-based study, prognosis was longer for each of the 16 diagnoses that were studied, 12 of which were advanced cancers [27].

Systematic reviews of the impact of specialised palliative care services suggest benefit in a number of domains [28-30]: pain and symptom control [31]; satisfaction with services, reduced hospital bed days and overall costs [32] and potential benefits for caregivers [33]. It has been more difficult to access people who have not accessed services, [34-36] explore the wide regional variation in referral and access patterns [37], or account for the variations in time from referral to death in different health systems but similar burdens of cancer [28,38-40].

Delivering supportive and palliative care services around the world

What are the supportive and palliative care services offered around the world? There is wide variation in the availability and structure of services around the world. These reflect:

- local philosophy relating to health service resource distribution;
- funding models within health systems (user pays versus universal health care);
- service development philosophies (supportive and palliative care services will be developed when all other oncology services are fully established compared with parallel growth of both);
- the availability of trained staff;
- the overall competing demands for health resources (or in many cases for any resources);
- communities' beliefs and values surrounding the infirm and dying; and
- the background disciplines (anaesthetics, psychiatry, surgery, oncology, family medicine, other branches of internal medicine) of people providing specialised supportive and palliative care.

Despite these wide variations, there is evidence of strong growth of supportive and palliative care services around the world, of the qualified staff to provide care and further develop services and of increasing infrastructure in research and education [41-44].

There are data to demonstrate that a start has been made in developing services in every region of the world. The capacity building to provide comprehensive supportive and palliative care around the world includes:

- providing the skills for all health professionals to optimise care for people wherever they are in the cancer trajectory (living with cancer, having survived cancer with no known disease, or facing premature death because of cancer);
- employing core staff who will take responsibility for providing care for people with more complex needs, service planning, seeking funding, research and education; and
- making available key medications, including opioids for pain.

In high-resource countries, there are still cancer centres and services that refuse to invest in either the staff to provide supportive and palliative care, nor the inpatient beds for acute symptom assessment units. Without these resources, cancer services cannot claim to be comprehensive. These centres often have limited links to the community care needed by people as they become more frail.

In resource-challenged countries, issues include workforce, competing demands for scarce health resources and the predictable supply of medications used in symptom control, especially opioids for analgesia [45,46]. The continuing struggle to provide predictable access to therapeutic opioids is an indictment of health and regulatory systems around the world that needs urgent and effective action [47].

In recognition of the need for models of sustainable practice, the World Health Organization has collaborating centres in places such as Jordan and Spain [48,49].

Fig. 1.8.1 *Supportive and palliative care services should be developed in parallel with cancer services*

The Future

As mapped by the World Health Organization, there is much that needs to be done in every country around the globe to improve access to specialist supportive and palliative care at every level of the health system from university teaching hospitals (which should all have acute inpatient symptom assessment units) to community-based care, continued development of the clinical workforce at all levels and in all disciplines, improved infrastructure (most notably equitable access to opioid analgesia) and community care that can support people who want their care to be at home [2]. This is a challenging agenda, but much has been achieved since the publication of the first IARC World Cancer Report in 2003 [50].

REFERENCES

1. Sepulveda C, Marlin A, Yoshida T, et al. (2002). Palliative Care: the World Health Organization's global perspective. *J Pain Symptom Manage* 24: 91-96.

2. WHO. (2007). *Cancer control : knowledge into action : WHO guide for effective programmes. Module 5: Palliative care*. Geneva: World Health Organization.

3. Lynn J, Adamson DM (2003). *Living well at the end of life: Adapting health care to serious chronic illness in old age*. Santa Monica,CA: Rand.

4. Maguire P (1985). Barriers to psychological care of the dying. *Br Med J (Clin Res Ed)* 291: 1711-1713.

5. Johnson CE, Girgis A, Paul CL, et al. (2008). Cancer specialists' palliative care referral practices and perceptions: results of a national survey. *Palliat Med* 22: 51-57.

6. Hearn J and Higginson IJ (1997). Outcome measures in palliative care for advanced cancer patients: a review. *J Public Health Med* 19: 193-199.

7. Bodenheimer T (1997). The Oregon Health Plan--lessons for the nation. First of two parts. *N Engl J Med* 337: 651-655.

8. Cancer care during the last phase of life (1998). *J Clin Oncol* 16: 1986-1996.

9. Steinhauser KE, Christakis NA, Clipp EC, et al. (2000). Factors considered important at the end of life by patients, family, physicians, and other care providers. *JAMA* 284: 2476-2482.

10. Smith TJ and Schnipper LJ (1998). The American Society of Clinical Oncology program to improve end-of-life care. *J Palliat Med* 1: 221-230.

11. Currow DC, Ward AM, Plummer JL, et al. (2008). Comfort in the last 2 weeks of life: relationship to accessing palliative care services. *Support Care Cancer* 16: 1255-1263.

12. Wallston KA, Burger C, Smith RA, et al. (1988). Comparing the quality of death for hospice and non-hospice cancer patients. *Med Care* 26: 177-182.

13. Miller SC, Mor V, Teno J (2003). Hospice enrollment and pain assessment and management in nursing homes. *J Pain Symptom Manage* 26: 791-799.

14. Miller SC, Mor V, Wu N, et al. (2002). Does receipt of hospice care in nursing homes improve the management of pain at the end of life? *J Am Geriatr Soc* 50: 507-515.

15. Jack B, Hillier V, Williams A, et al. (2003). Hospital based palliative care teams improve the symptoms of cancer patients. *Palliat Med* 17: 498-502.

16. Teno JM, Clarridge BR, Casey V, et al. (2004). Family perspectives on end-of-life care at the last place of care. *JAMA* 291: 88-93.

17. Brumley RD, Enguidanos S, Cherin DA (2003). Effectiveness of a home-based palliative care program for end-of-life. *J Palliat Med* 6: 715-724.

18. Hughes SL, Cummings J, Weaver F, et al. (1992). A randomized trial of the cost effectiveness of VA hospital-based home care for the terminally ill. *Health Serv Res* 26: 801-817.

19. Kane RL, Wales J, Bernstein L, et al. (1984). A randomised controlled trial of hospice care. *Lancet* 1: 890-894.

20. Abernethy AP, Currow DC, Fazekas BS, et al. (2008). Specialized palliative care services are associated with improved short- and long-term caregiver outcomes. *Support Care Cancer* 16: 585-597.

21. Aoun SM, Kristjanson LJ, Hudson PL, et al. (2005). The experience of supporting a dying relative: reflections of caregivers. *Prog Palliat Care* 13: 319-325.

22. Christakis NA and Iwashyna TJ (2003). The health impact of health care on families: a matched cohort study of hospice use by decedents and mortality outcomes in surviving, widowed spouses. *Soc Sci Med* 57: 465-475.

23. Costantini M, Higginson IJ, Boni L, et al. (2003). Effect of a palliative home care team on hospital admissions among patients with advanced cancer. *Palliat Med* 17: 315-321.

24. Shelby-James TM, Currow DC, Phillips PA, et al. (2007). Promoting patient centred palliative care through case conferencing. *Aust Fam Physician* 36: 961-964.

25. Taylor DH, Jr., Ostermann J, Van Houtven CH, et al. (2007). What length of hospice use maximizes reduction in medical expenditures near death in the US Medicare program? *Soc Sci Med* 65: 1466-1478.

26. Ahlner-Elmqvist M, Jordhoy MS, Jannert M, et al. (2004). Place of death: hospital-based advanced home care versus conventional care. A prospective study in palliative cancer care. *Palliat Med* 18: 585-593.

27. Connor SR, Pyenson B, Fitch K, et al. (2007). Comparing hospice and nonhospice patient survival among patients who die within a three-year window. *J Pain Symptom Manage* 33: 238-246.

28. Finlay IG, Higginson IJ, Goodwin DM, et al. (2002). Palliative care in hospital, hospice, at home: results from a systematic review. *Ann Oncol* 13 Suppl 4: 257-264.

29. Goodwin DM, Higginson IJ, Edwards AG, et al. (2002). An evaluation of systematic reviews of palliative care services. *J Palliat Care* 18: 77-83.

30. Higginson IJ, Finlay I, Goodwin DM, et al. (2002). Do hospital-based palliative teams improve care for patients or families at the end of life? *J Pain Symptom Manage* 23: 96-106.

31. Higginson IJ, Finlay IG, Goodwin DM, et al. (2003). Is there evidence that palliative care teams alter end-of-life experiences of patients and their caregivers? *J Pain Symptom Manage* 25: 150-168.

32. Hearn J and Higginson IJ (1998). Do specialist palliative care teams improve outcomes for cancer patients? A systematic literature review. *Palliat Med* 12: 317-332.

33. Harding R and Higginson IJ (2003). What is the best way to help caregivers in cancer and palliative care? A systematic literature review of interventions and their effectiveness. *Palliat Med* 17: 63-74.

34. Christakis NA, Iwashyna TJ, Zhang JX (2002). Care after the onset of serious illness: a novel claims-based dataset exploiting substantial cross-set linkages to study end-of-life care. *J Palliat Med* 5: 515-529.

35. Currow DC, Abernethy AP, Fazekas BS (2004). Specialist palliative care needs of whole populations: a feasibility study using a novel approach. *Palliat Med* 18: 239-247.

36. McNamara B, Rosenwax LK, Holman CD (2006). A method for defining and estimating the palliative care population. *J Pain Symptom Manage* 32: 5-12.

37. Connor SR, Elwert F, Spence C, et al. (2007). Geographic variation in hospice use in the United States in 2002. *J Pain Symptom Manage* 34: 277-285.

38. Iwashyna TJ, Zhang JX, Christakis NA (2002). Disease-specific patterns of hospice and related healthcare use in an incidence cohort of seriously ill elderly patients. *J Palliat Med* 5: 531-538.

39. Lamont EB and Christakis NA (2002). Physician factors in the timing of cancer patient referral to hospice palliative care. *Cancer* 94: 2733-2737.

40. Palliative Care Australia (1998). State of the nation 1998 : report of national census of palliative care services. Canberra, Australia: Palliative Care Australia.

41. Centeno C, Clark D, Lynch T, et al. (2007). Facts and indicators on palliative care development in 52 countries of the WHO European region: results of an EAPC Task Force. *Palliat Med* 21: 463-471.

42. Clark D, Wright M, Hunt J, et al. (2007). Hospice and palliative care development in Africa: a multi-method review of services and experiences. *J Pain Symptom Manage* 33: 698-710.

43. Goh CR (2007). The Asia Pacific hospice Palliative Care Network: supporting individuals and developing organizations. *J Pain Symptom Manage* 33: 563-567.

44. Harding R and Higginson IJ (2005). Palliative care in sub-Saharan Africa. *Lancet* 365: 1971-1977.

45. Joranson DE, Rajagopal MR, Gilson AM (2002). Improving access to opioid analgesics for palliative care in India. *J Pain Symptom Manage* 24: 152-159.

46. Rajagopal MR and Joranson DE (2007). India: opioid availability. An update. *J Pain Symptom Manage* 33: 615-622.

47. Brennan F, Carr DB, Cousins M (2007). Pain management: a fundamental human right. *Anesth Analg* 105: 205-221.

48. Gomez-Batiste X, Porta-Sales J, Pascual A, et al. (2007). Catalonia WHO palliative care demonstration project at 15 Years (2005). *J Pain Symptom Manage* 33: 584-590.

49. Stjernsward J, Ferris FD, Khleif SN, et al. (2007). Jordan palliative care initiative: a WHO Demonstration Project. *J Pain Symptom Manage* 33: 628-633.

50. Stewart BW, Kleihues P (2003). *World Cancer Report*. Lyon, France: International Agency for Research on Cancer.

WEBSITES

World Health Organization 'New guide on palliative care services for people living with advanced cancer.'
www.who.int/cancer/palliative/en/

World Health Organization (WHO) Cancer Pain Program
www.whocancerpain.wisc.edu

International Association for Hospice and Palliative Care
www.hospicecare.com

Asia Pacific Hospice Palliative Care Network
www.aphn.org

Latin American Association for Palliative Care
www.cuidadopaliativos.org

European Association for Palliative Care
www.eapcnet.org

African Palliative Care Association
www.apca.co.ug

Institute of Medicine. 'Approaching Death. Improving care at the end of life.'
www.nap.edu/readingroom/books/approaching/

Caresearch – evidence-based resources for clinicians
www.caresearch.com.au

Brown University Toolkit of Instruments to Measure End-of-life care (TIME)
www.chcr.brown.edu/pcoc/toolkit.htm

1.9 Psycho-Oncology

Summary

> Psycho-oncology addresses the psycho-pathological and psychosocial impact of cancer on patients and their relatives

> This discipline is integrated into oncology supportive care and fosters a global approach to the care of cancer patients

> Across countries, up to 50% of cancer patients have been reported with psychological distress, with rates depending on medical, individual, interpersonal or social factors

> Lack of attention to cancer patients' psychosocial needs or deficiencies in physician-cancer patient communication may exacerbate cancer patients' psychological distress

> Psycho-oncology offers evidence-based psycho-social interventions targeted at patients, families or their social milieu, or focusing on caregivers and healthcare professionals to address psychosocial concerns, foster adaptation to the disease and treatment course, and therefore improve healthcare outcomes

Psycho-oncology is a subspecialty of oncology that has developed rapidly over the past 30 years with the recognition of the psychosocial impact of cancer and its treatment and the need to foster global, holistic care of the person confronted with this disease. Global care refers to the consideration of the multidimensional aspects of health, i.e. the physical health, mental health, social well-being and role functioning. Human aspects of care have been underscored in the face of increasing emphasis on bio-technological aspects of medicine, especially in Western countries.

The global care approach is particularly relevant in the field of cancer. Cancer and its associated conditions may significantly damage patients' quality of life. Complementary to therapy for cancer, the care provided in oncology must include the management of disease symptoms, treatment side effects and sequelae, as well as psychosocial distress and needs that arise in that context.

A dimension of quality of life is psychological well-being, which may be considerably affected by the diagnosis of cancer and the therapeutic process. Patients as well as their family members are confronted with a number of distressing emotions and experiences, including fear of death and uncertainty about the nature, evolution and prognosis of the disease. Individuals affected by cancer have to face a reduced ability to control their life, increased dependency on others, and disequilibrium in familial, professional and social life. Untreated psychological conditions may further damage quality of life as well as increase medical costs by longer hospital stays or higher rates of utilisation of primary care medical services [1,2].

Psycho-oncology addresses the psychosocial needs of patients and their family members across the continuum of care, from prevention and early detection through treatment and survivorship to palliative and end-of-life care [3]. Psychosocial interventions in oncology include the facilitation of patients' and families' coping, relief of psychological distress and also address the wellbeing of oncology professionals. The psycho-oncology discipline also strives to contribute to World Health Organization efforts in cancer prevention and engaging community-based interventions to enhance health promotion (e.g. smoking cessation, sun protection, physical activity and healthy diet endorsement, early detection of cancer).

The psycho-oncology field promotes a multidisciplinary co-ordinated approach in the psychosocial care of cancer patients. As a component of supportive care, psycho-oncology concerns a number of health professions such as psychiatry, psychology, social work, nursing, integrative medicine, allied health practitioners or spiritual/religious counsellors, who work in close collaboration with other supportive care professionals. Activities of psycho-oncology professionals are integrated into supportive care services that provide treatment to prevent, control or relieve complications and side effects of cancer treatment (e.g. pain, anaemia, fatigue, infections, nausea and emesis) in order to improve the patient's comfort and quality of life.

Although psycho-oncology has become an important part of cancer care in many countries, at present it has only been fully integrated in a few countries [4]. This is highlighted by the numerous unmet care needs in cancer patients, not only while under treatment across the entire spectrum of psychological needs, health system inadequacies, need for information, physical and daily living, patient care and support, and sexuality [5] but also in the survivorship phase, with regard to emotional, physical, treatment-related and home care, and social (insurance, employment) domains of life [6] The use of mental health services is significantly higher in cancer survivors compared to the general population, although a significantly higher proportion of cancer survivors compared to those without such history reported needing mental health services but not having access to them because of cost [7].

On the other hand, various reports across countries have demonstrated patients' dissatisfaction with care in oncology, especially with regard to aspects of their interaction with providers (e.g. information provision, attention to psychosocial needs) [8], underscoring the need to improve the psychosocial care of cancer patients, provided not only by experts in psycho-oncology but also by first-line healthcare professionals (physicians, nurses, etc.).

To this end, there are a large number of evidence-based interventions available for cancer patients and their families [9] as well as for healthcare providers [10,11] that may improve outcomes in cancer care.

Depending on the culture, economics and healthcare systems, psychosocial issues in oncology may vary widely across countries and thus call for different priorities of interventions. On one hand, low-resource countries should rather focus attention on cancer prevention and education to improve early detection of cancer, especially cervical cancer; and on palliative care, considering the limited opportunity for cancer treatment in these countries [3]. On the other hand, in high-resource countries, cancer care is confronted with complex decisions (e.g. treatment or surveillance in prostate cancer, prophylactic mastectomy or intensive surveillance in women at high risk for breast cancer, types of adjuvant hormone therapy in early stage breast cancer) while therapeutic alternatives present equivalent survival efficacy but different effects on quality of life. Physician-patient shared decision making has to have high priority, requiring superior physician communication skills to prevent exacerbation of patients' psychological distress.

This chapter presents the main psychosocial concerns patients and families face when confronted with cancer, and addresses health care providers' own difficulties in facing and dealing with these psychosocial cancer consequences. It also provides information about interventions that have proved useful and efficient to manage these problems.

Psychosocial issues in patients and relatives

Quality of life. An increase in attention to cancer patients' quality of life has been witnessed in the past few decades. The ultimate goal of medicine is not solely health or the prolongation of life but also the preservation or improvement of quality of life. Instruments have been developed and validated to measure this key concept in oncology with objectives such as describing and monitoring patients' symptoms, difficulties or needs, or assessing medical treatment or psychosocial interventions. The term "quality of life" is commonly used in the cancer literature to mean health status, physical functioning, severity of symptoms, psychosocial adjustment, well-being or satisfaction with life. Broad quality of life domains have been described, comprising the physical, psychological, economic, spiritual and social domains.

Studies have shown how cancer and its treatment may entail problems along these different quality of life dimensions. At the psychological level, the cancer diagnosis in itself even if associated with a good prognosis and absence of aggressive therapy (e.g. a small cutaneous melanoma, or an intra-epithelial lesion of the uterine cervix), may be perceived as synonymous with death, pain and suffering, and cause significant psychological distress. Mood disturbance (depression, anxiety) or cognitive abnormalities (poor concentration, memory impairment) may be observed. At the physical functioning level, the principal means of treating cancer—surgery, chemotherapy and radiation—are powerful but often associated with significant sequelae. All these interventions, including hormonal therapy, have physical side-effects, which may be short-term or time-limited, or chronic and persistent, or develop after treatment has ended [12]. Decreased performance status and physical functioning may lead to problems in carrying out daily activities; treatments may involve physical mutilations (e.g. disfigurement, creation of a stoma, hair loss) and symptoms (e.g. pain, nausea and vomiting, fatigue, sleep disturbance). At the social level, concerns with regard to relationships with a partner, family members or with the social network may be raised. Cancer patients may experience feelings of loneliness, abandonment or lack of support; financial or work problems may also emerge; in the survivorship phase, for example, patients may encounter problems in returning to work, feeling marginalised or even stigmatised as a result of having been affected by cancer.

Psychological distress and disorders. Psycho-oncology mainly addresses the psychopathological or psychosocial consequences that arise specifically as a result of cancer and its treatment. Usual diagnostic criteria, like those listed in the Diagnostic and Statistical Manual of Mental Disorders [13], do not necessarily adequately reflect the psychological disorders resulting from a somatic condition such as cancer. Psychological suffering may be perceived as a "normal" reaction to the traumatic event that represents a cancer diagnosis. To underline a continuous psychological phenomenon from "normal" feelings to psychological disturbance

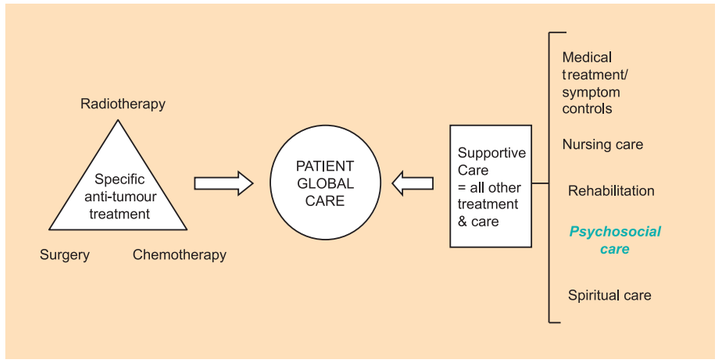


Fig. 1.9.1 *Specific anti-tumour treatment and supportive care including psychosocial care for the global care of the cancer patient*

requiring specialized intervention and to avoid psychopathological stigmatisation, Holland and colleagues [14] has proposed the word "distress" to account for the psychological experience of oncology patients. They defined this term as a *"multifactorial unpleasant emotional experience of a psychological (cognitive, behavioural, emotional), social, and/or spiritual nature that may interfere with the ability to cope effectively with cancer, its physical symptoms and its treatment. Distress extends along a continuum, ranging from common normal feelings of vulnerability, sadness and fears, to problems that can become disabling, such as depression, anxiety, panic, social isolation, and existential and spiritual crisis"*.

Faced with a diagnosis of cancer, most people react initially with numbed shock and disbelief, followed by anxiety, anger or depression. In most cases, this stress reaction subsides within a few weeks as patients learn to come to terms with their disease. Nonetheless, a significant number of cancer patients may develop persistent psychological disorders that call for professional attention.

Studies conducted in recent decades have revealed that pathological levels of distress were more prevalent in patients with cancer than in the general population [15]. One third of all cancer patients experience prolonged high levels of distress that contribute to ongoing adjustment difficulties and can potentially interfere with treatment compliance [16].

As presented in Table 1.9.1, among mood and anxiety disorders, figures range from 6.3% and 47.2% for anxiety, 7.8% and 57% for depression and 7.1% and 48% for general distress and are found in North America [1,17] as well as in Australia [18], European countries [19-23], the middle East [24,25], South Africa [26]; South America [27] and Asia [28]; and across the trajectory of the illness–from the time of the diagnosis of treatment to termination of treatment, survivorship, or recurrence and palliation [20,29].

Author, country, year	Sample size assessment mode	General distress	Anxiety	Depression
Berard, South Africa, 1998[26]	N=456 HAD-S, BSI, Psychiatric interview	-	-	14%
Brédart, Italy, 1999[19]	N=190 HAD-S	-	16%	
Pascoe, Australia, 2000[18]	N=504 HAD-S		11.5%	7.1%
Zabora, US, 2001[17]	N=4496 BSI	35.1%	-	-
Uchitomi, Japan, 2003[28]	N=212 DSM-III SCID, POMS	-	-	4.7-8% within 1 year post-surgery
Carlson, Canada, 2004[1]	N=3095 BSI-18	37.8%	-	-
Grassi, Mediterranean countries, 2004[21]	N=277 HAD-S	-	34%	24.9%
Burgess, UK, 2005[20]	N=222 DSM SCID	48% first year/ 15% fifth year post-diagnosis	-	-
Santos, Brazil, 2006[27]	N=107 HAD-S, IES		20.5%	16.8%
Mehnert, Germany, 2007[22]	N=127 DSM SCID	7.1% adjustment disorder	6.3% generalised anxiety disorder	7.8% major depression + dysthymic disorder
Strong, UK, 2007[23]	N=3071 HAD-S	22%	-	-
Tavoli, Iran, 2007[25]	N=142 HADS	-	47.2%	57%
Ozalp, Turkey, 2008[24]	N=204 HAD-S	37.3%	-	-

Table 1.9.1 *Prevalence figures for anxiety or depressive disorders in cancer patients across countries*
HAD-S = Hospital Anxiety and Depression Scale, BSI = Brief Symptom Inventory, DSM SCID = structured clinical interview for the Diagnostic and Statistical Manual of Mental Disorders, POMS=Profile of Mood Scale, IES= Impact of Event Scale

Post-traumatic stress disorders as a result of the stress event that represents confrontation with a life-threatening illness such as cancer are also found in the cancer setting, with prevalence rates of 19% in breast cancer patients post-surgery and 16% at 6 months [22].

In advanced cancer, about half of patients express some level of suffering, with physical symptoms, psychological distress and existential concerns contributing to the prediction of this experience [30].

Acute confusional states are less common in patients with cancer overall but develop frequently in advanced cancer, and are a leading source of distress for family caregivers [31]. Patients become restless, suspicious and confused, with impaired concentration, memory and orientation in time and space. Opioid analgesics essentially, but also chemotherapy agents, cerebral tumours or encephalopathy are common causes.

Predictors of psychological disturbance in cancer patients have been highlighted including medical (staging of disease, physical or psychological symptoms), individual (age, gender, past history of psychiatric disorder, personality) or interpersonal and social factors (marital status, social network, education, current concerns) [1,17,20,32]. Potential predictors are not very useful clinically as they only partly explain the development of psychological disturbances. There is meanwhile a consensus to consider the systematic screening of these disturbances as useful in order to allow early treatments of these conditions [33,34].

Couple and family issues. Cancer is a family affair and not the patient's problem alone [35]. The effect of cancer on family members, in turn, may affect the patient's adjustment to illness. The well-being of close relatives is of concern especially since contexts of scarce psychosocial resources lead to reliance of this only source of support to patients.

Marital relationships may be altered, especially in the case of pre-existing problems whereas good marital relationship may buffer the stress of cancer, and are associated with less distress in the patient.

An insufficiently recognised complication of cancer is sexual functioning [36]. Sexual problems can be a consequence of cancer-related anxiety and depression or result from psychological and physical damage following certain treatment such as disfiguring surgery, ostomies, surgically induced nerve damage, radical pelvic irradiation, side-effects of chemotherapy or hormone treatment. Treatment for prostate cancer such as prostatectomy or hormone therapy can diminish a man's self-esteem as a sexual partner [37]. Body image and sexual problems were experienced by a substantial proportion of women in the early months after diagnosis of breast cancer and were associated with mastectomy and possible reconstruction, hair loss from chemotherapy, concern about weight gain or loss, poorer mental health, vaginal dryness and partner's difficulty in understanding patients' feelings [38].

Less well recognised than marital problems is the effect that breast cancer may have on the mother-daughter relationship. Daughters' distress levels have been found to be significantly related to mothers' distress levels [35]. Considering children/adolescents more generally, the family characteristics such as the family's communication or expressiveness are associated with children/adolescents psychosocial outcomes; a particular risk factor may be maternal depression which can affect the parenting role [39].

Specific issue: breast cancer genetic risk. Development of medical knowledge and technology brings definite benefit to the health of individuals; however, new associated psychosocial problems may be elicited, which the psycho-oncology field must address. One of these is related to the psychosocial issues associated with breast cancer genetic testing and subsequent health care management, in terms of intensive medical surveillance or prophylactic interventions. The familial breast cancer syndrome associated with a BRCA1 or BRCA2 mutation is thought to confer in a woman a lifetime risk of breast cancer of between 50 and 85% [40]. Since the discovery of these mutations a decade ago, familial cancer services have been set up in many countries (e.g. Australia, Canada, France, Germany, Netherlands, UK and the USA) to respond to the increasing demand for breast cancer genetic counselling and testing [41].

Breast cancer susceptibility testing offers the potential for early detection of breast cancer, since a positive test result points to the need for increased surveillance, i.e. regular mammography or magnetic resonance imaging (MRI) or indicates the possibility of reducing cancer risk through chemoprevention and risk-reducing surgery. A positive test may also present psychological benefits in reducing the individual's uncertainty and doubts. However, cancer-susceptibility testing also encompasses limitations and potential risks, depending on the test result. The test result may be: 1) positive in an unaffected, at-risk individual when a disease-related mutation has been identified in the family, 2) positive in an individual who is the first identified mutation carrier in a family, 3) negative when a disease-related mutation has been identified in the family or, 4) uninformative or of uncertain significance.

A positive test result may lead to heightened anxiety about being a mutation carrier or induce guilt about possible transmission of genetic risk to children. Mutation carriers may be confronted with the medical and psychological risks of increased screening or surgical prophylactic interventions or of potential insurance,

employment or social discrimination. When the genetic test result is uninformative or of uncertain significance, continuing anxiety, depression or confusion considering the lack of evidence-based guidance regarding prevention or surveillance strategies may appear. A negative test result may offer reassurance and reduction of anxiety about personal cancer risk due to heredity; however, it may result in strained family relationships or guilt, and potential inappropriate routine surveillance.

Research results to date do not indicate harmful psychological consequences following a positive test result [41-44]; however, most studies have been undertaken in settings devoted to clinical research and care by specialists in hereditary cancer and have addressed individuals of prevailing cultures. These studies do not provide long-term information on the emotional and health behavioural effects of this new technology. Although counselees seem to improve their knowledge about genetic aspects after genetic counselling, their risk perception remains incorrect [42], suggesting the need for professional support in helping individuals make informed decisions when considering the option of performing genetic tests or managing their high risk of cancer.

Studies on the psychological consequences of intensive screening or prophylactic interventions require careful attention. In the general population, if mammography screening does not appear to have a negative psychological impact on the majority of women, those who are recalled for further investigations after screening are subject to significant adverse consequences which may remain in the long term [45]. Additionally, regarding prophylactic mastectomy in particular, although the literature indicates a high level of satisfaction among women overall, a subset may report regret post surgery and are likely to experience high levels of psychological distress, sexual dysfunction and concern with body image [44].

Psychosocial issues in oncology professionals

In the context of cancer care, the relationship between patients and healthcare providers and the standards of communication are of the utmost importance. Inadequate explanations may lead to patients being confused about their diagnosis, prognosis and potential therapeutic options, thereby promoting dissatisfaction and psychological distress. This can affect attitudes towards treatment and care, difficulty adhering to medical recommendations, and may result in poorer outcomes. However, the information that must be conveyed to patients—disclosing a cancer diagnosis or explaining aggressive treatments—often has 'threatening' content, making the task of healthcare providers particularly difficult.

The care of patients with cancer may be particularly stressful. In particular, dealing with cancer patients' psychosocial issues entails an emotional burden that can lead to burnout [46]. A high level of morbidity and mortality, confronting death, treatments with limited efficacy that are powerful but toxic or mutilating, difficult therapeutic decisions, medical or nursing staff conflicts, patients' or family emotional or behavioural reactions may all contribute to the stress associated with cancer care. For example, healthcare professionals may report feelings of helplessness, anger, or occasional identification with the patient. In communicating with cancer patients, doctors are often confronted with a number of difficult issues for which they are usually unprepared, such as communicating bad news, preparing for aversive procedures, exploring treatment options, enrolling in clinical trials, discussing prognosis, or switching from curative treatment to supportive care [47]. In cancer care, professionals need to accept that care can be of good quality and effective without necessarily leading to a cure; this may challenge their original motivation in entering the medical profession.

Management of psychosocial issues

Interventions targeted at health care professionals.
Lack of skills and training in the detection of cancer patients' and families' psychosocial needs has been identified as a substantial barrier to the provision of evidence-based psychosocial care in oncology [2]. Studies suggest that clinicians do not identify patients with high levels of anxiety or depression [48-50] and need for psychosocial counselling [50]. Physical symptoms are more frequently addressed by the treatment team than are psychological concerns, although patients expect clinicians to initiate discussions about psychosocial issues [51].

Oncologists play an important role not only in identifying psychological distress but also in preventing it by providing adequate information and basic emotional support to patients and their relatives. Adequate communication skills are required to deal with issues that regularly arise in the cancer setting (e.g. complex treatment decision-making, treatment refusals, euthanasia requests).

Interventions have been designed to facilitate the detection of physical and psychological problems through the use of quality of life questionnaires in routine oncology practice [52], the provision of assessment tools [16] and guidelines for psychosocial management [14], as well as to train healthcare professionals in psychosocial issues [53] and in communication skills [54,55].

Psychological distress screening tools and psychosocial guidelines. Oncologists' estimation of whether and how severe a patient is distressed is often complicated by patients' denial [50]; besides, common somatic symptoms found in cancer, such as pain, fatigue, weakness, reduced energy and appetite/weight changes, are also common psychopathological symptoms: breathlessness, muscle pain, dizziness and palpitation for anxiety and panic attack; fatigue or appetite/weight for depression.

These somatic signs create difficulty in diagnosing depression and anxiety in cancer patients, and lead to highlighting more reliable symptoms such as, for depression, anhedonia, guilt, suicidal thinking and hopelessness [49].

In the United States, through the National Comprehensive Cancer Network (NCCN) (www.nccn.org), specific tools and procedures have been tested to trigger referral by the oncology staff to the psychosocial services. Similar to the pain management guidelines, a rapid psychological screen measure, the Distress Thermometer coupled with a Problem List to identify sources of distress (psychological, family, social, spiritual, practical, physical), are provided to patients in the ambulatory setting to identify those at risk for psychosocial problems and facilitate appropriate interventions.

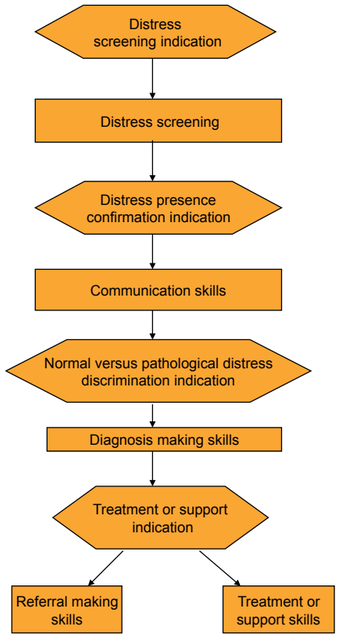


Fig. 1.9.2 *Optimisation of distress treatment : importance of screening. Used with permission: Razavi D, Delvaux N. Précis de psycho-oncologie de l'adulte. Masson. 2008, p 311*

Clinical practice guidelines based on comprehensive review of evidence-based psychosocial interventions have been produced in different countries as benchmarks against which the quality of psychosocial care in cancer can be assessed. In Canada, such guidelines allow regional and federal governments in planning and budgeting psychosocial care in cancer (www.capo.ca); in Australia, the implementation of the guidelines has been performed through demonstration projects, doctor communication skills training and forming partnerships with patient advocacy groups (http://www.nhmrc.gov.au/); in the United Kingdom, the National Institute for Health and Clinical Excellence also offers clinical guidance from a critical and comprehensive appraisal of studies assessing the effectiveness of psychosocial, supportive and palliative care services for cancer patients (http://guidance.nice.org.uk/csgsp). Other countries with guidelines in use are Germany, Hungary, Italy, Israel, Spain and Japan; in still others, guidelines are at different stages of development. Figure 1.9.2 illustrates the steps of interventions and skills needed to optimize the care of emotional distress [57].

Communication skills training. Good doctor-patient communication is essential, since it increases patients' coping and satisfaction with care, enhances informed consent and cooperation with care, reduces the probability of malpractice litigation and decreases professionals' burnout. Doctor-patient communication encompasses: 1) creating a good interpersonal relationship (a clear, warm and reassuring setting); 2) exchanging information (eliciting patients' information on their difficulties, preferences and expectations as well as providing complex medical information); and 3) making treatment-related decisions (which require an adequate understanding of the medical and psychosocial stakes associated with possible therapeutic options) [56].

Communication skills training is aimed at improving health care providers' ability to elicit patients' concerns and needs as well as to offer emotional support. Facilitating (e.g. use of open questions, expressions of empathy, appropriately responding to patients' cues) or blocking (e.g. exclusive focus on physical symptoms) communication behaviours have been described; these are promoted in training programmes [11].

A patient-centred care approach is encouraged; this entails the following specific features:

- an individualized, bio-psycho-social attention to the patient confronting the difficulties the disease imposes in his/her daily life;
- the consideration of a patient who is no longer a passive recipient of care, but perceived as possessing resources to deal with his/her condition, such as the capacity to understand medical information and share medical decision making; and
- a non-judgmental, genuine and comprehensive caring attitude.

Cancer patients generally prefer a collaborative role in deciding on a treatment plan; however a significant number prefer to remain passive, deferring to their physicians on treatment decisions [58]. Physicians are not necessarily attuned to patients' wishes regarding their involvement in shared decision-making. An uneven balance of power in treatment decision-making (either making all the decision or leaving it all to the patients) may affect patients' well-being and satisfaction with care.

Recent systematic reviews have provided evidence for the effectiveness of communication training in improving basic communication skills in the cancer setting [10]. These must comprise the following specific features: learner-centered, skills-focused, and practice-oriented, organised

in small groups and lasting at least 20 hours. Communication skills training courses should be proposed during academic training and pursued in continuing education programmes.

Interventions targeted at patients or relatives

Improving quality of life. There is now a considerable body of evidence concerning the effectiveness of psychosocial interventions for individuals or families confronted with cancer [9]. Because of the various individuals' needs and contexts, different types of professional psychosocial interventions have been developed and tested. These comprise individual interventions such as education, counselling (crisis-oriented or psychodynamic), cognitive (cognitive reframing, problem solving) therapy or mind-body techniques (relaxation, hypnosis, meditation), group interventions (expressive-existential, cognitive-behavioural, psycho-educational) and couple or family interventions. They are usually targeted to specific episodes of the illness trajectory: diagnosis/pre-treatment, immediately post-treatment or during extended treatment (chemotherapy or radiotherapy), and advanced disease or death, through the bereavement period when addressed to relatives [1]. More specific interventions have also been designed for particular problems (e.g. sexual dysfunction, sleep disturbance). Careful psychosocial assessment at appropriate time points in the patient's journey may channel to specific interventions.

Cancer patients' psychological adjustment results from the interaction between their appraisals of the stresses associated with the disease and their internal or external resources, in terms of their coping style, personality traits or available support resources. Psychological therapy in people with cancer strives at facilitating coping in favour of improved patient well-being. For example, cancer patients with a hopeless/helpless or anxious preoccupied adjustment style perceive the disease as a major threat, loss or defeat, which may lead to depressive or anxious mood disorders. During psychological therapy, these negative thoughts may be challenged, new ways of thinking about the disease and its impact on life explored and new methods to cope with the illness experimented [59].

In group therapy, expressing feelings and fear about the illness and encouraging mutual support is emphasised [60]. Emotional expression helps adjust to the stressful experience of cancer through the opportunity to identify one's feelings and to process them at a deep level.

Recently, the importance of finding meaning in life to the preservation of positive effects has been underlined in face of the catastrophic event of experiencing cancer. Additionally, a posttraumatic growth phenomenon, or positive changes has been reported as a result of this experience. These observations have triggered the development of new forms of psychological therapy for advanced cancer patients [61].

Considering the effects of psychological therapy in oncology, research evidence suggests that it does not promote survival but may affect this outcome in addressing patients' depression, hopelessness/helplessness and promoting improved adherence to anti-cancer treatments. The relevant outcomes are indicators of quality of life such as anxiety and depression or adjustment to the disease, as well as aspects of interpersonal and social functioning.

Following a critical review of 329 trials in cancer psychological therapy and considering various aspects of quality of life, Newell et al. [9] concluded that group therapy, education, structured and unstructured counselling, and cognitive behavioural therapy offer promise for many of the psychosocial outcomes explored (e.g. depression, anxiety, overall quality of life and physical symptoms such as fatigue or conditioned nausea).

Further studies need to address the appropriateness of existing forms of psychological therapy for subgroups of patients so as to design or adapt interventions accordingly (e.g. patients from rural areas, with psychopathological antecedents or from varying cultural backgrounds). For example, these may rather attract patients belonging to higher socioeconomic classes [62], although cancer patients from lower socioeconomic status have been shown to present greater morbidity and poorer perseverance with anti-tumour treatment. Psychosocial factors, like optimism, unmitigated communion, or negative social interaction have been shown to moderate the effect of psycho-oncological interventions, highlighting a specific group of participants more susceptible to benefit from currently proposed interventions [63]. Henceforth, it would also be useful to determine the optimal time to offer psychological interventions to patients for they may not be open to address their distress at any time, especially as long as a treatment decision has not yet been made [64].

Conclusions and recommendations

Cancer and its treatment may considerably affect patients' physical and psychosocial functioning, hence overall quality of life. The psycho-oncology discipline has been developed and implemented in an increasing number of countries to respond to the psychosocial needs raised in oncology at the different phases of the cancer journey, including prevention and early detection, diagnosis and first treatments, survivorship, recurrence, terminal stages and bereavement.

Evidence-based psychosocial interventions addressing patients, families or their social milieu, or focusing on caregivers and healthcare professionals have been designed and tested, and are presently available in many settings to address psychosocial concerns, foster adaptation to the disease and treatment course, and therefore improve healthcare outcomes.

However, at an international level, the integration of psychosocial oncology within oncological care is still deficient. Clinical and educational recommendations based on current scientific knowledge have been provided [3,65]; these should be more largely endorsed. The psychosocial components of oncological care should be included in every national cancer care plan and psycho-oncology services made available in every cancer care service. Cancer patients and close relatives should be offered psycho-oncology consultations and a range of psychosocial services during and after the treatment course; they should be provided with clear, free-of-charge information on their condition, respecting their needs and preferences. Healthcare professionals should be provided with validated psychosocial assessment tools, training and continuous supervision to be supported in addressing and adequately responding to the psychosocial needs of patients and relatives, engaging good communication and shared medical decision making.

The International Psycho-Oncology Society (IPOS) was implemented in 1984 to bring together investigators and clinicians dedicated to the clinical, educational and research aspects of psycho-oncology, in order to spread knowledge and practice in the psychosocial care of cancer patients worldwide while taking into account the diversity of problems and needs according to the cultural, economical or healthcare system background. Thanks to an initiative from the Psycho-Oncology Co-operative Research Group in Australia, a world map showing psycho-Oncology research groups is now available (http://www.ipos-society.org/professionals/tools-resources/research-centers.htm)

Cross-national psycho-oncology research is now possible thanks to the international development and validation of psychosocial instruments allowing monitoring of patients' difficulties and assess interventions effectiveness [66, 67] or evaluate the quality of cancer care provided [68].

The further mission of the IPOS is to assist the WHO in shaping priorities of action regarding the psychosocial element of national cancer control programmes [3].

Psychosocial oncological care is an essential component of high-quality cancer care that should be made available across countries to improve cancer patients' and relatives' health outcomes, their quality of life and satisfaction with care, and to ensure healthcare providers' well-being while carrying out the activities of their caring profession.

Fig. 1.9.3 *Communication skill training is aimed at improving health care providers' ability to elicit patients' concerns and needs as well as to offer emotional support*

REFERENCES

1. Aaronson, N.K., Ahmedzai, S., Bergman, B., et al. (1993). The European Organization for Research and Treatement of Cancer QLQ-C30: A Quality of life Instrument for Use in International Clinical Trials in Oncology. *J Nat Can Inst, 85,* 365-75.

2. Akizuki, N., Yamawaki, S., Akechi, T., Nakano, T., & Uchitomi, Y. (2005). Development of an Impact Thermometer for use in combination with the Distress Thermometer as a brief screening tool for adjustment disorders and/or major depression in cancer patients. *J Pain Symptom Manage,* 29(1), 91-99.

3. Akechi T, Okuyama T, Akizuki N, et al. Course of psychological distress and its predictors in advanced non-small cell lung cancer patients. Psychooncology 2006;15:463-73.

4. American Psychiatric Association. DSM-IV-TR® Diagnostic and Statistical Manual of mental disorders, Fourth Ediction, 2003.

5. Back AL, Arnold RM, Baile WF, Fryer-Edwards KA, Alexander SC, Barley GE, Gooley TA, Tulsky JA. Efficacy of communication skills training for giving bad news and discussing transitions to palliative care. Arch Intern Med. 2007 12;167(5):453-60.

6. Baider L, Goldzweig G, Ever-Hadani P, Peretz T. Breast cancer and psychological distress: mothers' and daughters' traumatic experiences. Support Care Cancer. 2008 Apr;16(4):407-14

7. Barg FK, Cronholm PF, Straton JB, Keddem S, Knott K, Grater J, Houts P, Palmer SC. Unmet psychosocial needs of Pennsylvanians with cancer: 1986-2005. Cancer. 2007 Aug 1;110(3):631-9.

8. Berard RM, Boermeester F, Viljoen G. Depressive disorders in an out-patient oncology setting: prevalence, assessment, and management. Psychooncology 1998;7:112-20.

9. Boesen E, Boesen S, Christensen S, Johansen C. Comparison of participants and non-participants in a randomized psychosocial intervention study among patients with malignant melanoma. Psychosomatics. 2007 Nov-Dec;48(6):510-6.

10. Brédart A, Didier F, Robertson C, et al. Psychological distress in cancer patients attending the European Institute of Oncology in Milan. Oncology 1999;57:297-302.

11. Brédart A, Robertson C, Razavi D, et al. Patients' satisfaction ratings and their desire for care improvement across oncology settings from France, Italy, Poland and Sweden. Psychooncology 2003;12:68-77.

12. Brédart, A., Bottomley, A., Blazeby, J. M., Conroy, T., Coens, C., D'Haese, S., et al. (2005). An international prospective study of the EORTC cancer in-patient satisfaction with care measure (EORTC IN-PATSAT32). *Eur J Cancer, 41*(14), 2120-2131.

13. Breitbart W, Bruera E, Chochinov H, Lynch M. Neuropsychiatric syndromes and psychological symptoms in patients with advanced cancer. J Pain Symptom Manage. 1995 Feb;10(2):131-41.

14. Brett J, Bankhead C, Henderson B, Watson E, Austoker J. The psychological impact of mammographic screening. A systematic review. Psychooncology. 2005 Nov;14(11):917-38.

15. Burgess C, Cornelius V, Love S, Graham J, Richards M, Ramirez A. Depression and anxiety in women with early breast cancer: five year observational cohort study. BMJ 2005;330:702.

16. Carlson LE, Bultz BD. Efficacy and medical cost offset of psychosocial interventions in cancer care: making the case for economic analyses. Psychooncology. 2004 Dec;13(12):837-49; discussion 850-6.

17. Cella DF, Tulsky DS, Gray G, Sarafian B, Linn E, Bonomi A, Silberman M, Yellen SB, Winicour P, Brannon J, et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. J Clin Oncol. 1993 Mar;11(3):570-9.

18. Chochinov HM, Hack T, Hassard T, Kristjanson LJ, McClement S, Harlos M. Dignity therapy: a novel psychotherapeutic intervention for patients near the end of life. J Clin Oncol. 2005 Aug 20;23(24):5520-5.

19. Couper J, Bloch S, Love A, Macvean M, Duchesne GM, Kissane D. Psychosocial adjustment of female partners of men with prostate cancer: a review of the literature. Psychooncology. 2006 Nov;15(11):937-53.

20. Detmar SB, Aaronson NK, Wever LD, Muller M, Schornagel JH. How are you feeling? Who wants to know? Patients' and oncologists' preferences for discussing health-related quality of life issues. J Clin Oncol. 2000 Sep 15;18(18):3295-301.

21. Eide H, Graugaard P, Holgersen K, Finset A. Physician communication in different phases of a consultation at an oncology outpatient clinic related to patient satisfaction. Patient Educ Couns. 2003 Nov;51(3):259-66.

22. Fobair P, Stewart SL, Chang S, D'Onofrio C, Banks PJ, Bloom JR. Body image and sexual problems in young women with breast cancer. Psychooncology. 2006 Jul;15(7):579-94.

23. Ford D, Easton DF, Stratton M et al. Genetic heterogeneity and penetrance analysis of the BRCA1 and BRCA2 genes in breast cancer families. The Breast Cancer Linkage Consortium. Am J Hum Genet. 1998 Mar;62(3):676-89.

24. Gagnon P, Charbonneau C, Allard P, Soulard C, Dumont S, Fillion L. Delirium in advanced cancer: a psychoeducational intervention for family caregivers. J Palliat Care. 2002 Winter;18(4):253-61.

25. Grassi L, Travado L, Moncayo FL, Sabato S, Rossi E. Psychosocial morbidity and its correlates in cancer patients of the Mediterranean area: findings from the Southern European Psycho-Oncology Study. J Affect Disord 2004;83:243-8.

26. Grassi L, Travado L. The role of psychosocial oncology in cancer care, in Responding to the challenge of cancer in Europe, Coleman MP, Alexe D-M, Albrecht T, McKee M (Eds). European Observatory on Health Systems and Policies, 2007.

27. Graves KD, Arnold SM, Love CL, Kirsh KL, Moore PG, Passik SD. Distress screening in a multidisciplinary lung cancer clinic: prevalence and predictors of clinically significant distress. Lung Cancer 2007;55:215-24.

28. Greer S, Moorey S. Adjuvant psychological therapy for cancer patients. Palliat Med. 1997 May;11(3):240-4.

29. Gysels M, Richardson A, Higginson IJ. Communication training for health professionals who care for patients with cancer: a systematic review of effectiveness. Support Care Cancer. 2004 Oct;12(10):692-700.

30. Hack TF, Degner LF, Parker PA; SCRN Communication Team. The communication goals and needs of cancer patients: a review. Psychooncology. 2005 Oct;14(10):831-45; discussion 846-7.

31. Helgeson VS. Recent advances in psychosocial oncology. J Consult Clin Psychol. 2005 Apr;73(2):268-71.

32. Hewitt M, Rowland JH. Mental health service use among adult cancer survivors: analyses of the National Health Interview Survey. J Clin Oncol. 2002 Dec 1;20(23):4581-90.

33. Holland JC. IPOS Sutherland Memorial Lecture: an international perspective on the development of psychosocial oncology: overcoming cultural and attitudinal barriers to improve psychosocial care. Psychooncology. 2004 Jul;13(7):445-59.

34. Holland JC, Jacobsen PB, Riba MB; NCCN Fever and Neutropenia Practice Guidelines Panel. NCCN: Distress management. Cancer Control. 2001 Nov-Dec;8(6 Suppl 2):88-93.

35. Hopwood P. Psychosocial aspects of risk communication and mutation testing in familial breast-ovarian cancer. Curr Opin Oncol. 2005 Jul;17(4):340-4.

36. Kash KM, Holland JC, Breitbart W, Berenson S, Dougherty J, Ouellette-Kobasa S, Lesko L. Stress and burnout in oncology. Oncology (Williston Park). 2000 Nov;14(11):1621-33; discussion 1633-4, 1636-7.

37. Kissane DW, Bloch S, Miach P, Smith GC, Seddon A, Keks N. Cognitive-existential group therapy for patients with primary breast cancer-techniques and themes. Psychooncology. 1997 Mar;6(1):25-33.

38. Kissane DW. Psychosocial oncology: Present status, Future directions. Multinational Association of Supportive Care in Cancer. 16th International Symposium Proceedings, 2004.

39. Lispscomb, J., Gotay, C.C., Snyder, C. (2005). Outcome assessment in cancer: Measures, methods, and applications. Cambridge University Press.

40. Mehnert A, Koch U. Psychosocial care of cancer patients–international differences in definition, healthcare structures, and therapeutic approaches. Support Care Cancer 2005;13:579-88.

41. Mehnert A, Koch U. Prevalence of acute and post-traumatic stress disorder and comorbid mental disorders in breast cancer patients during primary cancer care: a prospective study. Psychooncology 2007;16:181-8.

42. Meiser B. Psychological impact of genetic testing for cancer susceptibility: an update of the literature. Psychooncology. 2005 Dec;14(12):1060-74.

43. Meiser B, Gaff C, Julian-Reynier C, et al. International perspectives on genetic counseling and testing for breast cancer risk. Breast Dis 2006;27:109-25.

44. Merckaert I, Libert Y, Razavi D. Communication skills training in cancer care: where are we and where are we going? Curr Opin Oncol 2005;17:319-30.

45. Newell S, Sanson-Fisher RW, Girgis A, Bonaventura A. How well do medical oncologists' perceptions reflect their patients' reported physical and psychosocial problems? Data from a survey of five oncologists. Cancer 1998;83:1640-51.

46. Newell SA, Sanson-Fisher RW, Savolainen NJ. Systematic review of psychological therapies for cancer patients: overview and recommendations for future research. J Natl Cancer Inst. 2002 Apr 17;94(8):558-84.

47. Ong LM, de Haes JC, Hoos AM, Lammes FB. Doctor-patient communication: a review of the literature. Soc Sci Med. 1995 Apr;40(7):903-18.

48. Osborn T. The psychosocial impact of parental cancer on children and adolescents: a systematic review. Psychooncology. 2007 Feb;16(2):101-26.

49. Ozalp E, Soygur H, Cankurtaran E, Turhan L, Akbiyik D, Geyik P. Psychiatric morbidity and its screening in Turkish women with breast cancer: a comparison between the HADS and SCID tests. Psychooncology 2007.

50. Pascoe S, Edelman S, Kidman A. Prevalence of psychological distress and use of support services by cancer patients at Sydney hospitals. Aust N Z J Psychiatry 2000;34:785-91.

51. Passik SD, Dugan W, McDonald MV, Rosenfeld B, Theobald DE, Edgerton S. Oncologists' recognition of depression in their patients with cancer. J Clin Oncol. 1998 Apr;16(4):1594-600.

52. Razavi, D., Delvaux, N., Farvacques, C., & Robaye, E. (1990). Screening for adjustment disorders and major depressive disorders in cancer in-patients. *Br J Psychiatry, 156,* 79-83.

53. Razavi, D., Merckaert, I., Marchal, S., Libert, Y., Conradt, S., Boniver, J., et al. (2003). How to optimize physicians' communication skills in cancer care: results of a randomized study assessing the usefulness of posttraining consolidation workshops. *J Clin Oncol, 21*(16), 3141-3149.

54. Sanson-Fisher R, Girgis A, Boyes A, Bonevski B, Burton L, Cook P. The unmet supportive care needs of patients with cancer. Supportive Care Review Group. Cancer 2000, 88: 226-37.

55. Santos FR, Kozasa EH, Chauffaille Mde L, Colleoni GW, Leite JR. Psychosocial adaptation and quality of life among Brazilian patients with different hematological malignancies. J Psychosom Res 2006;60:505-11.

56. Razavi D, Delvaux N. Précis de psycho-oncologie de l'adulte. Masson, Paris, 2008, p 311.

57. Scheier MF, Helgeson VS, Schulz R, et al. Moderators of interventions designed to enhance physical and psychological functioning among younger women with early-stage breast cancer. J Clin Oncol 2007;25:5710-4.

58. Schofield P, Carey M, Bonevski B, Sanson-Fisher R. Barriers to the provision of evidence-based psychosocial care in oncology. Psychooncology. 2006 Oct;15(10):863-72.

59. Sellick SM, Edwardson AD. Screening new cancer patients for psychological distress using the hospital anxiety and depression scale. Psychooncology. 2007 Jun;16(6):534-42.

60. Stead ML, Brown JM, Fallowfield L, Selby P. Lack of communication between healthcare professionals and women with ovarian cancer about sexual issues. Br J Cancer. 2003 Mar 10;88(5):666-71.

61. Söllner W, DeVries A, Steixner E, Lukas P, Sprinzl G, Rumpold G, Maislinger S. How successful are oncologists in identifying patient distress, perceived social support, and need for psychosocial counselling? Br J Cancer. 2001 Jan;84(2):179-85.

62. Strong V, Waters R, Hibberd C, et al. Emotional distress in cancer patients: the Edinburgh Cancer Centre symptom study. Br J Cancer 2007;96:868-74.

63. Tavoli A, Mohagheghi MA, Montazeri A, Roshan R, Tavoli Z, Omidvari S. Anxiety and depression in patients with gastrointestinal cancer: does knowledge of cancer diagnosis matter? BMC Gastroenterol 2007;7:28.

64. Uchitomi Y, Mikami I, Nagai K, Nishiwaki Y, Akechi T, Okamura H. Depression and psychological distress in patients during the year after curative resection of non-small cell lung cancer. J Clin Oncol 2003;21:69-77.

65. Vadaparampil ST, Miree CA, Wilson C, Jacobsen PB. Psychosocial and behavioral impact of genetic counseling and testing. Breast Dis. 2006-2007;27:97-108.

66. Velikova G, Booth L, Smith AB, et al. Measuring quality of life in routine oncology practice improves communication and patient well-being: a randomized controlled trial. J Clin Oncol 2004;22:714-24.

67. Wells KB, Stewart A, Hays RD, Burnam MA, Rogers W, Daniels M, Berry S, Greenfield S, Ware J. he functioning and well-being of depressed patients. Results from the Medical Outcomes Study. JAMA. 1989 Aug 18;262(7):914-9.

68. Wilson KG, Chochinov HM, McPherson CJ, LeMay K, Allard P, Chary S, Gagnon PR, Macmillan K, De Luca M, O'Shea F, Kuhl D, Fainsinger RL. Suffering with advanced cancer. J Clin Oncol. 2007 May 1;25(13):1691-7.

69. Zabora J, BrintzenhofeSzoc K, Curbow B, Hooker C, Piantadosi S. The prevalence of psychological distress by cancer site. Psychooncology 2001;10:19-28.

WEBSITES

1. The International Psycho-Oncology Society: http://www.ipos-society.org/

2. The Canadian Association for Psychosocial Oncology: http://www.capo.ca/eng/

3. Australian Practice Guidelines for the Psychosocial Care of Adults with Cancer: http://www.nhmrc.gov.au/

4. The National Institute for Health and Clinical Excellence guidance: http://guidance.nice.org.uk/

5. The National Comprehensive Cancer Network (NCCN), guidelines for supportive care, distress management: www.nccn.org

6. World map of psycho-oncology research groups: http://www.ipos-society.org/professionals/tools-resources/research-centers.htm

1.10 Rehabilitation in Oncology

Summary

> Rehabilitation is an essential part of a comprehensive concept of cancer care starting from early detection of cancer and covering the entire continuum from diagnostic assessment to treatment, rehabilitation and aftercare including end-of-life phases

> Cancer rehabilitation is defined as a process of helping the patient to regain physical, social, psychological and work-related functionality after cancer treatment

> Rehabilitation programmes include an interdisciplinary and comprehensive approach providing support to patients and their families to cope with treatment sequelae and to allow them to regain quality of life and functional status

> Rehabilitation needs must be assessed individually by instruments measuring physical performance and quality of life

> Research results provide good empirical evidence for effects of rehab programmes, especially on important outcome domains such as health-related quality of life, psychosocial status and psychiatric comorbidity

Due to early detection and improvement of cancer therapy, survival times for many types of cancer have increased over the past few decades, whereas the cure rates have improved in only a few instances. Oncologic treatment including surgery, chemotherapy and radiation has become more aggressive and is often long-lasting. Cancer therapies are producing toxicities which cause substantial short- and long-term side effects, functional loss and psychosocial distress. As a consequence, in many cases cancer has to be regarded as a chronic disease involving great challenges for patient care. Many cancer patients require repeated oncologic treatment with substantial impact on quality of life and functional status. The demands on the patients to adapt to those changes may vary depending on their extent as well as whether they are temporary or permanent. Patients themselves have higher expectations of medical treatment for participation in an active life. Against this background, cancer rehabilitation has become more important during the last decades. Today, rehabilitation is an essential part of a comprehensive concept of cancer care starting from early detection of cancer and covering the entire continuum from diagnostic assessment to treatment, rehabilitation and aftercare including end-of-life phases.

Basic concepts and structure of cancer rehabilitation

Cancer rehabilitation may be defined as a process of helping the patient to regain physical, social, psychological, and work-related functionality after cancer treatment [1]. Rehabilitation as a process starts during or immediately after the end of the primary treatment in terms of secondary and tertiary prevention. Cancer rehabilitation includes a comprehensive approach to providing support to patients and their families to cope with treatment sequelae and to allow them to regain quality of life and functional status [2].

As a conceptual basis for rehabilitation, the WHO classification for functioning, disability and health (ICF, former ICIDH=International classification of impairment, disability and handicap) describes how people live with their health condition [3]. ICF is a classification of health and health-related domains that describes body functions and structures, activities and participation. The domains are classified from body, individual and societal perspectives. ICF also includes a list of environmental factors. ICF is useful to understand and measure health outcomes. It can be used in clinical settings, research, health services or surveys at the individual or population level [3]. A first version of the ICF classification for breast cancer has been published [4].

Cancer rehabilitation services can be effectively introduced in a variety of institutional settings. In most European countries as well as in the USA rehabilitation services are mostly based in outpatient settings. Many cancer centres and hospitals offer a variety of cancer rehabilitation services to their patients. Germany provides a unique system of rehabilitation clinics delivering inpatient rehabilitation programmes for all chronic diseases [5,6].

Rehabilitation needs

There are multiple rehabilitation-related issues in different stages throughout the course of the disease. Problems during the initial phase after treatment are different from those that may arise from phases after recurrence or at the end of life [7]. Therefore rehabilitation needs must be assessed individually [8]. The need for rehabilitation in cancer patients is assessed by instruments measuring physical performance and quality of life [9,10]. Cancer-specific scales attempt to assess how illness and treatment affect an individual's quality of life. Those instruments are useful in clinical and research settings and are also used for evaluation of the effects of rehab programmes. Some of those scales can be used along with more in-depth interviews and case-management interventions. They may be also used to document cancer-related problems, assess patient needs and provide information to enhance outcomes.

Goals and interventions

Cancer rehabilitation is aimed at regaining or restoring physical function and independence, often following surgical and medical therapies. Over and above that, an important task of rehabilitation is also to prevent impairment. Although reemployment may not be attained for all patients, vocational reintegration is an important goal of rehabilitation, especially for younger patients [11]. In detail, the goals in cancer rehabilitation are:

- to cope with the physical and emotional changes;
- to improve physical condition and performance status focused on strength, endurance and mobility;
- to improve social, emotional and mental functioning ;
- to identify and treat rehabilitation problems and treatment sequelae (e.g. pain, fatigue, lack of stamina, polyneuropathy, sleeping disorders)
- to enhance self-help strategies, competence and resourcefulness in disease management;
- to improve dietary habits through nutritional counselling; and
- to help the patients to become reemployed or retrain.

Goals are based on individual needs and, ideally, should be attainable within a reasonable amount of time. As each person with cancer has unique physical and emotional needs, each requires an individual rehabilitation plan. Patients and their family members are encouraged to be active and fully-informed partners in the rehabilitation process and thereby contribute to reaching their goals.

Having completed a need and goal assessment the composition of the rehab interventions is to be designed according to the patient's stages of recovery. Rehabilitation programmes include a wide spectrum of treatment options (Table 1.10.1).

- Medical treatment including pain management and complementary medicine
- Exercise programs
- Physical therapy
- Diet counselling
- Pain management
- Smoking cessation education
- Psychological counselling/individual psychotherapy
- Psychological education
- Art therapy/Occupational Therapy
- Neuropsychological training

Table 1.10.1 *Interventions in cancer rehabilitation*

Specialised programs have been developed for diagnostic subgroups (e.g. breast cancer, prostate cancer) and treatment subgroups (e.g. after stem cell transplantation). For example, specified rehabilitation programmes for breast cancer in women may focus on comprehensive management of lymphedema, exercise, diet counselling, post-operative management of breast reconstruction, psychological counselling and psychotherapy, or dance therapy addressing body image and self-esteem. As another example, patients after stem cell transplantation with their severe fatigue and decreased physical performance often require special training, psychological education and a prolonged period of recovery.

Psycho-oncology in rehabilitation

Psychosocial interventions are an essential part of a comprehensive rehabilitation programme. During the last few decades psychosocial interventions based on individual or group therapy have been developed [12,13], which are carried out also in rehabilitation centres. Meta-analyses and systematic reviews have proven those interventions on highest EBM levels I or II [14-17]. Psychoeducational group interventions in rehabilitation are mostly based on the cognitive behavioural approach including various elements (Table 1.10.2). They encompass 6 to 12 sessions based on a structured agenda focusing on the most prominent issues of cancer patients and initiating active coping behaviour.

- Information about cancer and its treatment
- Social and emotional support, sharing of experience
- Stress management
- Cognitive behavioural self-instruction and self-control techniques
- Relaxation, guided imagery

Table 1.10.2 *Elements of psychoeducational programs in cancer rehabilitation*

Cancer rehabilitation as a multidisciplinary task

Comprehensive cancer rehabilitation is provided by a multidisciplinary team of healthcare professionals. Health-care professionals involved in cancer rehabilitation are all committed to help an individual return to the highest possible level of function and independence and to ensure the best possible quality of life. These professionals may include oncologists, psychologists, rehabilitation nurses, dieticians/nutritionists, physical therapists, occupational therapists, art therapists (including music therapy, dance therapy, bibliotherapy etc.), social worker/vocational counsellors and also clergy of different persuasions. All of those professionals are coordinated mostly under the guidance of an oncologist. They work together very closely and should provide a regularly based interchange through multidisciplinary case conferences throughout rehabilitation. Structured meetings as well as external supervision are elements of quality assurance of the rehabilitation.

Evaluation of cancer rehabilitation

Systematic investigation and evaluation in rehabilitation began about 1980. Research programs have been developed to assess the effectiveness and quality of rehabilitative interventions. Compared with other research areas, only a few empirical studies have been conducted in the field of oncological rehabilitation programs. Some studies provide good empirical evidence for effects of rehab programmes, especially on important outcome domains such as health-related quality of life, psychosocial status, and psychiatric comorbidity [18-23]. However, some longitudinal studies showed that the effects of rehabilitation programs could not be proven as stable in catamnestic follow-up assessments [23,24]. In some studies, scores of many outcomes measures tend to decrease to baseline level or even below [23]. Only some studies with short term follow-up [20] showed that the improvements achieved in rehabilitation measures could be preserved during the follow up period. Factors like gender, age,

social status as well as psychological status have been shown to be of prognostic relevance concerning the success of rehabilitation over time [22]. Some studies have found that specified outpatient rehabilitation programs are effective in reducing fatigue while changes in fatigue were associated with changes in physical parameters [25]. Some other studies verify the effects of exercise and training programs for cancer patients [26,27]. There is some evidence that patients prefer multidimensional programmes to programmes with only one component [28]. In the future, further research is required, especially in terms of prospective longitudinal studies to improve effectiveness of the rehabilitation programs.

REFERENCES

1. Gerber L, Vargo M, Smith R (2005). Rehabilitation of the cancer patient. In: DeVita VT, Hellman S, Rosenberg SA, eds., *Cancer : principles and practice of oncology*. Philadelphia, PA: Lippincott Williams & Wilkins. 3089-3110.

2. Fialka-Moser V, Crevenna R, Korpan M, et al. (2003). Cancer rehabilitation: particularly with aspects on physical impairments. *J Rehabil Med* 35: 153-162.

3. WHO (2001). *International classification of functioning, disability and health : ICF*. Geneva: World Health Organization. Available from: http://www.who.int/classifications/icf/en/ Date Accessed: November 15, 2008.

4. Brach M, Cieza A, Stucki G, et al. (2004). ICF Core Sets for breast cancer. *J Rehabil Med* 121-127.

5. Koch U and Weis J (1992). Cancer rehabilitation in the Federal Republic of Germany--a critical review from the perspective of rehabilitation psychology. *Strahlenther Onkol* 168: 622-627.

6. Koch U (2000). Current developments in rehabilitation. *Rehabilitation (Stuttg)* 39: 315-316.

7. Gerber LH (2001). Cancer rehabilitation into the future. *Cancer* 92: 975-979.

8. Lehmann JF, DeLisa JA, Warren CG, et al. (1978). Cancer rehabilitation: assessment of need, development, and evaluation of a model of care. *Arch Phys Med Rehabil* 59: 410-419.

9. Ganz PA, Schag CA, Lee JJ, et al. (1992). The CARES: a generic measure of health-related quality of life for patients with cancer. *Qual Life Res* 1: 19-29.

10. Schag CA, Ganz PA, Heinrich RL (1991). Cancer Rehabilitation Evaluation System-short form (CARES-SF). A cancer specific rehabilitation and quality of life instrument. *Cancer* 68: 1406-1413.

11. Spelten ER, Verbeek JH, Uitterhoeve AL, et al. (2003). Cancer, fatigue and the return of patients to work-a prospective cohort study. *Eur J Cancer* 39: 1562-1567.

12. Newell SA, Sanson-Fisher RW, Savolainen NJ (2002). Systematic review of psychological therapies for cancer patients: overview and recommendations for future research. *J Natl Cancer Inst* 94: 558-584.

13. Holland JC, Breitbart W (1998). *Psycho-oncology*. New York: Oxford University Press.

14. Edwards AG, Hailey S, Maxwell M (2004). Psychological interventions for women with metastatic breast cancer. *Cochrane Database Syst Rev* CD004253.

15. Meyer TJ and Mark MM (1995). Effects of psychosocial interventions with adult cancer patients: a meta-analysis of randomized experiments. *Health Psychol* 14: 101-108.

16. Sheard T and Maguire P (1999). The effect of psychological interventions on anxiety and depression in cancer patients: results of two meta-analyses. *Br J Cancer* 80: 1770-1780.

17. National Breast Cancer Centre and The National Cancer Control Initiative (2003). *Clinical Practice Guidelines for the Psychosocial Care of Adults with Cancer*. Camperdown, Australia: National Breast Centre.

18. Bartsch HH, Weis J, Moser MT (2003). Cancer-related fatigue in patients attending oncological rehabilitation programs: prevalence, patterns and predictors. *Onkologie* 26: 51-57.

19. Berglund G, Bolund C, Gustafsson UL, et al. (1994). A randomized study of a rehabilitation program for cancer patients: The starting again group. *Psychooncology* 3: 109-120.

20. Heim ME, Kunert S, Ozkan I (2001). Effects of inpatient rehabilitation on health-related quality of life in breast cancer patients. *Onkologie* 24: 268-272.

21. Schwiersch M, Stepien J, Schroeck R (1994). Veränderungen der lebensqualität von tumorpatientinnen und -patienten nach stationärer onkologischer rehabilitation. Die psychosoziale situation zu beginn und am ende eines stationären heilverfahrens sowie ein jahr danach. *Prax Klin Verhaltensmedizin Rehab* 28: 230-240.

22. Teichmann JV (2002). Evaluation der effektivität stationärer onkologischer rehabilitationsmaßnahmen. *Rehabilitation (Stuttg)* 41: 53-63.

23. Weis J and Domann U (2006). Interventions in the rehabilitation of breast cancer patients--a critical literature review of the state of the art. *Rehabilitation (Stuttg)* 45: 129-145.

24. Krischke N, Niebrugge S, Petermann F (1996). Stationäre onkologische rehabilitation: veränderung der lebensqualität, programmerwartung und -beurteilung von krebspatienten. *Prax Klin Verhaltensmedizin Rehab* 35: 186-193.

25. van Weert E, Hoekstra-Weebers J, Otter R, et al. (2006). Cancer-related fatigue: predictors and effects of rehabilitation. *Oncologist* 11: 184-196.

26. Dimeo FC, Stieglitz RD, Novelli-Fischer U, et al. (1999). Effects of physical activity on the fatigue and psychologic status of cancer patients during chemotherapy. *Cancer* 85: 2273-2277.

27. Spence RR, Heesch KC, Eakin EG, et al. (2007). Randomised controlled trial of a supervised exercise rehabilitation program for colorectal cancer survivors immediately after chemotherapy: study protocol. *BMC Cancer* 7: 154.

28. van Weert E, Hoekstra-Weebers J, Grol B, et al. (2005). A multidimensional cancer rehabilitation program for cancer survivors: effectiveness on health-related quality of life. *J Psychosom Res* 58: 485-496.

1.11 Modern Imaging in Oncology

Summary

> The growth of tumour tissue is a multi-step process traditionally studied by anatomic imaging modalities

> Since molecular processes are the basis of oncology, anatomical imaging has nowadays been enhanced by new technology that illuminates these subcellular events

> The state of the art of modern anatomic imaging modalities includes new applications of well-known techniques, recent developments in molecular imaging studies

Ultrasound. Ultrasound is a safe, noninvasive imaging modality used worldwide for initial investigation of many symptomatic oncologic patients who will subsequently undergo Computerized Tomography (CT) or Magnetic Resonance (MR) imaging for further, more refined assessment. Performance of ultrasound includes detection of tumours of any accessible solid organ, based on lesion morphology and on a specific gray-scale. Optimal contrast resolution is achieved in deep solid organs, such as thyroid, liver, spleen, pancreas, uterus, ovaries and prostate, and superficial structures such as lymph nodes.

Ultrasound can also be used for intra-operative diagnosis because of the superb vision of tiny lesions when the probe is placed intimately close to the region of interest. Furthermore, ultrasound is the ideal mode of guidance for interventional procedures because of its real-time multiplanarity. However, despite the low cost and widespread availability of this modality, its high operator-dependence makes it less reliable in routine staging of proven malignancies, search for metastases and evaluation of response to treatment [1].

CT. CT is currently used for diagnosis, staging and follow-up of almost all tumours. CT imaging is based on X-ray attenuation (Figure 1.11.1 a). The introduction of the spiral scanning mode in the 1990s allowed continuous data acquisition and improvement of dynamic studies (Figure 1.11.1 b). The introduction of multislice CT scanners in 1998 allowed much faster scanning with thinner slices (up to 0.6 mm) and higher power levels (Figure 1.11.1 c), with the current most important application in cardiac imaging. However, the use of iodinated contrast medium is still frequently necessary because of the intrinsic low resolution of tumour tissue to normal tissue.

Traditional use of CT imaging, lacking of multiplanarity, has been enhanced by many image-processing methods. These include: multiplanar reformatting views (MPR) for sagittal, coronal and oblique visualisation (Figure 1.11.2 a,b,c); maximum-intensity projections (MIP) for displaying only structures with the maximum density within a mass, such as vascularisation of lesions (Figure 1.11.3 a); volume rendering (VR) reconstructions to display entire organs at varying opacity levels (Figure 1.11.3 b); surface rendering (SR) reconstructions to display enhancing voxels on the edge of structures with different densities, for virtual bronchoscopy and colonoscopy.

Because of its reproducibility, CT has also been included as a standard examination for monitoring response to therapies by the standard World Health Organization (WHO) criteria, and by the Response Evaluation Criteria in Solid Tumors (RECIST) [2].

MRI. Magnetic resonance imaging (MRI) is based on the use of a magnetic field and high-frequency electromagnetic pulses to generate images of anatomic structures with superb soft-tissue contrast, even without using contrast medium. Modern MR sequences have significantly reduced acquisition times and motion artefacts.

MRI does not apply ionizing radiation; therefore repeated examinations may be performed without risk of radiation damage to tissues, although frequent exposure is now being examined by an expert committee in the United Kingdom to check for any possible predisposition to cancers. Unavailability due to high costs makes MRI difficult to disseminate for routine use worldwide.

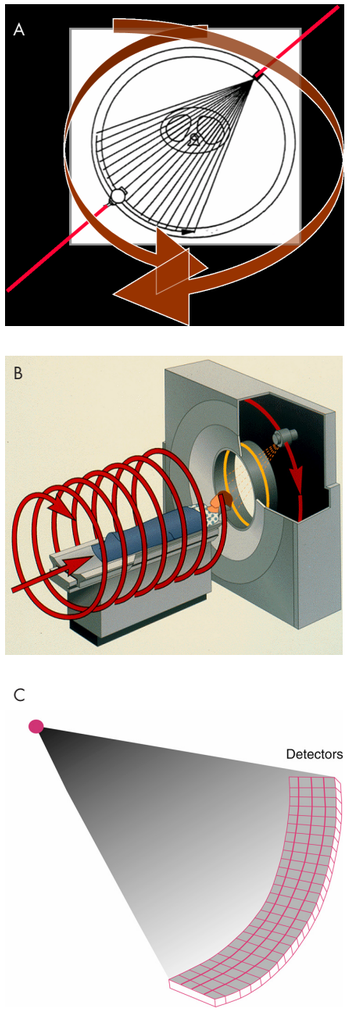


Fig. 1.11.1 *a,b,c. Beyond many years of studies performed by Conventional CT (a), the introduction of spiral CT allowed continuous data acquisition (b) and the consequent development of multislice CT allowed faster scanning by adding more rows of detectors (c)*

Recent developments in MRI imaging are Diffusion Weighted Imaging (DWI-MRI) and Dynamic Contrast-Enhanced (DCE-MRI). In DWI, image contrast derives from differences in water-motion of molecules (Figure 1.11.4 a,b,c); it can be performed quickly and yields insights about tumour cellularity and integrity of cell membranes [3]. In DCE, differences between tissues are highlighted by heterogeneous contrast medium uptake and varied degree of tumour angiogenesis; it can therefore monitor the effectiveness of treatments such as traditional cytotoxic chemotherapy, novel antiangiogenic drugs, hormonal and other targeted therapy, and radiotherapy [4].

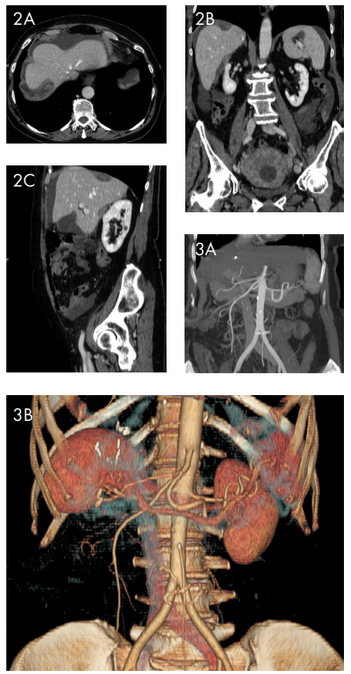


Fig. 1.11.2 *a,b,c. Multiplanar (MPR) CT reconstructions of an ovarian cancer patient, showing an hepatic lesion on the axial image (a), which is clearly located on the liver surface on the coronal (b) and sagittal (c) images, thus making the patient a stage III instead of stage IV*

Fig. 1.11.3 *a,b. Volume Rendering (VR) and coronal Maximum-Intensity Projection(MIP) from a multislice CT study, acquired using 2.5 mm slices in the early post-contrast phase, showing arterial vascularisation of liver*

PET. Most tumour cells use glucose uptake to supply energy. Therefore, the administration of a radiolabeled glucose analogue such as 18-fluorodeoxyglucose (18FDG), shows tumour tissue as "hotter" than normal tissue. Several cancers can be diagnosed and staged using 18-FDG with accuracy rates of 80–98%.

Positron Emission Tomography (PET) imaging can be used for staging and assessing response to treatment, as well described in lymphoma and melanoma patients. Advantages of PET for monitoring response to therapy rely on characterisation of post-therapy masses as metabolically active (residual tumour) or inactive (post-treatment fibrosis). PET imaging can give this information before other anatomic modalities because metabolic changes usually precede anatomical response [5]. However, FDG is excreted by the kidneys in urine, so tumours of the urinary tract may be misdiagnosed. New PET contrast agents that will further expand the range of applications of the technique are currently under evaluation.

Virtual Colonoscopy. Virtual Colonoscopy (VC) is a noninvasive CT method for detection of colorectal polyps and cancers (Figure 1.11.5). In contrast to endoscopic colonoscopy, it is fast, noninvasive, does not require sedation and, although the experience is still short, its rate of morbidity and mortality is very low.

Currently, with the use of multislice CT, the mean scan time is 4–10 seconds, and thin slices of 0.6mm enable high-quality MPR (Multiplanar reconstruction) and 3D reconstruction.

VC can demonstrate lesions behind haustral folds and beyond bends of the colon by providing endoluminal views of the interior of the bowel in both forward and reverse direction. It is also able to detect extra-colonic abnormalities.

Limitations of this technique can be false negatives related to retained fluid, incomplete distension, and difficulty to demonstrate flat lesions [6]. The most important disadvantage of virtual colonoscopy, compared to endoscopic colonoscopy, is the lack of ability to perform biopsies and remove detected polyps under vision. Another less critical disadvantage, when VC is considered as a screening modality for colorectal cancer, is the exposure to ionizing radiation. However, VC is usually performed at a low radiation dose due to the high natural contrast between the colon wall and the endoluminal gas.

Molecular imaging

Most of diagnostic imaging is based on anatomic techniques. Recently radiological research has been focussing on complementing anatomical imaging with functional imaging. Molecular imaging in oncology encompasses new techniques and probes to study processes at the cellular and molecular levels. Molecular imaging methods can be used to stage patients, to predict response to treatments and to provide information on bio-distribution of targeted molecules. The use of specifically targeted contrast agents along with high-resolution imaging modalities are aimed at delivering earlier diagnoses and guiding the choice of new cancer-targeted drugs.

Depending on the properties of the tracers, various aspects of cancer cells including signal transduction, apoptosis and protein interactions can be targeted and visualised.

Several modalities can be used for molecular imaging; mainly single photon emission com-

puted tomography (SPECT), positron emission tomography (PET), magnetic resonance (MR) and computed tomography (CT).

For instance, the use of superparamagnetic iron oxide (SPIO) particles for cellular trafficking has enabled the visualisation of a single cancer cell by using a clinical MR [7].

Furthermore, positron-emitting analogues of chemotherapeutic agents, such as paclitaxel or fluorouracil, are under evaluation for assessment of a tumour's ability to sequester the radiolabelled analogue [8] and of the consequent advantage for the patient to undergo that specific chemotherapy.

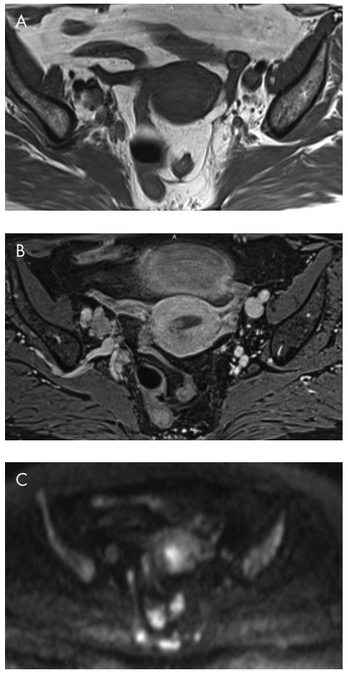


Fig. 1.11.4 *a,b,c. Pelvic MR study of an endometrial cancer patient. T1 pre-contrast (a) and post-contrast (b) images show an enlarged pathologic right obturator lymph node. Diffusion-Weighted Image (DWI) acquired with a 900 b-value (c) shows hyper-intensity of the lymph node due to low water-motion of molecules, thus confirming its positivity*

The use of radiolabelled somatostatin analogues for imaging has become the gold standard for staging of neuroendocrine tumours, because the somatostatin receptor is strongly over-expressed in most tumours, resulting in high tumour-to-background ratios. Based on this attitude, a peptide receptor radionuclide therapy with radiolabelled somatostatin analogues is emerging as a treatment modality for patients with unresectable, somatostatin-receptor-positive neuroendocrine tumours [9].

Future directions for imaging in oncology

Advances in different imaging modalities and the possibility of their integration are predicted to show better outcomes than the sum of their single parts. CT, MR, US and PET may guide high-precision radiotherapy techniques, such as intensity-modulated RT (IMRT) [10].

An additional synergy may come from fusion of PET/SPECT and CT, where the use of common detectors may be used to detect emission of gamma rays and transmission X-rays to provide better localisation of metabolic processes.

The traditional low-spatial resolution of PET has been improved with co-registration and fusion of PET and anatomical images either on a software basis with CT and MR, or with integrated hardware with CT (PET-CT) (Figure 1.11.6).

Whole-body MR imaging is under evaluation as a diagnostic tool in cancer staging as an alternative to scintigraphy, in staging the skeletal spread of disease and in assessing tumour burden [11].

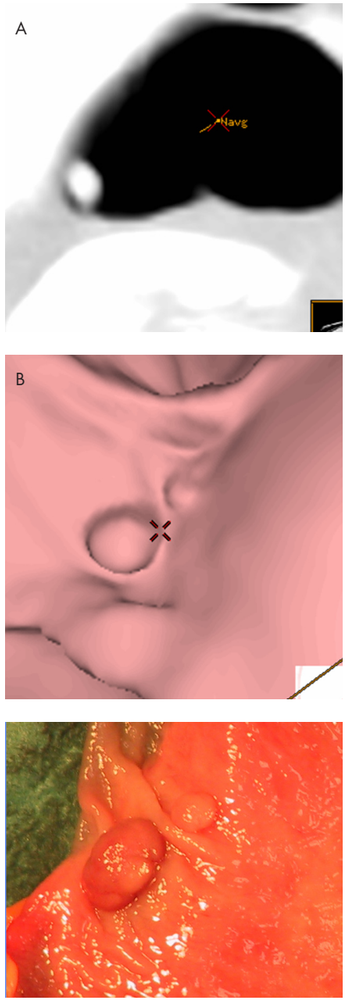


Fig. 1.11.5 *a,b,c. Virtual Colonoscopy (VC) can detect polyps as in the regular axial view (a) as in the volume view (b), and the visualization is comparable to endoscopic colonoscopy (c)*

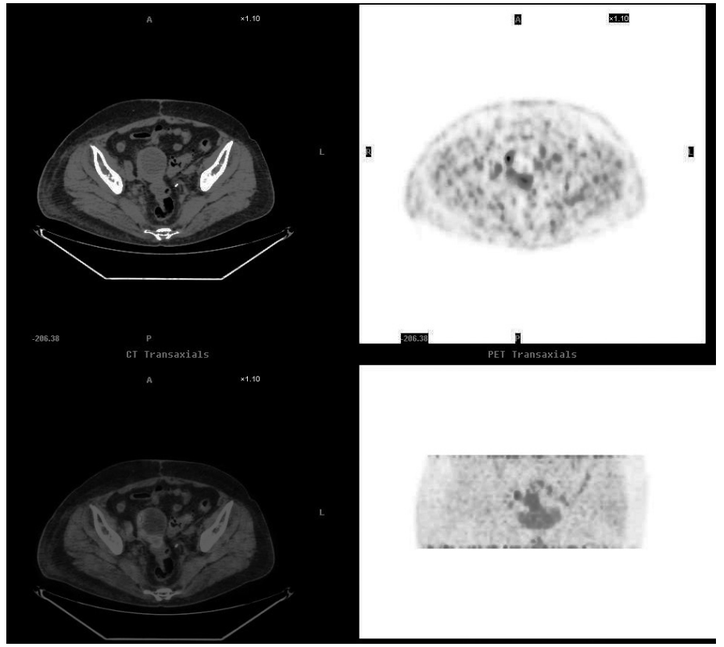


Fig. 1.11.6 *PET-CT integrative image showing a hypermetabolic lesion of the right uterine wall with a post-surgery diagnosis of endometrial adenocarcinoma*

Conclusions

Modern oncology relies on advances in cross-sectional imaging for diagnosis, staging and evaluation of treatment response. New molecular imaging techniques are promising to add information about tumour biology and function to the visualisation of disease by current imaging modalities. Imaging of anatomy and assessment of function are still in progress, and their advancements as single modalities and successive integration is heading for improving the ultimate management of cancer patients.

REFERENCES

1. Wilson SR, Burns PN (2003). The role of Microbubble-enhanced sonography in oncologic imaging. In: American Roentgen Ray Society. *Oncologic Imaging, Categorical Course Syllabus*. Leesburg, VA: ARRS.

2. Jaffe CC (2006). Measures of response: RECIST, WHO, and new alternatives. *J Clin Oncol* 24: 3245-3251.

3. Koh DM and Collins DJ (2007). Diffusion-weighted MRI in the body: applications and challenges in oncology. *AJR Am J Roentgenol* 188: 1622-1635.

4. Padhani AR and Husband JE (2001). Dynamic contrast-enhanced MRI studies in oncology with an emphasis on quantification, validation and human studies. *Clin Radiol* 56: 607-620.

5. Gambhir SS, Czernin J, Schwimmer J, et al. (2001). A tabulated summary of the FDG PET literature. *J Nucl Med* 42: 1S-93S.

6. Macari M, Bini EJ, Jacobs SL, et al. (2004). Colorectal polyps and cancers in asymptomatic average-risk patients: evaluation with CT colonography. *Radiology* 230: 629-636.

7. Harisinghani MG, Barentsz J, Hahn PF, et al. (2003). Noninvasive detection of clinically occult lymph-node metastases in prostate cancer. *N Engl J Med* 348: 2491-2499.

8. Gupta N, Price PM, Aboagye EO (2002). PET for in vivo pharmacokinetic and pharmacodynamic measurements. *Eur J Cancer* 38: 2094-2107.

9. Forrer F, Valkema R, Kwekkeboom DJ, et al. (2007). Neuroendocrine tumors. Peptide receptor radionuclide therapy. *Best Pract Res Clin Endocrinol Metab* 21: 111-129.

10. Lecchi M, Fossati P, Elisei F, et al. (2008). Current concepts on imaging in radiotherapy. *Eur J Nucl Med Mol Imaging* 35: 821-837.

11. Johnston C, Brennan S, Ford S, et al. (2006). Whole body MR imaging: applications in oncology. *Eur J Surg Oncol* 32: 239-246.

1.12 Breast Health Care Delivery in Low- and Middle-Income Countries

Summary

> Breast cancer is an international problem affecting countries at all economic levels, is the most common cancer among women, and worldwide is the most likely reason that a woman will die of cancer

> Despite the common misconception that breast cancer is predominantly a problem of wealthy countries, the majority of breast cancer deaths occur in low- and middle-income countries (LMCs)

> The breast cancer burden in LMCs will continue to increase in coming years on the basis of increasing life expectancy and shifting reproductive and behavioural patterns associated with heightened breast cancer risk

> The Breast Health Global Initiative (BHGI) has developed evidence-based, economically feasible, resource-sensitive guidelines for breast cancer early detection, diagnosis, treatment, and health care systems in LMCs

> BHGI guidelines can provide a framework for systematic, comprehensive improvement and are intended to assist ministers of health, policymakers, administrators, and institutions in prioritising resource allocation

> A systematic program of research to develop appropriate readiness assessment instruments and identify effective implementation strategies is needed to effectively apply BHGI guidelines in LMCs

Among women, breast cancer is the most common cause of cancer-related death worldwide, with case fatality rates highest in low- and middle-income countries (LMCs). Globally, breast cancer is the most common cancer among women, comprising 23% of all female cancers that are newly diagnosed in more than 1.1 million women each year [1]. Over 411 000 deaths result from breast cancer annually, accounting for over 1.6% of female deaths from all causes (Figure 1.12.1) [2]. Projecting to 2010, the annual global burden of new breast cancer cases will be 1.5 million, and an ever-increasing majority will be from LMCs [3]. Approximately 4.4 million women diagnosed with breast cancer in the last five years are currently alive, making breast cancer the single most prevalent cancer in the world [1]. Despite the common misconception that breast cancer is predominantly a problem of wealthy countries, the majority of breast cancer deaths in fact occur each year in developing rather than developed countries [3].

Health care disparities. Breast cancer already is an urgent public health problem in high-resource regions, and is becoming an increasingly urgent problem in low-resource regions, where incidence rates have been increasing by up to 5% per year [2,4]. In most LMCs, breast cancer incidence rates are increasing at a more rapid rate than in areas where incidence rates are already high. Global breast cancer incidence rates have increased by about 0.5% annually since 1990; by contrast, cancer registries in China are recording annual increases in incidence of 3–4% even in the absence of population-based breast cancer screening [1]. Among Asian countries with the most developed data registries, breast cancer rates in Japan, Singapore, and Korea have doubled or tripled in the past 40 years, and China's urban registries document 20–30% increases in the past decade alone [5]. In the urban areas of India, cervical cancer had the highest incidence among female cancers 15 years ago, but has now been overtaken by breast cancer as the most commonly diagnosed cancer among women [6]. Despite the younger age structure of most developing countries, breast cancer already accounts for about 45% of the incident cases and 54% of the annual deaths [3].

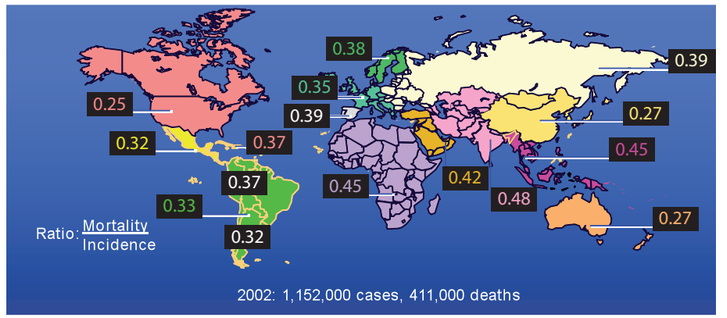
The breast cancer burden in LMCs will predictably continue to increase in coming years on the basis of 1) increasing life expectancy and 2) shifting reproductive and behavioural patterns associated with heightened breast cancer risk. Even conservatively assuming no change in underlying age-specific rates (Figure 2), there could be a nearly 50% increase in global incidence and mortality between 2002 and 2020 due to demographic change alone, with disproportionate shares of that increase occurring in the developing world–with increases of 55% in incidence and 58% in mortality in less than 20 years [3].

These statistics probably underestimate the actual rising breast cancer rates, since the few data available from LMCs reveal increases in breast cancer age-specific incidence and mortality rates, especially in recent birth cohorts. This is especially true among urban women and is probably due at least in part to the adoption of Western lifestyles that tend to promote decreased parity, delayed childbirth, decreased physical exercise, and dietary habits associated with earlier menarche, all of which have been associated with increasing rates of postmenopausal breast cancer [5,7,8].

Despite significant scientific advances in breast cancer management, most of the nations of the world face resource constraints that limit their capacity to improve early detection, diagnosis and treatment of the disease. In LMCs, worsened cancer survival is largely due to late stage at presentation, which leads to particularly poor outcome when coupled with limited diagnosis and treatment capacity [9]. Of the over 75 000 new cases presenting for treatment each year in India, between 50% and 70% have locally advanced (Stage III) or metastatic (Stage IV) breast cancer at diagnosis [10]. By comparison, 38% of European and 30% of American breast cancer cases were reported to be locally advanced at diagnosis in the EUROCARE study and SEER cancer registry between 1990 and 1992 [11].

Compounding the problem of late diagnosis, breast cancer case fatality rates are high because LMCs typically lack major components of health care infrastructure and resources necessary to implement improved methods for early detection, diagnosis and treatment of breast cancer [12,13]. Although most LMCs have not yet identified cancer as a priority health care issue, because infectious diseases are a predominant public health problem, cancer care will become an important health problem over the next decades as the control of communicable diseases improves and life expectancy rises [8].

Breast health care guidelines. Evidence-based guidelines outlining optimal approaches to breast cancer detection, diagnosis and treatment have been well-developed and disseminated in several high-resource countries [14,15]. These guidelines define optimal practice and therefore have limited utility in LMCs. Optimal practice guidelines may be inappropriate to apply in LMCs for numerous reasons, including inadequate personnel resources, limited healthcare infrastructure, lack of pharmaceuticals and cultural barriers. Hence, there is a need to develop clinical practice guidelines oriented towards LMCs, specifically considering and adapting to existing health care resources.



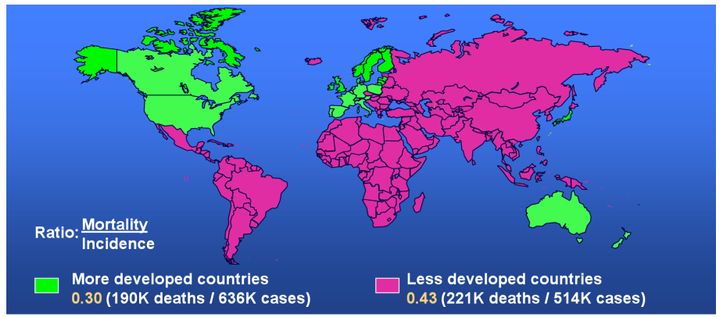


Fig. 1.12.1 *Estimated mortality-to-incidence ratios for breast cancer in 2002 by A) global geographic region of the world and B) more developed vs. less developed countries [3]. The majority of breast cancer cases are diagnosed in high-resource countries, but the majority of breast cancer deaths occur in the low- and medium-resource countries*

Co-sponsored by the Fred Hutchinson Cancer Research Center and Susan G. Komen for the Cure, the Breast Health Global Initiative (BHGI) strives to develop evidence-based, economically feasible and culturally appropriate guidelines that can be used in nations with limited health care resources to improve breast cancer outcomes. The BHGI held three Global Summits to address ***health care disparities*** (Seattle 2002), [16] ***evidence-based resource allocation*** (Bethesda 2005) [17] and ***guideline implementation*** (Budapest 2007) [18] as related to breast cancer in LMCs. Modelled after the approach of the National Comprehensive Cancer Network (NCCN), BHGI developed and applied an evidence-based consensus panel process now formally endorsed by the Institute of Medicine [19] to create resource-sensitive guidelines for breast cancer early detection, [20,21,22] diagnosis, [23,24,25] treatment [26,27,28] and health care systems, [29, 30] as related to breast care in LMCs. The BHGI guidelines are intended to assist ministers of health, policymakers, administrators and institutions in prioritising resource allocation as breast cancer treatment programs are implemented and developed in their resource-constrained countries.

Guideline dissemination and implementation (D&I) research. The dominant paradigm even now in the medical community is that good research and publication should be sufficient to ensure the translation of scientific findings into general practice [31]. Unfortunately, a landmark Institute of Medicine (IOM) report from 2001 clearly identified the failure of much scientific innovation to be translated into practice [32,33]. More recently, Rubenstein and Pugh separated the IOM's second translational block–clinical research to practice–into two parts: 1) clinical research to guidelines and 2) guidelines to practice [34]. D&I researchers maintain that the process is complex and have begun to identify factors and processes critical to the adoption of new technologies and practices [35]. While there has already been some D&I work on assessing readiness for change, it has usually focused on just one component,

such as providers or health units, or has focused on intention without considering self-efficacy or environment. As a conclusion in her extensive review of the implementation literature, Greenhalgh notes the need for more research on system readiness for innovation and for more studies evaluating implementation of specific interventions [36].

A review of available information strongly suggests a crucial role for research in applying the experience and knowledge of high income societies to the challenges of women and breast cancer throughout the world. A recent survey of oncology experts from Latin American countries found that 94% of the surveyed experts consider clinical-epidemiologic research development on breast cancer insufficient in their country [37]. The main reasons identified were insufficient economic retribution and lack of available time.

Very little research on guideline implementation has been done in LMCs. It is necessary to see whether the basic frameworks and instruments being described in high-income countries apply in these very different environments and what adaptation is needed to make them both valid and feasible. A systematic program of research to develop appropriate readiness assessment instruments and identify effective implementation strategies is now needed in a variety of LMCs. As the adoption, implementation and maintenance of the new evidence-based principles embodied in the BHGI guidelines progresses, it is critical that careful evaluation be incorporated in the efforts to ensure that lessons about effectiveness and efficiency are captured. It is precisely because resources are scarce in these countries that it is even more imperative for LMCs to adopt effective practices as quickly as possible, and that implementation approaches are designed with limited resources in mind [31].

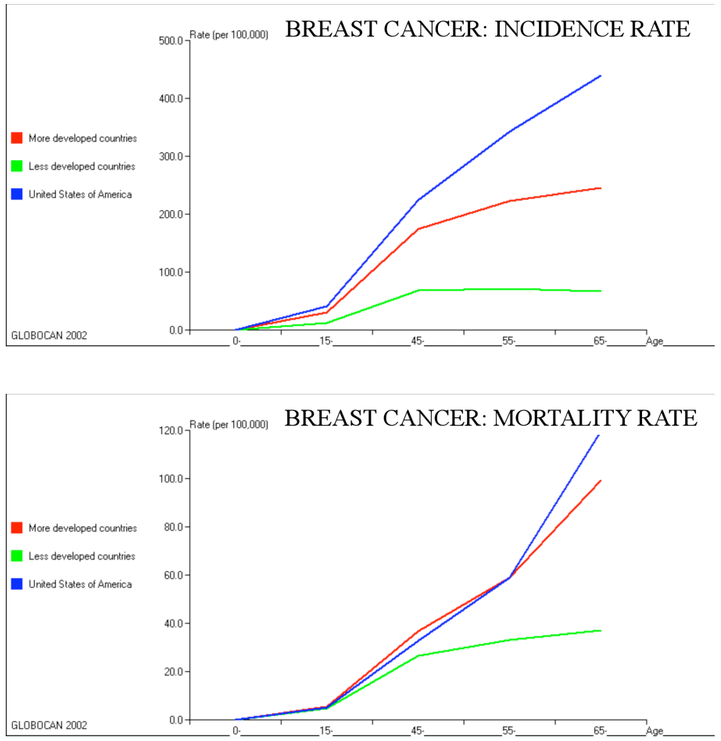


Fig. 1.12.2 *Age-specific breast cancer A) incidence and B) mortality in the United States, more developed countries and less developed countries [3]. Differences in breast cancer incidence between more developed and less developed countries are greatest in older (postmenopausal) women, but breast cancer mortality is very similar for women under age 50.*

REFERENCES

1. Parkin DM, Bray F, Ferlay J, et al. (2005). Global cancer statistics, 2002. *CA Cancer J Clin* 55: 74-108.

2. Stewart BW, Kleihues P (2003). *World Cancer Report*. Lyon, France: International Agency for Research on Cancer.

3. Ferlay J, Bray F, Pisani P, et al., (2004). GLOBOCAN 2002: Cancer Incidence, Mortality and Prevalence Worldwide. *IARC CancerBase* No. 5 Version 2.0. Lyon, France: International Agency for Research on Cancer. Available from: http://www-dep.iarc.fr Date Accessed: November 15, 2008

4. IARC (2002). *IARC Handbooks of Cancer Prevention, Volume 7, Breast cancer screening*. Lyon, France: International Agency for Research on Cancer.

5. Porter P (2008). "Westernizing" women's risks? Breast cancer in lower-income countries. *N Engl J Med* 358: 213-216.

6. Pal SK and Mittal B (2004). Improving cancer care in India: prospects and challenges. *Asian Pac J Cancer Prev* 5: 226-228.

7. Bray F, McCarron P, Parkin DM (2004). The changing global patterns of female breast cancer incidence and mortality. *Breast Cancer Res* 6: 229-239.

8. Parkin DM and Fernandez LM (2006). Use of statistics to assess the global burden of breast cancer. *Breast J* 12 Suppl 1: S70-S80.

9. Hisham AN and Yip CH (2003). Spectrum of breast cancer in Malaysian women: overview. *World J Surg* 27: 921-923.

10. Chopra R (2001). The Indian scene. *J Clin Oncol* 19: 106S-111S.

11. Sant M, Allemani C, Berrino F, et al. (2004). Breast carcinoma survival in Europe and the United States. *Cancer* 100: 715-722.

12. Greenlee RT, Murray T, Bolden S, et al. (2000). Cancer statistics, 2000. *CA Cancer J Clin* 50: 7-33.

13. Zotov V and Shyyan R (2003). Introduction of breast cancer screening in Chernihiv Oblast in the Ukraine: report of a PATH Breast Cancer Assistance Program experience. *Breast J* 9 Suppl 2: S75-S80.

14. Carlson LE and Bultz BD (2004). Efficacy and medical cost offset of psychosocial interventions in cancer care: making the case for economic analyses. *Psychooncology* 13: 837-849.

15. Goldhirsch A, Wood WC, Gelber RD et al. (2007). Progress and promise: highlights of the international expert consensus on the primary therapy of early breast cancer 2007. *Ann Oncol* 18(7):1133-44.

16. Anderson BO, Braun S, Carlson RW, et al. (2003). Overview of breast health care guidelines for countries with limited resources. *Breast J* 9 Suppl 2: S42-S50.

17. Anderson BO, Shyyan R, Eniu A, et al. (2006). Breast cancer in limited-resource countries: an overview of the Breast Health Global Initiative 2005 guidelines. *Breast J* 12 Suppl 1: S3-15.

18. Anderson BO, Yip CH, Smith RA, et al. (2008). Guideline implementation for breast healthcare in low-income and middle-income countries: Overview of the Breast Health Global Initiative Global Summit 2007. *Cancer* 113(8 suppl):2221-43.

19. Summary (2007). In: Sloan FA, Gelband H, eds., *Cancer control opportunities in low- and middle-income countries*. Washington, DC: National Academies Press 1-16.

20. Smith RA, Caleffi M, Albert US, et al. (2006). Breast cancer in limited-resource countries: early detection and access to care. *Breast J* 12 Suppl 1: S16-S26.

21. Anderson BO, Braun S, Lim S, et al. (2003). Early detection of breast cancer in countries with limited resources. *Breast J* 9 Suppl 2: S51-S59.

22 Yip CH, Smith RA, Anderson BO, et al. (2008). Breast health guideline implementation in low- and middle-income countries (LMCs): Early detection resource allocation. *Cancer* 113(8 suppl):2244-56.

23. Vargas HI, Anderson BO, Chopra R, et al. (2003). Diagnosis of breast cancer in countries with limited resources. *Breast J* 9 Suppl 2: S60-S66.

24. Shyyan R, Masood S, Badwe RA, et al. (2006). Breast cancer in limited-resource countries: diagnosis and pathology. *Breast J* 12 Suppl 1: S27-S37.

25. Shyyan R, Sener SF, Anderson BO, et al. (2008)Guideline implementation for breast healthcare in low-income and middle-income countries: Diagnosis resource allocation. *Cancer* 113(8 suppl):2257-68.

26. Eniu A, Carlson RW, Aziz Z, et al. (2006). Breast cancer in limited-resource countries: treatment and allocation of resources. *Breast J* 12 Suppl 1: S38-S53.

27. Carlson RW, Anderson BO, Burstein HJ, et al. (2007). Invasive breast cancer. *J Natl Compr Canc Netw* 5(3):246-312.

28. Eniu A, Carlson RW, El Saghir NS, et al. (2008) Breast health guideline implementation in low- and middle-income countries (LMCs): Treatment resource allocation. *Cancer* 113(8 suppl):2269-81.

29. Anderson BO, Yip CH, Ramsey SD, et al. (2006). Breast cancer in limited-resource countries: health care systems and public policy. *Breast J* 12 Suppl 1: S54-S69.

30. Harford J, Azavedo E, Fischietto M (2008). Breast health guideline implementation in low- and middle-income countries (LMCs): Breast healthcare program resource allocation. *Cancer* 113(8 suppl):2282-96.

31. McCannon CJ, Berwick DM, Massoud MR (2007). The science of large-scale change in global health. *JAMA* 298: 1937-1939.

32. IOM committee calls for complete revamping of health care system to achieve better quality (2001). *Qual Lett Healthc Lead* 13: 14-15.

33. Committee on Quality of Health Care in America. Institute of Medicine (2001). *Crossing the quality chasm: A new health System for the 21st century*. Washington, D.C.: National Academies Press.

34. Rubenstein LV and Pugh J (2006). Strategies for promoting organizational and practice change by advancing implementation research. *J Gen Intern Med* 21 Suppl 2: S58-S64.

35. Grimshaw J, Eccles M, Thomas R, et al. (2006). Toward evidence-based quality improvement. Evidence (and its limitations) of the effectiveness of guideline dissemination and implementation strategies 1966-1998. *J Gen Intern Med* 21 Suppl 2: S14-S20.

36. Greenhalgh T, Robert G, Macfarlane F, et al. (2004). Diffusion of innovations in service organizations: systematic review and recommendations. *Milbank Q* 82: 581-629.

37. Cazap E, Buzaid A, Garbino C, et al. (2008). Breast Cancer in Latin America: Results of the Latin American and Caribbean Society of Medical Oncology/Breast Cancer Research Foundation Expert Survey. *Cancer* 113(8 suppl):2359-65.

CANCER CONTROL IN LATIN AMERICA AND THE CARIBBEAN:
Pan American Health Organization (PAHO)

In Latin America and the Caribbean, cancer is the 2nd leading cause of death. The most common causes of cancer deaths are lung, stomach and prostate cancer among men, and cervix, breast and stomach cancer among women. Uruguay, Argentina, Colombia, Peru and Barbados are among the countries in the Region experiencing the greatest cancer burden.

The public health response to cancer has been varied, given that most countries in this Region are experiencing an epidemiological transition and facing the double burden of chronic diseases and infectious diseases. In a 2006 survey by PAHO, 75% of responding countries reported having national cancer control programs, yet only half of the countries reported having an acceptable degree of implementation of their programs. All countries report having a cervical cancer screening program; however, screening coverage is very low, as more than half of the countries reported 25% or less coverage. Cancer treatment centres exist in all countries, with the exception of several countries in the Caribbean, although access is far lower than in the industrialised countries. Radiotherapy treatment capacity is quite low in the region, with a reported number of radiation oncologists of 1.6 per million population and high-dose teletherapy units of 1.4 per million population, compared to 9 and 6.4 respectively in industrialised countries. Apart from being scarce, access to treatment services is inequitable, since most of these services are provided in health centres located in the largest cities, meaning a large proportion of the rural population has no access to them. Their high cost also makes them inaccessible to poor urban populations.

The common problems reported by all countries are:

- the advanced stages of diagnosis of cancer and the need for early detection programs;
- the need to improve access, availability and quality of cancer treatment centres, particularly outside of big cities;
- limited access to affordable cancer drugs;
- weak surveillance and cancer registry systems;
- inadequate opportunities for training and continuing education; and
- the need to increase the public health priority and resources for cancer in the public health agenda.

PAHO has been providing technical cooperation to countries in Latin America and the Caribbean, and responding to these problems and the needs expressed by the Ministries of Health. The main areas of cooperation have been in creating comprehensive national cancer control plans, cervical cancer prevention, tobacco control and radiotherapy services. As part of the Alliance for Cervical Cancer Prevention, PAHO has been assisting countries in improving the quality and coverage of screening programs and testing alternative screening approaches. The lessons learned from this work have culminated in the development of a Regional Strategy for Cervical Cancer Prevention and Control, which provides policy and technical guidance for comprehensive programs, and is anticipated to be presented to the 2008 PAHO Directing Council. In the subregion of Central America, the Ministers of Health have called for the creation of a sub-regional cancer plan, which is being coordinated by PAHO through a participatory process with the Ministries of Health. This subregional plan will elevate the political and technical commitments for national cancer programmes, as well as solidify a sub-regional response for common issues on cancer prevention, early detection, treatment and palliative care. PAHO continues to evaluate and improve the quality of radiation therapy through its longstanding radiological health program.

With an aging population and corresponding rise in cancer burden in Latin America and the Caribbean, health systems will need to be equipped to control cancer. The challenges remain in having adequate resources, applying current and new knowledge and sustaining the political will to achieve effective cancer control.

website: www.paho.org

2

Etiology of Cancer

2.1 Identifying Human Carcinogens

Summary

- Cancer prevention begins with identifying known and suspected human carcinogens
- Carcinogen identification involves the scientific evaluation of epidemiological studies, animal bioassays, and mechanistic and other relevant data
- Carcinogen identification is an important activity at IARC (the *IARC Monographs*) and at several national health agencies
- National and international health agencies use carcinogen identifications to guide their actions to prevent human exposure to known or suspected human carcinogens
- Carcinogen identification programmes should avoid real or apparent conflicts of interests in order to maintain public confidence in the integrity of their evaluations

The first step in cancer prevention is to identify the causes of human cancer. Carcinogen identification programmes at IARC and several national health agencies provide a scientific basis for government actions and private efforts to control cancer by preventing exposure to known and suspected carcinogens. Individuals, too, can use this information to make more informed choices to reduce their exposure to cancer-causing agents.

Carcinogen identification is the first step in the *risk assessment* of carcinogens. This first step is called *hazard identification* and can be followed by *dose-response assessment* to characterise the relation between the dose of a carcinogen and the incidence of tumours, *exposure assessment* to determine the extent of human exposure to the carcinogen, and *risk characterisation* to describe the nature and magnitude of the human cancer risk. Risk assessment is followed by *risk management*, which is the process of weighing policy alternatives and selecting the most appropriate action [1,2].

Under this paradigm, a cancer *hazard* is an agent that is capable of causing cancer while a cancer *risk* is an estimate of the incidence of cancer expected from exposure to a cancer hazard. Risk depends on both the existence of a hazard and exposure to that hazard. A cancer hazard exists even when current exposures suggest little or no cancer risk, because accidental or unanticipated exposures that are difficult to foresee may pose a risk for cancer.

Studies used to identify carcinogens

The term "carcinogen" generally refers to an agent, mixture or exposure that can increase the age-specific incidence of human cancer. Carcinogen identification is an activity grounded in the scientific evaluation of the results of human epidemiological studies, long-term bioassays in experimental animals, and mechanistic and other relevant data. Each source of data has a distinct role in the overall assessment.

Epidemiological studies provide information about the responses of humans exposed to potential carcinogens. Among these, cohort and case-control studies are especially useful for identifying causal relationships. Criteria for assessing the adequacy of epidemiological studies include selection of exposed and reference groups, characterisation of exposure, identification of confounding factors and possible bias, duration of follow-up in view of cancer's latent period, ascertainment of causes of disease and death, and statistical power to detect specific effects. In evaluating a body of epidemiological evidence, the key scientific questions are whether a causal interpretation is credible and whether chance, bias and confounding can be ruled out with reasonable confidence. Epidemiologists have found useful guidance in a set of factors known as the Hill criteria [3]. These assess:

- Consistency of the observed association
- Strength of the observed association
- Specificity of the observed association
- Temporal relationship of the observed association
- Biological gradient (exposure-response relationship)
- Biological plausibility
- Coherence
- Experimental evidence (from human populations)
- Analogy

There are, however, limitations to what epidemiology can tell us. For example, it is often difficult to attribute causality to a single factor or to rule out small risks below a study's level of sensitivity. In addition, cancer's latent period implies that many years of preventable human exposure could pass before informative epidemiological studies become available.

Some carcinogen identification programmes

International Agency for Research on Cancer *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans* http://monographs.iarc.fr/
U.S. National Toxicology Program Report on Carcinogens http://ntp.niehs.nih.gov/
U.S. Environmental Protection Agency Integrated Risk Information System (IRIS) http://cfpub.epa.gov/ncea/iris/
German Research Foundation (Deutsche Forschungsgemeinschaft, DFG) Maximum Allowable Concentrations (Maximale Arbeitsplatzkonzentrationen, MAK) and Biological Tolerance Values (Biologische Arbeitsstofftoleranzwerte, BAT) http://www.dfg.de/
California Environmental Protection Agency List of chemicals known to the State to cause cancer http://www.oehha.ca.gov/prop65.html

For these reasons, *long-term studies in experimental animals* generally provide the means of assessing potential risks to humans. In these studies, exposures can be tightly controlled and confounding factors can be excluded. It is also possible to examine all organs and tissues that may be potential sites of carcinogenic activity. The use of animal studies is based on the physiological similarity that exists across mammalian species and on the plausible scientific assumption that agents causing cancer in animals will have similar effects in humans [4,5]. In evaluating a body of cancer studies in experimental animals, the key scientific question is whether the results can plausibly be generalised to humans, as indicated by replication in independent studies, preferably in different experimental systems and species.

Mechanistic studies and other relevant data are used to assess the correspondence of response between animals and humans. Toxicokinetic studies allow cross-species comparisons of absorption, distribution, metabolism, and elimination. Mechanistic studies attempt to elucidate the multiple cellular processes involved in tumour development. This has the potential to improve the analysis of studies in both humans and experimental animals by giving insight into the biology of cancer and helping to identify susceptible individuals and developmental stages.

In evaluating a body of mechanistic and other relevant data, the key scientific questions are whether the mechanistic data are strong and whether the mechanisms leading to cancer in experimental animals could also operate in humans. Strong support can be obtained from studies that challenge a hypothesised mechanism experimentally, by demonstrating that the suppression of a key mechanistic step leads to the suppression of tumour development. It is important to consider that multiple mechanisms may contribute to tumour development, that different mechanisms may operate in different dose ranges, that separate mechanisms may operate in humans and experimental animals, and that a unique mechanism may operate in a susceptible group. It is also important to keep in mind that an uneven level of experimental support for different mechanisms may reflect that disproportionate resources have been focused on investigating one favoured mechanistic hypothesis [4].

The IARC Monographs

The *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans* are a series of scientific reviews that identify agents, mixtures or exposures that can increase the risk for cancer in humans. Each *Monograph* includes a critical review of the pertinent scientific literature and an evaluation of the weight of the evidence that the agent can alter the risk for cancer in humans.

The critical reviews and evaluations are developed by an interdisciplinary group of experts who conducted the original scientific research. The experts are selected on the basis of knowledge, experience, and absence of real or apparent conflicts of interests. The *IARC Monographs* are a worldwide scientific endeavour that has involved more than 1000 scientists from more than 50 countries.

IARC Monographs are developed during an 8-day meeting whose objectives are peer review and consensus. Before the meeting, each expert writes a portion of the critical review related to his or her area of expertise. At the meeting, four subgroups (exposure data, cancer in humans, cancer in experimental animals, and mechanistic and other relevant data) meet to review this text and develop a consensus subgroup draft.

When the subgroup of epidemiologists has reviewed the pertinent studies of cancer in humans, they characterise this evidence with a set of standard descriptors that span a range of levels of evidence [4]:

Sufficient evidence of carcinogenicity: A causal interpretation has been established, and chance, bias, and confounding could be ruled out with reasonable confidence.

Limited evidence of carcinogenicity: A causal interpretation is credible, but chance, bias, or confounding could not be ruled out with reasonable confidence.

Inadequate evidence of carcinogenicity: The available studies permit no conclusion regarding the presence or absence of a causal association.

Evidence suggesting lack of carcinogenicity: Several adequate studies are mutually consistent in not showing a positive association at any level of exposure.

Similarly, a subgroup of toxicologists and pathologists reviews the pertinent studies of cancer in experimental animals, then characterises that evidence using similar standard descriptors [4]:

Sufficient evidence of carcinogenicity: A causal interpretation has been established through either multiple positive results or a single, highly unusual result.

Limited evidence of carcinogenicity: The data suggest a carcinogenic effect but positive results come from a single study or there are limitations in the study design or results.

Inadequate evidence of carcinogenicity: The available studies permit no conclusion regarding the presence or absence of a causal association.

Evidence suggesting lack of carcinogenicity: Adequate studies in at least two species show that the agent is not carcinogenic.

Fig. 2.1.1 *The four heads of the IARC Monographs Programme (Harry Vainio, Vincent Cogliano, Lorenzo Tomatis and Jerry Rice)*

At the same time, another subgroup of experimental scientists reviews the mechanistic and other relevant data to characterise this evidence as weak, moderate or strong and to determine whether the mechanisms leading to cancer in experimental animals could also operate in humans. Then the entire Working Group meets in plenary session to review the work of the subgroups and to discuss and develop an overall evaluation of the weight of the evidence. Based on the epidemiological evidence, the evidence in experimental animals, and the mechanistic and other relevant data, the Working Group classifies each agent into one of the following groups [4]:

- Group 1: The agent is ***carcinogenic to humans***.
- Group 2A: The agent is ***probably carcinogenic to humans***.
- Group 2B: The agent is ***possibly carcinogenic to humans***.
- Group 3: The agent is ***not classifiable as to its carcinogenicity to humans***.
- Group 4: The agent is ***probably not carcinogenic to humans***.

The classification of an agent is a matter of scientific judgement. The use of a standard set of descriptors allows the *IARC Monographs* to provide evaluations for a wide variety of carcinogenic agents using comparable terms. These descriptors refer only to the strength of the evidence that an exposure is carcinogenic and not to its carcinogenic potency. The graded nature of the descriptors *(sufficient evidence, limited evidence, . . . ; carcinogenic, probably carcinogenic, . . .)* communicates the level of credibility of a potential cancer hazard in clear terms that can be understood by people who are not cancer specialists.

Similar terminology has been adopted by several national health agencies that identify carcinogens.

After the meeting IARC scientists review the final draft for accuracy and clarity before it is published. In order to communicate the outcomes of these Monograph meetings to the scientific community as quickly as possible, summaries of each meeting are now published in the scientific literature within 6–8 weeks after the meeting [6-18].

The scope of the *IARC Monographs* has expanded beyond an initial focus on single chemicals to also include complex mixtures, occupations, physical and biological agents, and lifestyle factors. As the world cancer burden has shifted from high-income to low- and moderate-income countries, the *IARC Monographs have* also included more agents that are of particular interest in the latter areas. Since the *IARC Monographs* began in 1971, more than 900 agents have been evaluated and more than 400 of these have been classified as *carcinogenic to humans, probably carcinogenic to humans,* or *possibly carcinogenic to humans.*

National and international health agencies use the *IARC Monographs* as a source of scientific information and as support for their actions to reduce or prevent human exposure to known or suspected carcinogens. Decisions about reducing exposure to suspected carcinogens are sometimes controversial, in part because the available data often cannot identify human carcinogens with certainty and because the costs and the benefits of exposure reduction go to different segments of society. For this reason, it is important that carcinogen identification programmes implement strong measures to avoid real or apparent conflicts of interests so that the public can have utmost confidence in the integrity of these classifications [19,20].

Some examples of carcinogenic agents

	Some agents that are *carcinogenic to humans*	**Some agents that are *probably carcinogenic to humans***
Chemicals	Benzene, 1,3-butadiene, formaldehyde, vinyl chloride	Trichloroethylene, styrene oxide
Complex mixtures	Aflatoxins, coal-tar, soots	PCBs, creosote, emissions from high-temperature frying
Occupations	Painting, chimney sweeping, coal gasification, coke production	Petroleum refining, hairdressing
Metals	Arsenic and compounds, beryllium and compounds, cadmium and compounds, chromium [VI]	Inorganic lead compounds, cobalt metal with tungsten carbide
Particles and fibres	Asbestos, crystalline silica, wood dust	Diesel engine exhaust
Pharmaceuticals	DES, estrogen-progestogen menopausal therapy, tamoxifen, phenacetin	Androgenic (anabolic) steroids, chloramphenicol
Radiation	Radon, solar radiation, X- and Gamma-radiation	
Biological agents	Hepatitis B and C, human papillomaviruses (type 16 and several others), *Helicobacter pylori*	
Lifestyle factors	Tobacco smoke (active and passive smoking), areca nut, alcoholic beverages, household combustion of coal	Shiftwork that involves circadian disruption, household combustion of biomass fuel (primarily wood)

Table 2.1.1 *Some examples of carcinogenic agents*
Source: IARC Monographs, http://monographs.iarc.fr/

Dr. Lorenzo Tomatis and the IARC Monographs Programme

The staff of the International Agency for Research on Cancer (IARC) were saddened to hear of the death on 21st September 2007 of Dr. Lorenzo Tomatis, the second Director of IARC and the founder of the *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*. After devoting more than 26 years to the IARC, the last 12 years as director, Lorenzo Tomatis retired in December 1993. Throughout these years he was the tireless embodiment of IARC's mission: to conduct and coordinate research at an international level aimed at cancer prevention through the application of scientific knowledge of the causes of cancer.

Dr. Tomatis joined IARC in November 1967 at the age of 38. He arrived to create and establish the Unit of Chemical Carcinogenesis, and spent his career there developing the field in which he had already established his reputation. One of Tomatis's major contributions to IARC and to global public health was to establish the evidence of animal carcinogenicity in long-term experiments as a valid criterion for evaluating possible carcinogenic risks to humans, alongside or, even more importantly in the absence of, epidemiological evidence. Tomatis worked to establish this balanced perspective in which human epidemiology and experimental results are both seen as essential to the identification of human risks.
The overall objective of IARC is to prevent human cancer, and identifying environmental carcinogens as the prerequisite for their removal or reduction is a major step toward that goal. In 1969, Tomatis initiated what has become in the eyes of many IARC's most important contribution to cancer prevention, *the IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*. This programme has won an international reputation for its scientific validity, impartiality and integrity, and for its contribution to preventive measures for the benefit of public health.
The first Working Group of internationally recognised experts met in Lyon in December 1970 to prepare the scientific criteria that would be used in the Monographs and to make preliminary evaluations of the data on 5 substances. These 5 evaluations, together with those of 14 more substances, were considered by a Working Group that met in December 1971, and made up the first volume of the *IARC Monographs* Series, published in 1972 and covering organic, inorganic and natural products.
Since then, with the scientific collaboration and financial support of the US National Cancer Institute, the U.S. National Institute of Environmental Health Sciences and the Commission of the European Communities, among others, the programme has undergone considerable expansion. To date, 91 volumes of the Monographs have been published, with more currently in press. It is perhaps for his continuous efforts in publishing the Monographs series that Lorenzo Tomatis was most highly regarded, and for which he will be long remembered by the scientific community.

REFERENCES

1. National Research Council (U.S.) (1983). *Risk assessment in the federal government: managing the process*. Washington, D.C.: National Academy Press.
2. National Research Council (U.S.) (1994). *Science and judgement in risk assessment*. Washington, D.C.: National Academy Press.
3. Hill AB (1965). The environment and disease: association or causation? *Proc R Soc Med* 58: 295-300.
4. IARC. *Preamble to the IARC Monographs*. Available from: http://monographs.iarc.fr Date Accessed: October 12, 2008.
5. National Toxicology Program (2004). *11th Report on Carcinogens (RoC)*. Washington, D.C.: U.S. Department of Health and Human Services.
6. Cogliano V, Grosse Y, Baan R, et al. (2004). Advice on formaldehyde and glycol ethers. *Lancet Oncol* 5: 528.
7. Cogliano V, Straif K, Baan R, et al. (2004). Smokeless tobacco and tobacco-related nitrosamines. *Lancet Oncol* 5: 708.
8. Cogliano V, Baan R, Straif K, et al. (2005). Carcinogenicity of human papillomaviruses. *Lancet Oncol* 6: 204.
9. Cogliano V, Grosse Y, Baan R, et al. (2005). Carcinogenicity of combined oestrogen-progestagen contraceptives and menopausal treatment. *Lancet Oncol* 6: 552-553.
10. Straif K, Baan R, Grosse Y, et al. (2005). Carcinogenicity of polycyclic aromatic hydrocarbons. *Lancet Oncol* 6: 931-932.
11. Baan R, Straif K, Grosse Y, et al. (2006). Carcinogenicity of carbon black, titanium dioxide, and talc. *Lancet Oncol* 7: 295-296.
12. Grosse Y, Baan R, Straif K, et al. (2006). Carcinogenicity of nitrate, nitrite, and cyanobacterial peptide toxins. *Lancet Oncol* 7: 628-629.
13. Straif K, Baan R, Grosse Y, et al. (2006). Carcinogenicity of household solid fuel combustion and of high-temperature frying. *Lancet Oncol* 7: 977-978.
14. Baan R, Straif K, Grosse Y, et al. (2007). Carcinogenicity of alcoholic beverages. *Lancet Oncol* 8: 292-293.
15. Grosse Y, Baan R, Straif K, et al. (2007). Carcinogenicity of 1,3-butadiene, ethylene oxide, vinyl chloride, vinyl fluoride, and vinyl bromide. *Lancet Oncol* 8: 679-680.
16. Straif K, Baan R, Grosse Y, et al. (2007). Carcinogenicity of shift-work, painting, and fire-fighting. *Lancet Oncol* 8: 1065-1066.
17. Baan R, Straif K, Grosse Y, et al. (2008). Carcinogenicity of some aromatic amines, organic dyes, and related exposures. *Lancet Oncol* 9: 322-323.
18. Cogliano V, Baan R, Straif K, et al. (2008). Future priorities for IARC Monographs. *Lancet Oncol* 9: 708.
19. Cogliano V, Baan R, Straif K, et al. (2004). The science and practice of carcinogen identification and evaluation. *Environ Health Perspect* 112: 1269-1274.
20. Cogliano V, Baan R, Straif K, et al. (2005). Transparency in IARC Monographs. *Lancet Oncol* 6: 747.

2.2 Tobacco Smoking

Summary

- Tobacco smoking causes 13 different cancers: lung, oral cavity, nasal cavity and nasal sinuses, pharynx, larynx, oesophagus, stomach, pancreas, liver, urinary bladder, kidney, uterine cervix and myeloid leukaemia. In high-resource countries, tobacco smoking accounts for approximately 30% of all human cancers
- Lung cancer has the highest smoking attributable fraction among all cancers induced by smoking. Duration of smoking is the strongest determinant of excess lung cancer risk in smokers, with risk increasing proportionally with the number of cigarettes smoked. Tobacco smoking raises the excess risk of all histological types of lung cancer
- Pooled estimates from a recent meta-analysis of smoking and cancer shows, persuasively, very similar risks of cancer associated with smoking in males and females
- Tobacco smoke is the most common source of carcinogens to human, including polycyclic aromatic hydrocarbons (i.e. benzo[a] pyrene) and tobacco specific nitrosamines (i.e. NNK). The chronic presentation of carcinogens to the airway epithelial cells, through sustained smoking, can lead to molecular lesions which, in the presence of reduced metabolic detoxification, can diminish repair capability, overwhelming cellular defences and leading to lung cancer
- About 1.3 billion people smoke globally, making tobacco a major avoidable cause of disease and mortality worldwide. Approximately 150 million deaths from tobacco use are projected worldwide for the period 2000–2024 if current smoking patterns persist; this number of deaths will not be much reduced unless a sizeable proportion of adults who are established smokers quit

Tobacco-related cancer burden

Tobacco smoking is the major cause of cancer in humans, inducing cancer of the lung, oral cavity, nasal cavity and nasal sinuses, pharynx, larynx, oesophagus, stomach, pancreas, liver, urinary bladder, kidney and uterine cervix, and myeloid leukaemia [1]. In addition, involuntary or secondhand smoke (SHS) causes lung cancer [1,2]. Furthermore, the detrimental effects of tobacco use, smoking in particular, are seen in the causation of other important chronic conditions: cardiovascular disease, cerebrovascular disease, peripheral vascular disorders, abdominal aortic aneurysm and chronic obstructive pulmonary diseases [3].

In the year 2000, 1.42 (95% CI 1.27–1.57) million cancer deaths in adults (≥30 years) were reported worldwide due to smoking [4]. This global estimate translated into a proportion of cancer mortality attributable to smoking of 21%, representing 32% and 8% of adult cancer mortality in males and females respectively. In high-resource countries, tobacco smoking has been estimated to cause approximately 30% of all human cancers [5-7]. Table 2.2.1 shows the regional distribution of cancer mortality attributable to smoking, indicating higher values in more developed regions, where widespread consumption of cigarettes had an earlier start in the 20th century. A pronounced disparity in cancer mortality attributable to smoking is seen between males and females, reflecting dissimilar incidence rates caused by the fact that in most countries women took up smoking a few decades after men and never reached their consumption levels.

Lung cancer has the highest smoking-attributable fraction among all neoplasms induced by tobacco smoking, and although not all cancer at this site is caused by smoking, a glance at the lung cancer incidence and mortality rates by country and region reveals the cumulative hazard of smoking and the underlying dimension of the tobacco epidemic in those areas of the world. Table 2.2.2 displays countries and populations with the highest and lowest age-standardised lung cancer incidence rates in males and females by continent. Age-standardised lung cancer incidence and mortality rates (per 100 000), on average, are higher in developed (54.9 and 47.6 respectively) than less-developed regions (25.9 and 22.9 respectively) reflecting past uptake and cessation of smoking in those populations [8]. Countries in these regions are at different stages of the tobacco epidemic and its subsequent effect on lung cancer mortality [9](Figure 2.2.1). In many medium- and low-resource countries, the burden of tobacco-related cancer is lower, given the relatively recent start of the smoking epidemic, which will result in a greater number of cancers in the future. In several low/medium-resource countries, however, the epidemic of tobacco-related lung cancer has already reached its maturity: for example, Kazakhstan with an incidence rate of 77.4 and a mortality rate of 66.8, Armenia (58.9 and 50. 4 respectively) and the Philippines (50. 2 and 46.6 respectively) in South-Central Asia and South

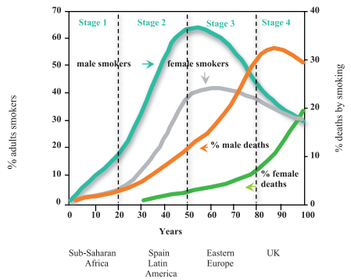


Fig. 2.2.1 *Stages of the tobacco epidemic*
Deaths from tobacco related disease vary markedly from country to country and these differences are determined, to a great extent, by differences in the rates of smoking initiation two to seven decades earlier and the rates of cessation five and more years prior to the year of the death rate. As a result, differences in the prevalence of current smoking for a given year in different countries may not match differences in lung cancer rates in the same year. These differences have been described as falling into four stages of the tobacco epidemic (adapted from Lopez et al., 1994)

east Asia respectively as compared to the USA (61.9 and 48.7 respectively), France (52.6 and 47.5 respectively) and Japan (38.1 and 32.4 respectively) in North America, Western Europe and Eastern Asia [8].

Tobacco use

About 1.3 billion people smoke globally [10], making tobacco a major avoidable cause of disease and mortality worldwide. Gajalakshmi and colleagues [11], using earlier estimates of the global prevalence of smoking (1.1 billion people in 1995) estimated the proportion of daily smokers ≥15 years of age to be 29% of the world population in 1995 (including users of cigarettes and/or bidis in South Asia). The majority of those daily smokers resided in less-developed areas of the world, with wide variations in prevalence across regions in both males and females, but with overall prevalence being higher in males (47%) than in females (11%). However, the proportion of male daily smokers ≥15 years of age can be significantly higher than the above average in many countries: 82% in Indonesia, 78% in the Philippines and 72% in Colombia, to illustrate a few high estimates [11]. The percentage of daily smokers ≥15 years of age is lower in the European Union but with contrasting differences by sex and across countries (Figure 2.2.2). The preceding data suggest that if smoking patterns continue unaltered, the habit will cause approximately 1 000 000 000 deaths this century, representing a tenfold increase over the previous century [12]. These data also highlight how large the population is that would benefit from interventions aimed at reducing tobacco use. Given the number of smokers worldwide, achieving tobacco abstinence is an urgent public health priority with no geographic limits.

World production of tobacco is approximately 6.6 million tonnes annually, with China being the leader in production (41% of total) [13].

WHO Region*	Smoking-Attributable Cancer Mortality					
	Male		Female		Total	
	N	%	N	%	N	%
Europe C	133 000	49	11 000	5	144 000	29
Europe B	72 000	44	9 000	8	81 000	29
Southeast Asia (India and others)	174 000	43	16 000	4	190 000	24
Southeast Asia B	45 000	43	2 000	4	47 000	24
North America	131 000	42	80 000	26	211 000	34
Western Europe	225 000	40	47 000	10	272 000	27
Western Pacific A	69 000	36	18 000	13	87 000	27
Eastern Mediterranean B	12 000	30	2 000	7	14 000	21
Eastern Mediterranean B	26 000	28	3 000	3	29 000	16
Americas B	48 000	27	12 000	6	60 000	17
Western Pacific (China and others)	209 000	20	35 000	5	244 000	14
Africa E	23 000	17	5 000	4	28 000	10
Africa D	5 000	9	400	1	5 400	5
Americas D	2 000	6	300	1	2 300	3

Table 2.2.1 *Estimated cancer mortality attributable to smoking by WHO Region in 2000*
** A, very low child mortality and very low adult mortality; B, low child mortality and low adult mortality; C, low child mortality and high adult mortality; D, high child mortality and high adult mortality; E, high child mortality and very high adult mortality.*
From Ezzati et al., 2005 (WHO estimates reported)

Continent	Country	Males		Country	Females	
		ASR (W)	Std. Error		ASR (W)	Std. Error
Highest rates						
Africa	Tunisia, Centre	37.1	2.05	Zimbabwe, Harare	4.8	0.69
	Algeria, Setif	19.9	1.05	Uganda, Kyadondo	3.8	0.69
America	USA, New Orleans: Black	96.6	3.30	USA, Kentucky	50.3	0.59
North	USA, Kentucky	90.1	0.84	USA, Pennsylvania: Black	46.8	1.09
America	Argentina, Bahia Blanca	45.5	2.42	Brazil, Brasilia	12.5	0.75
Central & South	Brazil, Sao Paolo	33.5	0.42	Brazil, Sao Paolo	11.7	0.21
Asia	Turkey, Izmir	74.5	0.98	China, Nangang District	34.6	1.20
	China, Guangzhou City	71.9	1.19	Thailand, Lampang	27.0	1.09
Europe	Poland, Kielee	76.9	1.39	UK, Scotland	34.9	0.39
	Croatia	72.1	0.67	UK, England: Merseyside	31.9	0.54
Oceania	French Polynesia	62.3	4.06	French Polynesia	23.6	2.45
	Australia, Northern Territory	51.4	4.07	Australia, Northern Territory	22.7	2.87
Lowest rates						
Africa	Zimbabwe, Harare	9.5	0.90	Tunisia, Centre	1.7	0.43
	Uganda, Kyadondo	4.8	0.84	Algeria, Setif	1.7	0.29
America	USA, California, L.A.: Hispanic	23.2	0.66	USA, California, L.A.: Hispanic	12.3	0.41
North	USA, New Mexico: Amer. Indian	12.2	1.91	USA, New Mexico: Amer. Indian	3.9	0.96
America	Ecuador, Quito	7.9	0.56	Costa Rica	4.5	0.24
Central & South	Peru, Trujillo	5.9	0.83	Ecuador, Trujillo	4.1	0.37
Asia	India, Mumbai	9.7	0.23	India, Karunagappally	2.3	0.51
	India, Nagpur	7.5	0.45	India, Trivandrum	1.7	0.24
Europe	Portugal, Porto	30.5	0.56	Spain, Albacete	3.3	0.53
	Sweden	20.9	0.24	Spain, Granada	3.3	0.33
Oceania	Australia, Capital Territory	25.6	1.77	Australia, South	16.7	0.54
	New Zealand	35.3	0.53	Australia, Capital Territory	13.7	1.24

***Table* 2.2.2** *Highest and lowest lung cancer age-standardized (world) incidence rates (per 100 000) in males and females by continent as reported in CI5, Vol IX*

Location	Production (tonnes / annum)	Import** tonnes	Export** tonnes
China	2 688 500	69 404	161 850
Brazil	889 426	7 900	616 468
India	550 000	1 152	231 570
Europe	498 916	126 578	253 177
USA	290 170	261 067	152 978
Russian Federation	80	291 807	1 739
World	6 580 828		

***Table* 2.2.3** *Tobacco production, imports and exports in 2005*
** Data source: http://faostat.fao.org/*
*** Data source: http://unstats.un.org/unsd/comtrade/*

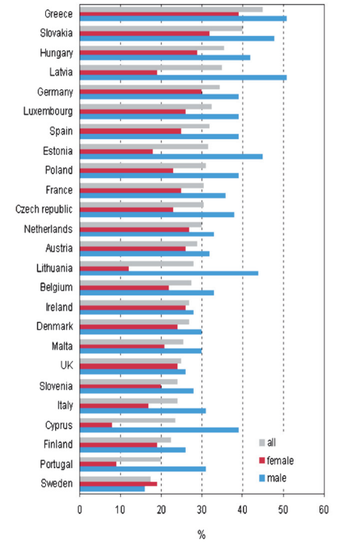


***Fig.* 2.2.2** *Percentage of daily smokers age 15+ in the EU-25 (WHO-HFA, 2005)*
Kaiser S, Gommer AM (RIVM). Percentage of daily smokers age 15+ in the EU-25. In: EUPHIX, ECHI Indicator & EUphact. Bilthoven: RIVM, <http://www.euphix.org> ECHI Indicator & EUphact\ Determinants of health\ Health behaviours\ Smoking, 13 March 2007

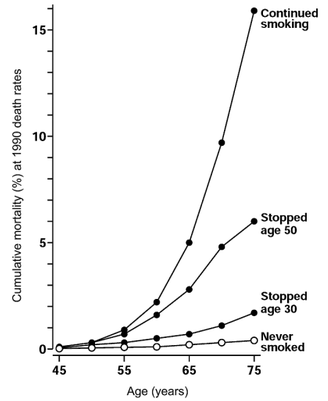


***Fig.* 2.2.3** *Lung cancer mortality in UK current and former male smokers by age at quitting*
Adapted from Peto *et al.*, 2000

Substances	Tobacco smoke	Smokeless tobacco ng / g
Volatile aldehydes		
Formaldehyde	70 - 100 µg	1600 - 7400
Acetaldehyde	500 - 1400 µg	1400 - 27 400
Crotonaldehyde		200 - 2400
N-Nitrosamines		
N-Nitrosodimethylamine	2 - 1000 ng	nd - 270
N-Nitrosodiethylamine	nd - 2.8 ng	
N-Nitrosopyrrolidine	3 - 110 ng	nd - 860
Tobacco specific nitrosamines		
N'Nitrosonornicotine (NNN)	45 - 58 000 ng/g	400 - 3 085 000
4-(Methylnitrosamino)-1-(3-pyrydyl)-1-butanone (NNK)	nd - 10 745 ng/cigarette	0.07 - 22 900
4-(Methylnitrosamino)-1-(3-pyrydyl)-1-butanol (NNAL)		
N'Nitrosoanabasine (NAB)		present - 2 370 000
Metals		
Nickel	nd - 600 ng	180 - 2700
Cadmiun	7 - 350 ng	
Polonium 210	0.03 - 1.0 pCi/g	0.16 - 1.22
Uranium 235 and 238		2.4 and 1.91
Arsenic	40 - 120 µg	500 - 900
Polycyclic aromatic hydrocarbons		
Benzo[a]pyrene	20 - 40 ng	> 0.1 - 90 ng/g
Benzo[a]anthracene	20 - 70 ng	
Benzo[b]fluoranthene	4 - 22 ng	
Chrysene		
Dibenzo[a,l]pyrene	1.7 - 3.2 ng	
Dibenzo[a,h]anthracene	4 ng	

Table 2.2.4 *Concentration of carcinogenic agents in mainstream tobacco smoke of non-filtered cigarettes and in smokeless tobacco*
Numbers in black derived from IARC Monographs volumes 83 and 89; numbers in red from Hoffman, Hoffman and El-Bayoumy, 2001

Brazil, Europe and India are major exporters in tobacco trade (Table 2.2.3). At present, cigarette smoking is by far the most common form of smoking tobacco worldwide, with a few important exceptions where other products prevail (e.g. bidi smoking in India, narghile among men in West Asia and North Africa). The use of cigars and pipe smoking is considerably lower and has declined over time. In India, the third-largest producer and consumer of tobacco in the world, the most common form of tobacco smoking is bidi smoking as opposed to smoking of manufactured cigarettes.

Smoking and cancer risk

All of the above-mentioned forms of tobacco smoking are harmful to health and have been unquestionably found to cause cancer. However, this link was not established until 1950, following the observed dramatic increase in lung cancer incidence in a few countries in Europe, the USA and Australia in the first half of the last century. The seminal large-scale studies of Wynder and Graham [14] and Doll and Hill [15] compared the smoking habits, a proposed possible cause at the time, in lung cancer cases and other individuals without cancer of the lung. Their results confirmed cigarette smoking as a cause of lung cancer: the frequency of smoking and amount smoked were significantly higher in patients with cancer of the lung than in controls. These results were promptly followed by many other studies and led to the 1964 Surgeon General's Report which established the causal link for the first time [16].

Duration of smoking is the strongest determinant of excess lung cancer risk in smokers [1]. The majority of lung cancer cases have smoked for decades. In the original British study and in the study by Wynder and Graham, 43–50% of lung cancer cases had smoked ≥40 years. Doll and Peto (1978) have calculated from the male British doctors' data an annual excess lung cancer incidence of 0.01%, 0.2% and 1% for 15, 30 and 45 years of smoking respectively. The excess risk of lung cancer increases proportionally with the number of cigarettes smoked [1].

Tobacco smoking raises the excess risk of all histological types of lung cancer [1]. However, there has been a shift over time in the frequency distribution of the major histological types observed in smoking-induced lung cancer cases. In more recent studies the proportion of adenocarcinoma of the lung has increased, considerably decreasing the ratio of squamous to adenocarcinoma cases typically reported in early studies. Several explanations have been proposed, including changes in the composition of cigarettes and in the nitrite content of tobacco used in manufactured cigarettes. Lower nitrate content may have caused modifications in the way people smoke by inducing deeper inhalation to compensate for the reduced nicotine content; smoke inhaled in this fashion may reach more peripheral parts of the bronchi. In addition, changes in the nitrate content in US blends of tobacco used to make cigarettes in more recent years may have increased the formation of nitrosamines during tobacco storage, processing and smoking. Nitrosamines, such as NNK, are carcinogens that induce the formation of adenocarcinoma [17,18].

Cigar and/or pipe smoking, with or without inhalation, causes lung cancer, and the risk increases with amount smoked and duration of smoking [1]. Inhalation increases the risk to a greater extent, and smokers who have switched from cigarettes to cigar/pipe have reported a higher risk of lung cancer than exclusive cigar/pipe smokers. Cigar or pipe smoking has also been associated with oral cancer, oropharyngeal, hypopharyngeal, laryngeal and oesophageal cancers [1]. Similarly, bidi smoking is associated with lung, oral, laryngeal, oesophageal and stomach cancer with the risk increasing with amount smoked and duration [1].

Mechanisms of carcinogenesis

Tobacco smoke is the most common source of carcinogens to humans. It includes about 10^{10} particles per ml and 4800 compounds, of which 66 are carcinogens [19,20]. Of these, polycyclic aromatic hydrocarbons and tobacco specific nitrosamines are the most important. In addition, inducers of reactive oxygen species like NO, NO_2, peroxynitrite and nitrosamines initiate, promote or amplify oxidative DNA damage [21-23]. Chemicals such as aromatic amines, benzene and heavy metals, independently established as carcinogenic to humans, are present in tobacco smoke as well (Table 2.2.4). Most carcinogens are oxygenated by cells using cytochrome P54 enzymes to be transformed into excretable forms. Electrophilic oxygenated carcinogens can form covalently bound DNA adducts. Six carcinogens present in tobacco smoke are known to form

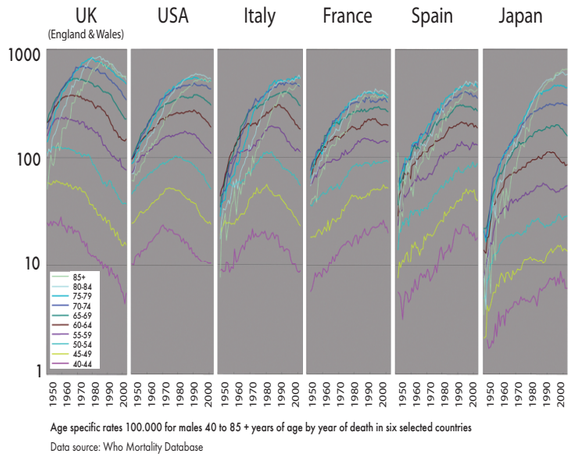


Fig. 2.2.4 *Trends in lung cancer mortality by age group and year of death in males*
Recent trends in lung cancer mortality rates differ by country even among high resource countries. Trends in birth-cohort specific lung cancer mortality rates generally follow trends in smoking behaviour by birth cohort with lag time of approximately 20 years. For several of the countries depicted, rates first began to decrease among younger age groups, and these decreasing trends gradually extended to older age groups (UK, USA, Italy). In France, Spain and Japan, decreasing trends were observed among some older age groups but younger age groups show increasing mortality rates.

DNA adducts in human tissue: benzo[a]pyrene (BaP), NNK, NDMA (N-nitrosodimethylamine), NNN (N'-nitrosonornicotine), ethylene oxide and 4-aminobiphenyl [22]. Cells can remove adducts and repair DNA. The balance between metabolic activation and metabolic detoxification and the efficiency of DNA repair pathways may define cancer risk in individuals exposed to polycyclic aromatic compounds, for example [22]. In summary, the chronic presentation of carcinogens through sustained smoking can lead to molecular lesions which in the presence of reduced metabolic detoxification can diminish repair capability, overwhelming cellular defenses and leading to lung cancer [22].

Pooled estimates of smoking-associated cancer risk

A recent meta-analysis of 177 case-control studies, 75 cohorts and 2 nested case-control studies reported in IARC Monograph 83 [1] has provided pooled estimates of the risk associated with smoking for 13 different cancer sites [24]. Accordingly, the pooled magnitude of the association in current smokers as compared to never smokers was RR = 8.96 (95% CI 6.73–12.11) for lung cancer, RR = 6.98 (95% CI 3.14–15.52) for laryngeal cancer, RR = 6.76 (95% CI 2.86–15.98) for pharyngeal cancer, 3.57 (95% CI 2.63–4.84) for the upper-digestive tract and RR = 3.43 (95% CI 2.37–4.94) for oral cancer. Table 2.2.5 shows pooled estimates from the above-mentioned meta-analysis stratifying results by sex and demonstrating very similar risks of cancer associated with smoking in males and females.

Smoking cessation

A benefit of quitting tobacco smoking in adulthood has been shown for lung cancer and other major cancers causally associated with the habit (Figure 2.2.3; [22]). This result emphasises the need to devise anti-smoking strategies that address avoidance of the habit among the young people as well as reduction of smoking and quitting among adults. In fact, the decline in tobacco consumption during the last 20 years among men in North America and several European countries, and which has resulted in decreased incidence of and mortality from lung cancer, has occurred primarily by increase in quitting at middle age (Figure 2.2.4). The great challenge for the control of tobacco-related cancer, however, lies today in low-resource countries, in particular in China and the other Asian countries; the largest increase in tobacco-related cancers has been forecast in this region of the world [25]. Despite growing efforts from medical and public health institutions and the growing involvement of non-governmental organisations, the fight against the spread of tobacco smoking among women and in low-resource countries remains the biggest and most difficult challenge of cancer prevention to face in the coming decades.

Cancer site	Sex	Pooled* Relative Risk (RR)	95% Confidence Interval
Lung	M	9.87	6.85, 14.24
(C 34)**	F	7.58	5.36, 10.73
Upper digestive tract	M	3.52	1.94, 6.37
(C10-15)	F	3.80	1.97, 7.33
Esophagus	M	2.52	1.81, 3.52
(C15)	F	2.28	1.51, 3.44
Stomach	M	1.74#	1.46, 2.07
(C16)	F	1.45	1.20, 1.75
Pancreas	M	1.63	1.32, 2.03
(C16)	F	1.73	1.31, 2.30
Liver	M	1.85	1.21, 2.83
(C22)	F	1.49	1.12, 1.98
Lower urinary tract	M	2.80	2.01, 3.92
(C65-67)	F	2.73	1.82, 4.10

Table 2.2.5 *Human cancers associated with smoking*
** Estimates as reported in Gandini et al., 2008 [24]*
*** Cancer site ICD- 10*
 # Statistically significant heterogeneity by sex at this cancer site

REFERENCES

1. IARC. (2004). *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 83, Tobacco smoke and involuntary smoking*. Iyon, France: International Agency for Research on Cancer.

2. U.S. Department of Health and Human Services (2006). *The Health Consequences of Involuntary Exposure to Tobacco Smoke: A Report of the Surgeon General*. Atlanta, GA: U.S. Department of Health and Human Services, CDC, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health.

3. U.S. Department of Health and Human Services (2004). *The Health Consequences of Smoking: A Report of the Surgeon General*. Atlanta, GA: U.S. Department of Health and Human Services, CDC, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health.

4. Ezzati M, Henley SJ, Lopez AD, et al. (2005). Role of smoking in global and regional cancer epidemiology: current patterns and data needs. *Int J Cancer* 116: 963-971.

5. International Union Against Cancer. *Deaths from smoking*. Available from: http://www.deathsfromsmoking.net/ Date Accessed: November 14, 2007.

6. IARC (2007). *IARC Working Group Reports, Volume 3, Attributable Causes of Cancer in France in the year 2000*. Iyon, France: International Agency for Research on Cancer.

7. Doll R, Peto R, Boreham J, et al. (2005). Mortality from cancer in relation to smoking: 50 years observations on British doctors. *Br J Cancer* 92: 426-429.

8. Ferlay J, Bray F, Pisani P, et al. *GLOBOCAN 2002: Cancer Incidence, Mortality and Prevalence Worldwide*. Available from: http://www-dep.iarc.fr/

9. Lopez AD, Collishaw NE, Piha T (1994). A descriptive model of the cigarette epidemic in developed countries. *Tob Control* 3: 242-247.

10. World Health Organization Tobacco Free Initiative. *Why is tobacco a public health priority?* Available from: http://www.who.int/tobacco/health_priority/en/index.html Date Accessed: October 14, 2008.

11. Gajalaksmi CK, Jha P, Ranson K, et al. (2000). Global patterns of smoking and smoking attributable mortality. In: Jha P, Chaloupka FJ, eds., *Tobacco control in developing countries*. Oxford: Oxford University Press. 11-39.

12. Peto R, Lopez A (2001). Future worldwide health effects of current smoking patterns. In: C.E.Koop, C.E.Pearson, M.R.Schwartz, eds., *Critical Issues in Global Health*. San Fransisco: Joosey-Bass. 154-161.

13. Food and Agriculture Organization of the United Nations. Available from: http://faostat.fao.org Date Accessed: September 12, 2008.

14. Wynder EL and Graham EA (1950). Tobacco smoking as a possible etiologic factor in bronchiogenic carcinoma; a study of 684 proved cases. *J Am Med Assoc* 143: 329-336.

15. Doll R and Hill AB (1950). Smoking and carcinoma of the lung; preliminary report. *Br Med J* 2: 739-748.

16. U.S. Surgeon General's Advisory Committee on Smoking and Health (1964). *Smoking and health: report of the advisory committee to the Surgeon General of the Public Health Service*. Washington, DC: U.S. Dept. of Health, Education, and Welfare, Public Health Service.

17. Hecht SS (1999). Tobacco smoke carcinogens and lung cancer. *J Natl Cancer Inst* 91: 1194-1210.

18. Wynder EL and Hoffmann D (1998). Re: Cigarette smoking and the histopathology of lung cancer. *J Natl Cancer Inst* 90: 1486-1488.

19. Hoffmann D, Hecht SS (1990). Advances in tobacco carcinogenesis. In: Beland FA, Cooper CS, Grover PL, eds., *Chemical carcinogenesis and mutagenesis*. Berlin: Springer-Verlag. 63-1002.

20. Hoffmann D, Hoffmann I, El-Bayoumy K (2001). The less harmful cigarette: a controversial issue. a tribute to Ernst L. Wynder. *Chem Res Toxicol* 14: 767-790.

21. Zhang J, Liu Y, Shi J, et al. (2002). Side-stream cigarette smoke induces dose-response in systemic inflammatory cytokine production and oxidative stress. *Exp Biol Med* 227: 823-829.

22. IARC (2007). *IARC Handbooks of Cancer Prevention, Tobacco Control. Volume 11, Reversal of Risk After Quitting Smoking*. Iyon, France: International Agency for Research on Cancer.

23. Church DF and Pryor WA (1985). Free-radical chemistry of cigarette smoke and its toxicological implications. *Environ Health Perspect* 64: 111-126.

24. Gandini S, Botteri E, Iodice S, et al. (2008). Tobacco smoking and cancer: a meta-analysis. *Int J Cancer* 122: 155-164.

25. Peto R, Chen ZM, Boreham J (1999). Tobacco–the growing epidemic. *Nat Med* 5: 15-17.

2.3 Passive Smoking

SUMMARY

> Passive smoking causes lung cancer and non-neoplastic diseases, such as coronary heart disease, chronic respiratory symptoms, and adverse effects on fetal growth.

> The epidemiological evidence is strongly supported by the chemistry of tobacco smoke, cancer bioassays and mechanisms of tobacco-related carcinogenesis.

> Nearly half of never-smokers are exposed to tobacco smoke at home and at work; bars and restaurants can be particularly polluted. About 10–15% of lung cancers in never-smokers are attributed to passive smoking.

> The WHO Framework Convention on Tobacco Control calls for protection from exposure to tobacco smoke.

> After the introduction of strict national smoking bans, beneficial effects on the respiratory and cardiovascular system have been shown

There is no doubt that passive smoking is carcinogenic to humans. Many national and international scientific expert committees have concluded that passive smoking (also called secondhand smoke, involuntary smoking or environmental tobacco smoke) causes lung cancer in humans. Like active smoking, passive smoking has also been causally associated with a number of non-neoplastic diseases, such as coronary heart disease, chronic respiratory symptoms, and adverse effects on fetal growth [1,2].

Constituents of secondhand tobacco smoke

Secondhand tobacco smoke is a mixture of exhaled mainstream smoke and sidestream smoke diluted with ambient air. Involuntary smoking involves inhaling the same carcinogens that are found in mainstream smoke, including benzo[a]pyrene, tobacco specific nitrosamines (NNN and NNK), and benzene (Table 2.3.1). Secondhand tobacco smoke also contains nicotine and other toxic components.

Measurement of exposure

There are several useful indicators of exposure to secondhand smoke, ranging from surrogate indicators to direct measurements of exposure and of biomarkers that reflect dose (Table 2.3.2). Assessment of exposure to secondhand smoke in epidemiological studies of cancer is often based on questionnaire information, and exposure may be further characterised by source: spousal or parental exposure at home, workplace exposure and exposure in social settings.

The most widely studied components of secondhand smoke in the air have been respirable suspended particles and carbon monoxide; both are nonspecific indicators of secondhand smoke. Nicotine in air, by contrast, is highly specific because smoking is its only source.

Cotinine is a metabolite of nicotine which can be measured in blood, urine or saliva and is highly specific for exposure to secondhand smoke; it is an integrative measure that reflects recent exposure to secondhand smoke in all environments and has also been used to assess misclassification of smoking status as derived from questionnaire information.

Exposure to passive smoking

Smoking prevalence (see *Tobacco smoking*, Chapter 2.2) can be used as a surrogate measure for exposure to SHS. The Global Youth Tobacco Survey (GYTS) data from 137 countries and territories during 2000–2007 among students aged 13–15 years who had never smoked indicated that nearly half of never-smokers were exposed to SHS at home (46.8%), and a similar percentage were exposed in places other than the home (47.8%) (Table 2.3.3); [3].

An estimated 7.5 million workers in the European Union and 24.6 million indoor workers in the USA are exposed to secondhand smoke at work, and environmental tobacco smoke was the second most prevalent carcinogen at the workplace in the EU [4,5].

Based on large numbers of measurements made in various indoor environments in the USA between 1957 and 1991, the average concentrations of nicotine in air showed about 100-fold variation, i.e. from 0.3–30 μg/m^3. The average concentrations of nicotine in air of homes with one or more smokers typically ranged from 2 to 10 μg/m^3 [6]. A review of exposure to secondhand smoke in bars, bowling alleys, billiard halls, betting establishments and bingo parlours found that nicotine concentrations in these places were 2.4 to 18.5 times higher than in offices or residences, and 1.5 to 11.7 times higher than in restaurants (Table 2.3.4; [7]). Personal exposure to respirable suspended particles associated with secondhand tobacco smoke was determined for workers in 11 countries and the mean concentrations ranged from 24 to 112 μg/m^3 [8].

Epidemiology of passive smoking and cancer

More than 50 studies of involuntary smoking and lung cancer risk in never-smokers, especially spouses of smokers, have been carried out in many countries. A meta-analysis of all the studies available to the IARC Monographs Working Group in 2002 showed that there is a statistically significant and consistent association between exposure to secondhand tobacco smoke from the spouse who smokes and lung cancer risk in spouses of smokers (women, RR, 1.24, 95% CI 1.14–1.34; men RR, 1.37, 95% CI 1.02–1.83), after controlling for some potential sources of bias and confounding. The magnitude of the observed risk is reasonably consistent with predictions based on studies of active smoking.

Case–control and cohort studies published after this comprehensive meta-analysis have further corroborated an increased risk of lung cancer for secondhand tobacco smoke exposure [9,10]. A pooled analysis of the two largest case–control studies with a total of more than 1200 never-smoking lung cancer patients found an increased risk of lung cancer for secondhand tobacco smoke exposure from the three main sources: spousal, workplace and social [9].

A recent meta-analysis of more than twenty studies of workplace exposure to secondhand smoke reported a summary relative risk of 1.24 (95% CI 1.18–1.29) for all studies, and of 1.59 when only the studies that adjusted for other occupational carcinogens were included. The meta-analytic result for the highest exposure in terms of cumulative exposure or intensity of exposure as provided by 7 studies was 2.01 (1.33–2.60) (Table 2.3.5; [11].

In 2002, the IARC Working Group concluded that the evidence linking passive smoking to other cancer sites was inconsistent. Since the US Surgeon General's Report in 1964 [12] established a causal link between cigarette smoking and lung cancer, more and more cancer sites have been causally associated with smoking of different tobacco products (see *Tobacco smoking*, Chapter 2.2). History may repeat itself in terms of causal associations between passive smoking and cancer sites other than lung. Several studies published since 2002 have suggested an association between passive smoking and cancers of the upper aero-digestive tract, the pancreas, urinary bladder, kidney, cervix, and childhood leukaemias. It had been suggested that exposure to secondhand tobacco smoke may also increase the risk of breast cancer. However, a recent prospective study and a meta-analysis including seven additional studies with prospectively recorded exposure information did not observe an increased incidence of breast cancer in never smoking women exposed to secondhand smoke (RR, 0.99, 95% CI 0.93–1.05) [13]. Volume 100 of the *IARC Monographs* (see *Identifying human carcinogens*, Chapter 2.1) will provide an opportunity to revisit the evidence for passive smoking and cancer sites other than lung.

Mechanisms of tobacco-related carcinogenesis

Metabolites of the tobacco specific nitrosamine NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone, have been found to be elevated in the urine of involuntary smokers [14], and studies in humans have shown that concentrations of adducts of carcinogens to biological macromolecules are higher in adult involuntary smokers and in the children of smoking mothers than in individuals not exposed to secondhand tobacco smoke. Protein adduct concentrations in fetal cord blood correlate with those in maternal blood [15].

In mice, inhalation of sidestream and mainstream smoke and implants of condensates of sidestream smoke in rat lungs have induced lung tumours; topical application of sidestream condensates has produced skin tumours in mice [1]. Together, these data provide supportive evidence for a causal link between exposure to secondhand tobacco smoke and development of lung cancer.

Burden of passive smoking-related lung cancer

In the US, 3423 annual lung cancer deaths in never-smokers are attributed to spousal smoking [16]. For Europe, Vineis et al [17] estimated the proportion of lung cancers in never- and ex-smokers attributable to secondhand smoke in the EPIC (European Prospective Investigation into Cancer and Nutrition) population to be between 16 and 24%, mainly due to work-related exposure. The proportion of lung cancers attributable to secondhand smoke from spouse and workplace among never-smokers in France was estimated to be 12.2% in men and 15% in women [18]. Work-related exposure to secondhand smoke was calculated to account for 5.7% of lung cancers in never-smokers in the USA [19].

Cancer control

Primary prevention is the only effective tool to decrease the burden of cancer related to passive smoking. General tobacco control interventions will also reduce exposure to secondhand smoke. With the Framework Convention on Tobacco Control (FCTC) the WHO has initiated a process to ban smoking globally ([20]; see Tobacco Control section). Moreover, the FCTC also addresses passive smoking specifically in Article 8, which calls "for protection from exposure to tobacco smoke in indoor workplaces, public transport, indoor public places and, as appropriate, other public places." Since the ratification of this first global treaty on health, several jurisdictions have introduced strict smoking bans (including Ireland, Norway, Italy, Sweden, Scotland, England, Wales and Northern Ireland) and other jurisdictions introduced bans in 2008 (e.g. France, and Bavaria with coverage including the Oktoberfest). The report of the U.S. Surgeon General [2] concluded that the scientific evidence indicates that there is no risk-free level of exposure to secondhand smoke. While eliminating smoking in indoor spaces fully protects non-smokers from exposure to secondhand smoke, separating smokers from non-smokers, cleaning the air and ventilating buildings cannot eliminate exposures of non-smokers to secondhand smoke.

Beneficial effects of workplace bans

Comparing pre- and post-ban exposure to secondhand smoke, several studies have showed substantial decreases in respirable suspended particles, nicotine, PAH, benzene and 1,3-butadiene in air and biomarkers of exposure (cotinine, exhaled carbon monoxide) (e.g. [21]; Figure 2.3.1). One of these studies further demonstrated significant improvements in measured pulmonary function tests and significant reductions in self-reported symptoms in non-smoking barmen after the ban [22]. Recently, studies reported a significant reduction in acute coronary events after the introduction of strict smoking bans in Italy and Scotland [23,24].

In the study from Scotland, persons who had never smoked reported a decrease in the exposure to secondhand smoke that was confirmed by a decrease in their serum cotinine levels, and the largest reduction in the number of hospital admissions for acute coronary syndrome was observed among persons who had never smoked.

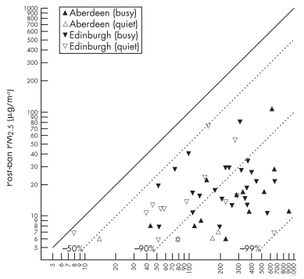


***Fig.* 2.3.1** *Log-log scatter plot comparing particulate matter, 2.5 mm in diameter PM2.5) concentrations at pre- and post-ban visits. Diagonal dotted lines indicate various ratios of reduction*

Compound	Type of Cigarette						
	Regular	Light	Extra light	Ultra light	Regular/ light	Regular/ extra light	Regular/ ultra light
IARC Group 1 carcinogens							
Benzene (µg/cig.)	222.0	250.0	260.0	296.0*	0.9	0.9	0.8*
Cadmium (ng/cig.)	438.0	484.0	502.0*	627.0*	0.9	0.9*	0.7*
2-Naphthylamine (ng/cig.)	157.0	147.0	175.0	186.0	1.1	0.9	0.8
Nickel (ng/cig.)	34.3	45.1	74.4*	73.0*	0.8	0.5*	0.5*
Chromium (ng/cig.)	61.0	62.0	121*	82.9*	1.0	0.5*	0.7*
Arsenic (ng/cig.)	ND	NQ	ND	ND			
4-Aminobiphenyl (ng/cig.)	22.1	19.5	21.0	21.2	1.1	1.1	1.0
Formaldehyde (µg/cig.)	378.0	326.0	414.0	431.0	1.2	0.9	0.9
1,3-Butadiene (µg/cig.)	196.0	185.0	264.0	299.0	1.1	0.7	0.7
Benzo[a]pyrene (ng/cig.)	48.8	98.3	92.2	113.0	0.5	0.5	0.4
NNK (ng/cig.)	95.2	153.4	38.3	34.7	0.6	2.5	2.7
NNN (ng/cig.)	23.3	53.9	43.7	45.2	0.4	0.5	0.5
IARC Group 2A carcinogens							
Lead (ng/cig.)	54.8	39.4	22.3	18.5	1.4	2.5	3.0
IARC Group 2B carcinogens							
Acetaldehyde (µg/cig.)	1416.0	1454.0	1449.0	1492.0	1.0	1.0	0.9
Isoprene (µg/cig.)	1043.0	1164.0	1060.0	1172.0	0.9	1.0	0.9
Catechol (µg/cig.)	130.0	117.0	149.0	148.0	1.1	0.9	0.9
Acrylonitrile (µg/cig.)	78.6	85.6	74.1	81.8	0.9	1.1	1.0
Styrene (µg/cig.)	74.0	84.7	87.5	108.0*	0.9	0.8	0.7*

***Table* 2.3.1** *Yields of IARC carcinogens in sidestream smoke of regular-sized Canadian cigarettes, International Organization for Standardization (ISO)[a] machine-smoking parameters[b]*
Adapted from IARC, 2004. (Source: Government of British Columbia, 2003)
NNN, N1-nitrosonornicotine; NNK, 4-(N-nitrosomethylamino)-1-(3-pyridyl)-1-butanone; ND, not detectable
a ISO smoking parameters: 35 mL puff in 2 sec, interval 60 sec, ventilation holes not blocked
b Reporting period: year 1999

Measure	Indicator
Surrogate measures	Prevalence of smoking in men and women
Indirect measures	Report of secondhand tobacco smoke exposure in the home and in the workplace Smoking in the household Number of smokers Smoking by parent(s) Number of cigarettes smoked Smoking in the workplace Presence of secondhand tobacco smoke Number of smokers
Direct measures	Concentration of secondhand tobacco smoke components Nicotine Respirable particles Other markers Biomarker concentrations Cotinine Carboxyhaemoglobin

***Table* 2.3.2** *Indicators of exposure to secondhand tobacco smoke*
From Samet & Yang [25]

WHO region	All students who never smoked, % (95% CI)	Never smokers	
		Exposed to SHS at home, % (95% CI)	Exposed to SHS in places other than home, % (95% CI)
Africa (n = 103 906)	79.3 (75.5-82.7)	22.6 (19.5-26.1)	38.2 (34.2-42.4)
Americas (n = 236 687)	54.9 (50.8-59.0)	39.1 (31.6-47.2)	41.7 (38.9-46.6)
Eastern Mediterranean (n = 92 075)	84.4 (80.2-87.8)	37.0 (33.7-40.4)	42.9 (39.0-47.0)
Europe (n = 154 759)	69.0 (65.0-70.8)	71.5 (64.6-76.0)	79.4 (73.9-83.7)
South-East Asia (n = 91 459)	87.4 (83.8-90.2)	42.8 (35.2-49.7)	38.8 (35.9-41.7)
Western Pacific (n = 68 717)	69.8 (66.1-73.2)	57.3 (48.5-65.3)	52.6 (49.2-56.1)
Total (N = 747 603)	80.3 (76.7-83.4)	46.8 (39.9-52.5)	47.8 (44.1-51.3)

***Table* 2.3.3** *Exposure* to second-hand smoke (SHS) at home and in places other than home and susceptibility to initiating smoking among students aged 13-15 years who had never smoked cigarettes, by World Health Organization (WHO) region – Global Youth Tobacco Survey, 2000-2007*
**Determined by answers to two questions: "During the past 7 days, on how many days have people smoked in your home, in your presence?" and "During the past 7 days, on how many days have people smoked in your presence, in places other than in your home?" Students who answered 1 or more days were considered exposed to SHS.*
CI= Confidence Interval

Type of Workplace	Number of studies	Number of establishments sampled	Weighted mean*	Range	Ratio†
Offices	22	940	4.1	0.8-22.1	1.0
Residences	7	91	4.3	1.6-21.0	1.0
Restaurants	17	402	6.5	3.4-34.0	1.6
Betting establishments	3	4	9.8	8.0-10.7	2.4
Bowling alleys	2	6	10.5	10.1-10.7	2.6
Billiard halls	2	3	13.0	9.8-19.4	3.2
Bars	10	27	31.1	7.4-105.4	7.6
Bingo parlours	2	3	76.0	65.5-81.2	18.5

Table 2.3.4 *Indoor air concentrations of nicotine (µg/m3) in a variety of workplaces*
**Mean of average nicotine values reported in individual studies weighted by number of establishments sampled in each study.*
†Ratio of weighted mean nicotine concentration in residences, restaurants, bowling alleys, billiard halls, betting establishments, bars, and bingo parlours to weighted mean nicotine concentration in offices.
Adapted from Siegel and Skeer, 2003 [7]

Reference	Sex	Exposure Measure	RR (95% CI)
Boffetta et al.	both	≥89 level x hours/day x years[b]	2.07 (1.33-3.21)
Johnson et al.	women	≥ 64 smokers x years	1.58 (0.6-4.0)
Kabat et al.	men	smokers x hours/week x years[c]	1.21 (0.47- 3.13)
Kabat et al.	women	smokers x hours/week x years[c]	1.35 (0.64-2.84)
Kalandidi et al.	women	duration x number of co-workers[d]	1.08 (0.24-4.87)
Kreuzer et al.	both	>100.6 level x hours/day x years[b]	2.64 (1.07-6.54)[e]
Lee et al.	men	Average to a lot	0.46 [0.05-4.65][f]
Zhong et al.	women	≥ 4 co-workers smoked	3.0 (1.8-4.9)
Meta-analysis Fixed effects Mixed effects			 2.01 (1.55-2.60) 2.01 (1.33-2.60)

Table 2.3.5 *Relative risk (RR) and 95% confidence intervals (95%CI) results for highest cumulative or intensity of exposure groups[a]*
[a]The measure of exposure used to categorize workers varied from study to study. For studies that presented more than one measure, preference was given to exposure measures reflecting both intensity and duration (i.e., cumulative exposures).
[b]The total number of years of exposure weighted for the number of hours of exposure per day and for a subjective index of level of smokiness at the workplace (1=very smoky, 0.5=fairly smoky and 0.2=little smoky).
[c]The highest tertile of exposure was compared with the lowest tertile. The actual values of the tertiles were not presented in the paper.
[d]The results are for a comparison between the highest and lowest quartiles of "the time weighted sum of exposure at work, the exposure being based on the number of smokers among people working in the same closed space". The units of these quartiles are not presented in the paper.
[e]Results are from an analysis excluding cases and controls that were in the analysis by Boffetta et al. 1999, which was not presented in the original analysis.
[f]Crude results not adjusted for any risk factors.
Adapted from Stayner et al, 2007 [11]

REFERENCES

1. IARC. (2004). *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 83, Tobacco smoke and involuntary smoking.* Lyon, France: International Agency for Research on Cancer.

2. U.S. Department of Health and Human Services (2006). The Health Consequences of Involuntary Exposure to Tobacco Smoke: A Report of the Surgeon General. Atlanta, GA: U.S. Department of Health and Human Services, CDC, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health.

3. Exposure to secondhand smoke among students aged 13-15 years worldwide, 2000-2007 (2007). *MMWR Morb Mortal Wkly Rep* 56: 497-500.

4. Kauppinen T, Toikkanen J, Pedersen D, et al. (2000). Occupational exposure to carcinogens in the European Union. *Occup Environ Med* 57: 10-18.

5. Ong MK and Glantz SA (2004). Cardiovascular health and economic effects of smoke-free workplaces. *Am J Med* 117: 32-38.

6. U.S. Environmental Protection Agency (1992). *Respiratory health effects of passive smoking: lung cancer and other disorders.* Washington, DC: U.S. Environmental Protection Agency, Office of Health and Environmental Assessment, ORD, Report No. EPA/600/6-90/006F.

7. Siegel M and Skeer M (2003). Exposure to secondhand smoke and excess lung cancer mortality risk among workers in the "5 B's": bars, bowling alleys, billiard halls, betting establishments, and bingo parlours. *Tob Control* 12: 333-338.

8. Properties and measure, of environmental tobacco smoke (2000). In: Jenkins RA, Guerin MR, Tomkins BA, eds., *The chemistry of environmental tobacco smoke: composition and measurement.* Boca Raton, FL: Lewis Publishers.

9. Brennan P, Buffler PA, Reynolds P, et al. (2004). Secondhand smoke exposure in adulthood and risk of lung cancer among never smokers: a pooled analysis of two large studies. *Int J Cancer* 109: 125-131.

10. Wen W, Shu XO, Gao YT, et al. (2006). Environmental tobacco smoke and mortality in Chinese women who have never smoked: prospective cohort study. *BMJ* 333: 376.

11. Stayner L, Bena J, Sasco AJ, et al. (2007). Lung cancer risk and workplace exposure to environmental tobacco smoke. *Am J Public Health* 97: 545-551.

12. U.S. Surgeon General's Advisory Committee on Smoking and Health (1964). *Smoking and health: report of the advisory committee to the Surgeon General of the Public Health Service.* Washington, DC: U.S. Dept. of Health, Education, and Welfare, Public Health Service.

13. Pirie K, Beral V, Peto R, et al. (2008). Passive smoking and breast cancer in never smokers: prospective study and meta-analysis. *Int J Epidemiol* 37: 1069-1079.

14: Stepanov I, Hecht SS, Duca G, et al. (2006). Uptake of the tobacco-specific lung carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone by Moldovan children. *Cancer Epidemiol Biomarkers Prev* 15: 7-11.

15. Husgafvel-Pursiainen K (2004). Genotoxicity of environmental tobacco smoke: a review. *Mutat Res* 567: 427-445.

16. California Environmental Protection Agency (2005). *Proposed Identification of Environmental Tobacco Smoke as a Toxic air Contaminant. Part B: Health Effects.* Sacramento, CA: California Environmental Protection Agency, Air Resources Board.

17. Vineis P, Hoek G, Krzyzanowski M, et al. (2007). Lung cancers attributable to environmental tobacco smoke and air pollution in non-smokers in different European countries: a prospective study. *Environ Health* 6: 7.

18. IARC (2007). *IARC Working Group Reports, Volume 3, Attributable Causes of Cancer in France in the year 2000.* Lyon, France: International Agency for Research on Cancer.

19. Steenland K, Burnett C, Lalich N, et al. (2003). Dying for work: The magnitude of US mortality from selected causes of death associated with occupation. *Am J Ind Med* 43: 461-482.

20. World Health Organization. *WHO Framework Convention on Tobacco Control.* Avaliable from: http://www.who.int/fctc/en/ Date Accessed: October 12,2008.

21. Semple S, Creely KS, Naji A, et al. (2007). Secondhand smoke levels in Scottish pubs: the effect of smoke-free legislation. *Tob Control* 16: 127-132.

22. Goodman P, Agnew M, McCaffrey M, et al. (2007). Effects of the Irish smoking ban on respiratory health of bar workers and air quality in Dublin pubs. *Am J Respir Crit Care Med* 175: 840-845.

23. Cesaroni G, Forastiere F, Agabiti N, et al. (2008). Effect of the Italian smoking ban on population rates of acute coronary events. *Circulation* 117: 1183-1188.

24. Pell JP, Haw S, Cobbe S, et al. (2008). Smoke-free legislation and hospitalizations for acute coronary syndrome. *N Engl J Med* 359: 482-491.

25. Samet JM, Yang G (2001). Passive smoking, women and children. In: Samet JM, Yoon SY, eds., *Women and the tobacco epidemic, challenges for the 21st century.* Geneva: World Health Organization. 17-45.

2.4 Smokeless Tobacco

Summary

> Smokeless tobacco products are widely used in Asia and Africa. These products cause cancers of the oral cavity, the pharynx and the oesophagus

> Use of smokeless tobacco is also common in Nordic European Countries. These products increase the risk of cancers of the oesophagus and pancreas

> Use of smokeless tobacco in Northern America has been associated with oral cancers

> Carcinogenicity is likely to be caused by a high concentration of nitrosamines.

During most of the 20th century, use of oral and nasal smokeless tobacco products has been significant in India and other Asian countries, as well as in some parts of Africa, although it has declined in Northern Europe and North America. However, during the last few decades an increase in use has been observed in the United States and some Northern European countries, in particular among young people.

Smokeless tobacco is consumed without burning the product, and can be used orally or nasally. Globally, a wide variety of different smokeless tobacco products are used. These may be used on their own, mixed with other products, such as slaked lime (khaini) or as ingredients to other products, such as betel quid (Figure 2.4.1).

The prevalence of use of smokeless tobacco varies substantially not only across countries, but also within countries, by gender, age, ethnicity and socioeconomic characteristics. In the United States in 2000, 4.4% of men and 0.3% of women were current users of smokeless tobacco products. Current use was more common among young men, non-Hispanic Whites, people of lower attained level of education, southern states and rural areas [1]. The major form of smokeless tobacco used in Sweden is moist snuff ("snus"). In 2004, 20% of men and 3% of women aged 16–75 years used moist snuff daily; the prevalence of use was higher in young adults, and among manual workers [2].

In India, a large variety of commercial or home-made smokeless tobacco products exist. The use of chewing tobacco (often chewed with betel quid or other preparations including areca nut) is more prevalent than the use of snuff; applying smokeless tobacco products as a dentifrice is also common. According to a 1998–99 survey, 28.1% of adult men and 12.0% of women reported chewing tobacco [3]. Smokeless tobacco products are also widely used in other countries in Southeast Asia. There are many other products used in other regions and countries, including naswar in Central Asia, zarda in Western Asia, maras in Turkey, toombak in Sudan, chimó in Venezuela and iq'mik in Alaska [4].

The available studies from countries in Northern Europe and the United States indicate an increased risk of oral cancer for use of smokeless tobacco in the United States, while results of studies in the Nordic countries do not support such an association [5,6]. In the case of esophageal and pancreatic cancer, the available evidence points toward the presence of a causal association, mainly based on the results of the studies from Nordic countries. Results on lung cancer risk are not conclusive, and data for other cancers are inadequate.

Betel quid without tobacco, as well as areca nut, the common ingredient of betel quid, have been classified as human carcinogens; they cause cancers of the oral cavity, the pharynx and the oesophagus [4]. Several case–control studies from India, Pakistan and Sudan provide strong and consistent evidence of an increased risk of oral cancer (or oral and pharyngeal cancer) for use of smokeless tobacco (or tobacco plus lime) products, with relative risks as high as 10 [6]. Additional evidence comes from ecological studies showing positive correlations between use of smokeless tobacco products and high rates of oral cancer (e.g. in Sudan, Central Asia and Saudi Arabia), as well as from case reports and case series from different regions across the world, in which cases of oral cancer reported high prevalence of use of smokeless tobacco products [6].

A few studies from India and North Africa support the hypothesis of an association between nasal snuff use and risk of cancer of the oral cavity, the esophagus and the lung [6].

In one study in the USA, men who switched from cigarette smoking to use of spit tobacco ("switchers") had a 2.6-fold higher mortality from cancer of the oral cavity and pharynx than men who quit using tobacco entirely ("quitters") [7]. Compared to men who never used any tobacco product, the risk of lung cancer among switchers was increased 5–6 fold.

There are over 30 carcinogens in smokeless tobacco, including volatile and tobacco specific nitrosamines, nitrosamino acids, polycyclic aromatic hydrocarbons, aldehydes, metals [6]. Smokeless tobacco use entails the highest known non-occupational human exposure to the carcinogenic nitrosamines, NNN and NNK (Figure 2.4.2). Exposure levels are 100 to 1000 times greater than in foods and beverages commonly containing nitrosamine carcinogens. The uptake of NNK and NNN by smokeless tobacco users has been demonstrated in many studies by detection of their metabolites in urine. Twenty years of smokeless tobacco use would expose its user to an amount of NNK (75–150 mg, or about 1.5 mg/kg body weight) similar to that which has caused tumours in rats (1.8 mg/kg body weight), in addition to considerable exposure to NNN [8].

There is also consistency among the target tissues for cancer in smokeless tobacco users and in rats treated with NNK or NNN, since a mixture of NNK and NNN swabbed in the rat oral cavity caused oral tumours, and NNK and its metabolite NNAL caused pancreatic tumours in rats upon administration in the drinking water, and NNN given in the drinking water to rats produces esophageal and lung tumours [5]. Tobacco specific nitrosamines and their metabolites have also been quantified in the urine of smokeless tobacco users, and their levels were generally higher than in smokers [9].

There is a spectrum of risk arising from use of tobacco products that is due to the wide variation in the types used, their chemical composition and the way in which they are used, leading to opportunities for harm reduction initiatives within the field. This is compounded by the fact that tobacco is marketed in sophisticated ways in high-resource countries and this practice is migrating to low-resource country markets with some rapidity.

Harm (risk) reduction can be achieved by reduction of dose or change of product. This may involve substitution of one risk for another but may nevertheless lead to a lower overall risk of cancer. A policy concession that switching to smokeless tobacco may benefit cigarette smokers, while certainly true in many cases, has the downside that it may have the side effect of actually increasing the number of continuing smokers. While there are arguments to support the notion that a global switch from smoking to smokeless tobacco would reduce global cancer risk over time [10], comparative risk estimates depend on many assumptions, including in particular the expected effect of the introduction of new smokeless products in populations where the habit has not been prevalent. Data are available on a possible beneficial effect of switching from smoking to smokeless tobacco a few studies and models in the United States and Sweden. Overall, there is not enough evidence to support promotion of such products as substitutes for cigarettes in populations with a high prevalence of smoking and no tradition of use of smokeless tobacco.

Fig. 2.4.1 *Selection of smokeless tobacco products*

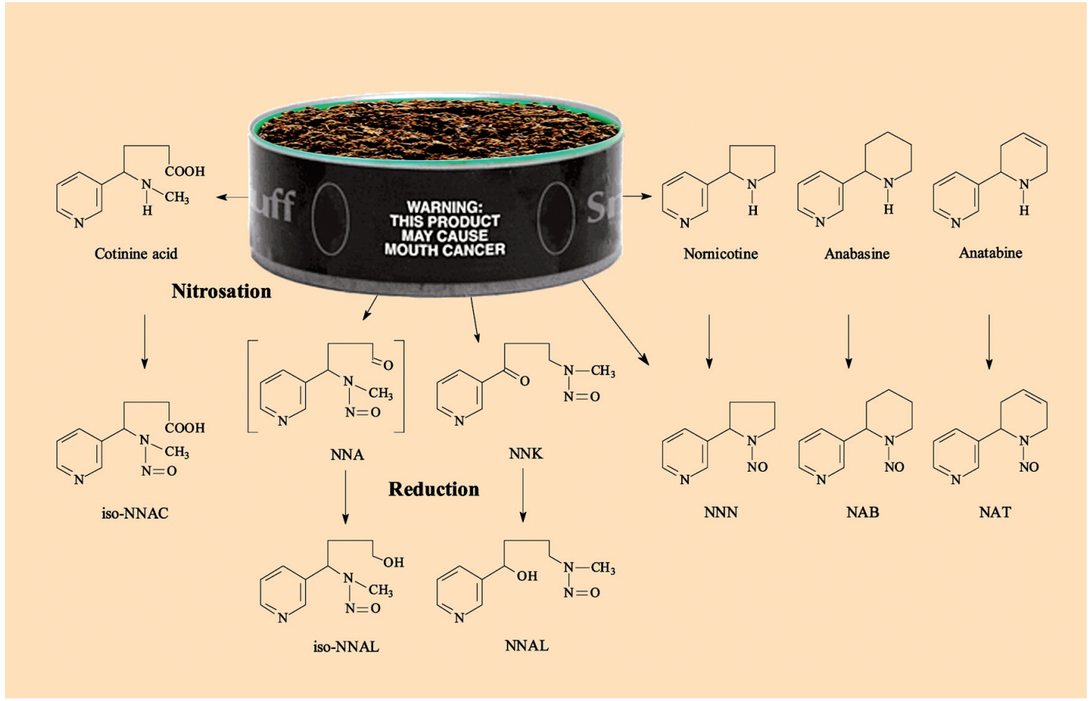


Fig. 2.4.2 *Smokeless tobacco chemistry*

REFERENCES

1. Tomar SL, Connolly GN, Wilkenfeld J, et al. (2003). Declining smoking in Sweden: is Swedish Match getting the credit for Swedish tobacco control's efforts? *Tob Control* 12: 368-371.

2. Wicklin B (2006). *Tobacco Statistics: Sales, Consumption and Lung Cancer*. Hasselby, Sweden: Statistical Bureau VECA.

3. Rani M, Bonu S, Jha P, et al. (2003). Tobacco use in India: prevalence and predictors of smoking and chewing in a national cross sectional household survey. *Tob Control* 12: e4.

4. IARC. (2004). *Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 85, Betel quid and areca nut chewing and some areca-nut-derived nitrosamines*. Lyon, France: International Agency for Research on Cancer.

5. Boffetta P, Hecht S, Gray N, et al. (2008). Smokeless tobacco and cancer. *Lancet Oncol* 9: 667-675.

6. IARC. (2007). *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 89, Smokeless tobacco and some tobacco-specific N-nitrosamines*. Lyon, France: International Agency for Research on Cancer.

7. Henley SJ, Thun MJ, Connell C, et al. (2005). Two large prospective studies of mortality among men who use snuff or chewing tobacco (United States). *Cancer Causes Control* 16: 347-358.

8. Belinsky SA, Foley JF, White CM, et al. (1990). Dose-response relationship between O6-methylguanine formation in Clara cells and induction of pulmonary neoplasia in the rat by 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone. *Cancer Res* 50: 3772-3780.

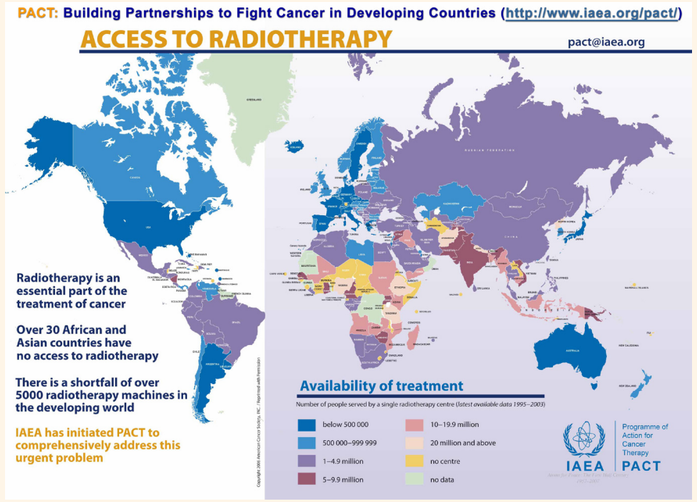
9. Stepanov I and Hecht SS (2005). Tobacco specific nitrosamines and their pyridine-N-glucuronides in the urine of smokers and smokeless tobacco users. *Cancer Epidemiol Biomarkers Prev* 14: 885-891.

10. Gartner CE, Hall WD, Vos T, et al. (2007). Assessment of Swedish snus for tobacco harm reduction: an epidemiological modelling study. *Lancet* 369: 2010-2014.

CANCER INSTITUTE PROFILE: PACT/IAEA

The International Atomic Energy Agency (IAEA) has a long, successful history of assisting cancer treatment programmes in the developing world with the use of radiotherapy. Radiation medicine techniques are indispensable in cancer care, where radiotherapy plays a fundamental role in treating and curing many forms of cancer. The IAEA's assistance has enabled many countries to establish safe and effective radiotherapy capabilities, but with a cancer epidemic looming in developing countries, the existing infrastructure is far from sufficient to respond to the growing demand (see Figure).

The Programme of Action for Cancer Therapy (PACT) was created within the IAEA in 2004 to build upon this experience to enable low- and middle-income countries to introduce, expand and improve their cancer care capacity by integrating radiotherapy into a comprehensive cancer control programme that maximises its therapeutic effectiveness and impact. Such a programme also addresses other challenges such as infrastructure gaps and builds capacity and long-term support for continuous education and training of cancer care professionals, as well as for community-based action.



PACT is working with WHO, IARC, UICC, INCTR and other leading organisations to build a global public-private partnership to assist low- and middle-income countries to develop cancer control programmes that meet the challenges posed by cancer in all its aspects by mobilising new resources from charitable trusts, foundations, and others in the public and private sectors.

To achieve its goals, PACT is being implemented in overlapping stages that raise awareness about cancer, assess cancer control needs, develop demonstration projects and attract donors to establish effective new funding mechanisms beyond those currently available from the IAEA and bilateral or multilateral donors. Through these collaborations, PACT and its partners will place cancer on the global health agenda and comprehensively address cancer control needs in the developing world over the next 10 to 20 years. The IAEA will continue to invest in PACT with personnel and resources as one of its key priorities.

website: www.iaea.org

2.5 Chronic Infections

Summary

> Approximately 15–20% of cancers worldwide have been attributed to infectious agents. However, this proportion is higher in low-resource countries (26%) than in the developed world (8%).

> Common cancers induced by specific infectious agents include hepatocellular carcinoma associated with human hepatitis B virus (HBV) or human hepatitis C virus (HCV), cervical cancer and other malignancies associated with human papillomavirus (HPV), lymphomas and others associated with Epstein-Barr virus (EBV), leukaemia associated with human T cell leukemia virus (HTLV), Kaposi sarcoma associated with human herpes virus 8 (HHV8), gastric cancer with Helicobacter pylori (H. pylori) and cancer of the urinary tract with Schistosoma haematobium

> HPV, EBV, HTLV1 and HHV8 play a direct role in carcinogenesis encoding oncoprotein, which are able to promote cellular transformation by altering the regulation of cell cycle, telomere/telomerase system, apoptosis and other cellular pathways

> Other infectious agents, e.g. HBV, HCV and *H. pylori*, appear to have an indirect role, inducing a chronic inflammation with tissue necrosis and regeneration. HIV also has an indirect role, mediating its effects on cancer risk by lowering host immunity to other oncogenic infections

> In the last two decades several strategies against cancer-associated infectious agents have been developed. These include antibiotic therapy against H. pylori and two prophylactic vaccines against HBV and HPV

The hypothesis of the contagious nature of a given cancer was envisaged in the beginning of the 20th century, when researchers could prove the transmission of cancer in animals using cell-free filtrates of cancer cells. Ellermann and Bang, and a few years later Rous, showed that inoculation of cell-free filtered tumour extracts from ill to healthy chickens could lead to development of cancer [1]. Similar experiments in other animals confirmed the contagious nature of certain types of cancers. These findings led to the discovery of several carcinogenic animal viruses, e.g. Rous-sarcoma virus, Lucké frog renal carcinoma virus, mammary murine tumour virus and many more [1]. However, despite the clear indications that cancer could be transmitted from ill to healthy animals, the idea of involvement of infectious agents in carcinogenesis was only accepted after several decades. This was mainly due to the lack of appropriate detection methods, such as electron microscopy and molecular biology techniques. Despite the isolation of EBV in Burkitt lymphoma cells in 1964, it took several years to completely accept the role of EBV in human cancer [1]. Around 1970, H. zur Hausen suggested the link between HPV and cervical cancer. A few years later, Gissmann and de Villiers, within the group of zur Hausen, isolated and characterised the first mucosal HPV type, HPV6, which then allowed the identification of several other mucosal HPV types, including HPV16, fully supporting their original idea [2]. Nowadays HPV is accepted as a necessary cause of cervical cancer.

Epidemiological and biological studies have now conclusively proved that a variety of infectious agents are among the main causes of cancer worldwide. At least six different viruses have been linked to the development of specific types of human cancers. Other infectious agents involved in human carcinogenesis include four parasites and one bacterium (Table 2.5.1).

Hepatitis B virus and hepatitis C virus

Hepatitis B virus (HBV) is a small partially double stranded hepatotropic DNA virus that belongs to the *Hepadnaviridae*. HBV infection is a major public health problem worldwide. Approximately two billion people are infected worldwide, and more than 400 million are chronic (lifelong) carriers of HBV [3]. However, the geographical distribution of chronic carrier state varies considerably. The majority of chronically infected people live in Southeast Asia and sub-Saharan Africa. HBV infections occur in all age groups; however, most of the chronic infection (70–80%) occurs during the perinatal period, 25–30% in infancy or early childhood, and less than 10% in adults [3]. Infection can be transmitted from mother to child (vertical transmission), child to child (horizontal transmission), through sexual transmission and by contact with infected blood (transfusion, non-sterilized needles and syringes, tattooing and scarification procedures) or blood products.

Hepatitis C virus (HCV), an enveloped single-stranded RNA virus, infects about 80 million people worldwide. The prevalence of HCV varies also from region to another. It is low (<1%) in Australia, Canada and northern Europe, intermediate (1%) in the USA, high (>2%) in the rest of Europe and high (2%) in many African countries, Southeast Asia, Italy and Egypt. HCV is mainly transmitted through unscreened blood transfusions and use of contaminated needles and syringes. Unlike HBV, where about 10% of those infected progress to chronicity, 80% of HCV newly infected people develop a chronic state [4]. Similar to HBV, HCV is clustered into distinct genotypes, probably with a different severity in inducing disease or in response to treatment [5,6]. Chronically infected persons with HBV and/or HCV are at high risk of developing cirrhosis and HCC, diseases that kill about half a million persons each year. The fraction of HCC attributable to HBV and HCV in 2002 have been estimated to be, respectively, 23 and 20% in developed countries and 59 and 33% in developing countries [7].

The molecular mechanisms by which HBV and HCV viruses induce tumours are far from being elucidated. The pathway shared by these viruses in inducing HCC in a multistep process is likely to be chronic injury by viral components and environmental factors resulting in inflammatory responses and apoptosis followed by hepatocellular regeneration. Interactions with other environment factors such as aflatoxins also contribute to carciongenesis. During this process, chromosomal rearrangements, gene mutations and other biological alterations that occur may provide a selective growth advantage to the initiated abnormal cell (Figures 2.5.4 and 2.5.5).

HBV infection is preventable with a safe and effective immunisation programme available since 1982. However, up to now, only a fraction of children in low- and medium-resources countries are vaccinated. No vaccine is currently available to prevent HCV infection. The control of HBV and HCV disease burden requires prevention strategies by reducing the risk of contamination (safe blood transfusion, safe infection practices, etc.).

Human papillomavirus

The family of the epithelio-tropic human papillomaviruses (HPV) comprises approximately 100 different types that have been sub-grouped in different genera according to their genomic DNA sequence [8]. In addition, the different HPVs appear to have a preferential tropism for the mucosa or the skin; therefore, they can be further subdivided into mucosal or cutaneous HPV types. The genus alpha comprises the mucosal HPV types that are preferentially detected in the female reproductive tract and are sexually transmitted. An IARC monograph has recently reported that the mucosal high-risk alpha HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52 56, 58, 59 and 66 are clearly associated with cervical cancer. In addition, HPV16 and HPV18, at much lower extent, have a causal role for a subset of anal cancers (80%) or vulva, vagina, penis and oro-pharynx (approximately 30% in all latter cases) [9]. Another group of mucosal alpha HPVs is termed "low risk" and is normally associated with benign genital lesions. HPV16 is the most frequently high-risk HPV type detected in pre-malignant and malignant cervical lesions [10]. The high frequency of HPV16 in the cervix is most likely linked to its biological properties: e.g. efficiency in promoting cellular proliferation and evading the immune surveillance (see paragraph "Mechanisms of carcinogenicity").

Emerging lines of evidence indicate that another group of HPVs that belongs to the genus beta may be involved in human carcinogenesis, i.e. non-melanoma skin cancer (NMSC) [11]. They were first isolated in skin cancer-prone patients suffering from a rare autosomal recessive genetic disorder called *Epidermodysplasia verruciformis* (EV), but it is now clear that they are very common in the skin of healthy individuals [11]. Although these HPVs are known to be responsible for NMSC development in EV patients, their direct role in skin carcinogenesis in normal population remains to be proven. It is possible that the cutaneous HPV types may promote the formation of malignant lesions acting as co-carcinogens together with UV.

Epstein-Barr virus

Epstein-Barr virus (EBV) is a ubiquitous human Gamma Herpes virus that infects most of human population early in life and usually causes mild disease. EBV was isolated for the first time from a biopsy of Burkitt's lymphoma (childhood B-cell-derived tumour common in sub-Saharan Africa), and was the first virus directly associated with human cancer [12]. EBV has a specific tropism for B-cells through a binding to B-cell surface receptor CD21 leading to the emergence of proliferating B-cell referred as lymphoblastoid cell

Infectious agent	IARC classification[1]	Cancer site/cancer	Number of cancer cases	% of cancer cases worldwide
H. Pylori	1	Stomach	490 000	5.4
HPV	1, 2A	Cervix and other sites	550 000	6.1
HBV, HCV	1	Liver	390 000	4.3
EBV	1	Lymphomas and nasopharyngeal carcinoma	99 000	1.1
HHV-8	2A	Kaposi sarcoma	54 000	0.6
Schistosoma haematobium	1	Bladder	9 000	0.1
HTLV-1	1	Leukaemia	2 700	0.1
Liver flukes Opisthorchis viverrini Clonochis sinensis	1 2A	Cholangiocarcinoma (biliary system)	800	
		Total infection-related cancers	1 600 000	17.7
		Total cancers in 1995	9 000 000	100

Table 2.5.1 *The burden of cancer caused by infectious agents worldwide*
[1]Group 1 = carcinogenic to humans, Group 2A = probably carcinogenic to humans

lines (LCLs). EBV can also infect other cell types, including epithelial, but with much less efficiency. EBV is thought to be transmitted orally, and primary infection is generally asymptomatic. However, when the infection occurs during adolescence, EBV can cause infectious mononucleosis, a benign self-limited disease. After remission, EBV remains in infected individuals for the lifetime, making it among the most persistent viruses that infect humans. In individuals with severe inherited or acquired deficiencies in T-lymphocyte response, EBV-infected B-lymphocytes can proliferate without immune control and cause fatal lymphoproliferative disease. EBV is also strongly associated with the development of several human cancers such as Burkitt's lymphoma, nasopharyngeal carcinoma, Hodgkin disease, sinonasal angiocentric-T-cell lymphoma, and gastric carcinoma [13]. EBV-induced growth transformation results in a complex interaction between viral encoded proteins and the cellular regulatory machinery, and the EBV latent proteins, particularly the Latent Membrane Protein 1 (LMP1), play an important role in this process (Klein E, Kis LL and Klein G, 2007).

Human T-cell lymphotropic virus

Human T-cell lymphotropic virus type 1 (HTLV-1) is part of the Deltaretrovirus family and is responsible for the development of adult-T-cell leukamia (ATL). Based on the divergence in the nucleotide sequence, HBV is classified into eight different genotypes (A to H) with different geographical distributions. Studies reported mainly from Asia indicate that HBV genotypes may influence the HCC outcome. Patients infected with HBV genotype C being more susceptible to develop HCC. Other types have been identified (HTLV-2-4). HTLV-2 was isolated from a few cases of leukemia and neurological disease, but its pathology is not clear. Little is known about HTLV-3 and HTLV-4. HTLV-1 is endemic in southwestern Japan, Africa, the Caribbean Islands and South America, while it is frequent in Melanesia, Papua New Guinea, the Solomon Islands and in Australia among the aboriginal population. In contrast, HTLV-1 is rarely detected in North American and European populations. All ATL cells contain integrated HTLV-1 provirus, highlighting its key role in leukaemogenesis. Nevertheless, only a small minority of HTLV-1-infected individuals progress to ATL. Indeed, the cumulative risks of developing ATL among virus carriers are estimated to be approximately 6.6% for males and 2.1% for females. As many as 20 million people worldwide may be infected with HTLV-1. Spread of the virus may occur from the mother to the child mainly through breast-feeding beyond six months, via sexual transmission and during blood transfusion.

Cancer	Relative Risk
HHV8-related	
Kaposi Sarcoma	3640 (3326 – 3976)
EBV-related	
Non-Hodgkin Lymphoma	77 (39 – 149)
Hodgkin's Lymphoma	11 (8.4 – 14)
HBV/HCV related	
Liver	5.2 (3.3 – 8.2)
HPV-related	
Cervix	5.8 (3.0 – 11)
Vulva and Vagina	6.5 (4.1 – 10)
Penis	4.4 (2.8 – 7.1)
Anus	29 (22 – 38)
Oral cavity	2.3 (1.7 – 3.3)
Non-melanoma skin	4.1 (1.1 – 17)
Conjunctiva	2.0 (1.0 – 3.8)
H.Pylori related	
Stomach	1.9 (1.5 – 2.4)

Table 2.5.2 *Relative risk for cancers related to chronic infection among more than 400 000 PHIV (adapted from Grulich et al, Lancet, 2007)*

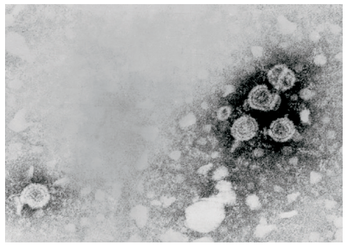


Fig. 2.5.1 *Electron microscopy of hepatitis B virus particles*

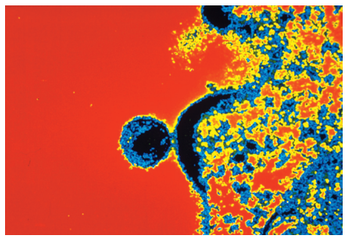


Fig. 2.5.2 *Electron microscopy of the human immunodeficiency virus entering into T-lymphocytes*

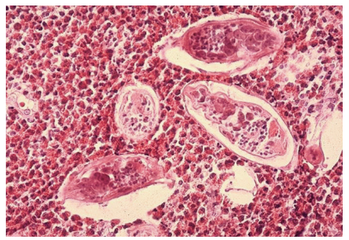


Fig. 2.5.3 *Schistosoma haematoilum chronic infection in the bladder causes inflammatory reaction with dense eosinophilic infiltrates which may promote the development of squamous-cell carcinoma*

KSHV/HHV8

Kaposi's sarcoma associated herpesvirus (KSHV), also termed human herpesvirus 8 (HHV8), is a gamma-2 herpesvirus, related genetically to simian herpesvirus saimiri, the prototype virus of this subgroup of the gammaherpesvirus subfamily. HHV8 is the etiological agent of all forms of Kaposi's sarcoma and primary effusion lymphoma (PEL) and most forms of multicentric Castelman's disease (MCD). HHV8 infection is normally associated with immunocompromised status and is therefore very frequent in geographical regions where HIV is highly prevalent, e.g. Africa. In addition, HHV8 is endemic in normal populations of the Mediterranean regions, such as South Italy and Israel. Horizontal transmission by saliva appears to be the most common route in population of endemic regions as well as in high-risk populations. However, also vertical, sexual, and blood and transplant-related transmission are also considered as additional routes.

HHV8 is able to establish a persistent infection in the host by two alternative genetic life-cycle programmes. The latent programme provides a stable and immunologically silent mode of persistence, while the lytic programme guarantees the release of virions and their propagation to other hosts. Several viral proteins are able to interfere with the immune-system related pathways facilitating the establishment of persistent infection.

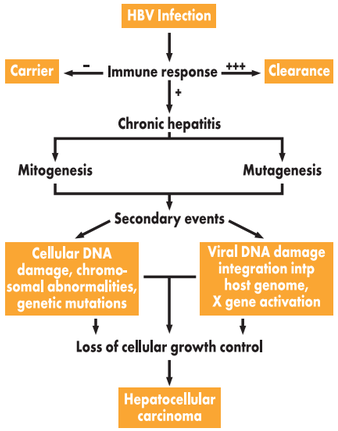


Fig. 2.5.4 *Hepatitis B virus and the chronic injury hypothesis. A strong immune response to hepatitis B virus (+++) leads to clearance of the infection. Lack of immune response (-) results in the "healthy" carrier state, while a weak response (+) produces chronic hepatitis that may eventually progress to Hepatocellular carcinoma*

Helicobacter pylori

Helicobacter pylori (*H. pylori*) is a non-spore forming and spiral-shape gram-negative bacterium that colonises the stomach and is possibly transmitted via the fecal-oral and/or oral-oral route. Epidemiological studies have clearly shown that *H. pylori* infection is associated with peptic ulcer diseases, gastric cancer and mucosa-associated lymphoma tissue (MALT). In 1994, it was classified as a group 1 carcinogen by the International Agency for Research on Cancer. *H. pylori* is one of the most common infections in humans, with an estimated prevalence of 50% worldwide and 90% in developing countries. One striking feature of *H. pylori* biology is its high allelic diversity and genetic variability. To date, an incredibly high number of strains have been described. In addition, the bacteria can undergo genetic alteration *during the infection*, due to an elevated mutation rate and frequent intraspecific recombination. Recent findings support the concept that this genetic variability, which affects both housekeeping and virulence genes, may contribute to host adaptation and persistence of the infection.

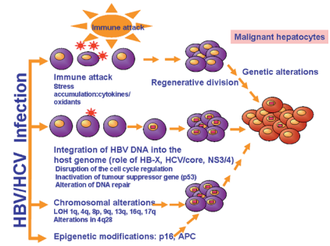


Fig. 2.5.5 *Hepatitis B and hepatitis C-induced liver carcinogenesis. Infection of most of the individuals with hepatitis viruses leads to immune-mediated viral clearance. Viral persistence in few individuals produce chronic hepatitis which may lead to hepatocellular carcinogenesis in a multistep process*

Parasites

Two liver flukes, *Opisthorchis viverrini* and *Clonorchis sinenesis,* have been associated with cholangiocarcinoma in parts of Asia. Infection by these flukes is acquired by eating raw or undercooked freshwater fish containing the infective stage of the fluke; the fluke matures and produces eggs in the small intrahepatic ducts. The evidence for cancer causation by *O. viverrini,* a parasite mainly prevalent in Thailand, is stronger than for *C. sinensis*. The incidence of

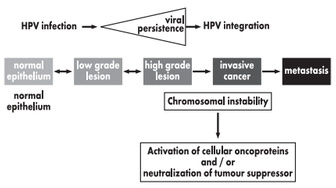


Fig. 2.5.6 *Proposed pathogenesis mechanism by which human papillomavirus infection causes cervical cancer*

cholangiocarcinoma in areas where these liver flukes are non-endemic is very low.

Schistosomes are trematode worms. The cercarial stage infects humans by skin penetration. The worms mature and lay eggs in the bladder or intestine of the host, provoking symptoms of a disease known as bilharzia. *Schistosoma haematobium* infection is prevalent in Africa and the Middle East and has been associated with bladder cancer (Figure 2.5.3). *Schistosoma japonicum* infection is prevalent in Japan and China and has been associated with cancers of the liver, stomach and colorectum, but the evidence is weak and inconsistent.

The impact of HIV on virus-induced cancers

An estimated 40 million people worldwide are infected with HIV, of whom 25 million live in sub-Saharan Africa [14]. HIV is not believed to have any direct carcinogenic effect, but exerts its effects on cancer risk by lowering host immunity. Persons infected with HIV (PHIV) are at increased risk for all those cancers that are known to be associated with chronic infection [15] (Table 2.5.2).

Incidence rates for Kaposi Sarcoma (KS) and Non-Hodgkin Lymphoma (NHL), etiologically linked to HHV8 and EBV, respectively, are the most highly elevated among PHIV compared to the general population. The risk for these cancers increases strongly as immunity declines (as measured by CD4 T-cell count), and can be reversed by the immune reconstitution offered by treatment with highly active antiretroviral therapy (HAART). HAART is also the first-line treatment for KS, often resulting in complete regression. The prognosis of HIV-related NHL remains poor.

For cancers other than KS and NHL, increases in risk among persons infected with HIV are smaller and do not show such strong linear relationships with degree of immune suppression. However, increased access to HAART and improvement in survival after HIV infection means that the consequences of mild but prolonged immune deficiency are being seen on a wide spectrum of infection-related cancers. EBV-related Hodgkin Lymphoma is increased about ten-fold in PHIV. The excess risk for HPV-related cancers of the cervix, vulva, vagina, anus and penis, as well as for HBV/HCV-related liver cancer were suspected to be related to heavy exposure to oncogenic viruses *per se* due to the lifestyle of PHIV, rather than immune impairment. It is known that low CD4 T-cell counts are associated with increased HPV persistence and with risk of development of advanced precancerous lesions of the cervix and anus, and that co-infection with HIV and HCV or HBV leads to higher mortality from liver cancer than does

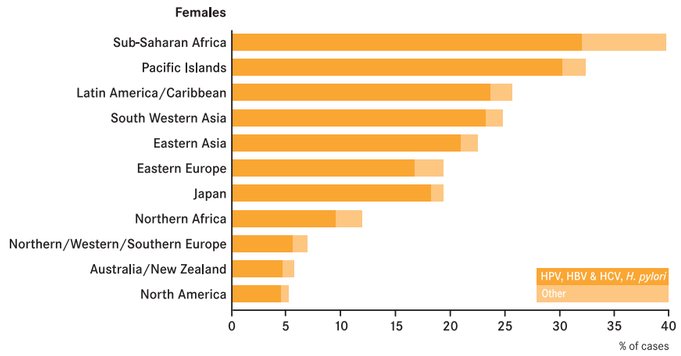


Fig. 2.5.7 *The burden of cancers caused by infections in women*

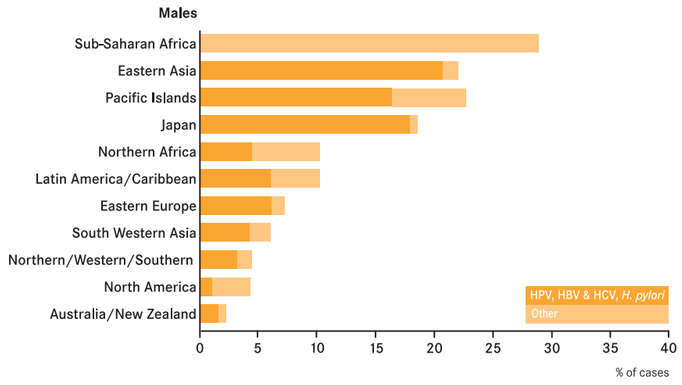


Fig. 2.5.8 *The burden of cancers caused by infections in men*

Global burden of cancer attributed to infectious agents

The total of infection-attributable cancer in the year 2002 has been estimated at 1.9 million cases, or 17.8% of the global cancer burden [7]. The principal agents are Helicobacter pylori (5.5% of all cancer), HPV (5.2%), HBV and HCV (4.9%), EBV (1.0%) and HHV8 (0.9%). The proportion of infection-attributable cancer is higher in developing countries (26%) than in developed countries (8%), reflecting the higher prevalence of infection with the major causative agents (e.g. HBV, HP, HPV and HIV), and lack of screening for HPV-related precancerous cervical lesions.

The calculation of attributable fractions is largely based on two parameters, the population prevalence of infection, and the relative risk for developing cancer given infection. These parameters may remain under-estimated for certain infections. For example, HCV seroprevalence surveys tend to over-sample young individuals at low risk of HCV infection (e.g. blood donors and pregnant women), and a review of liver cancer cases, suggested that the attributable fraction of HCV might be higher, particularly in developing countries [20]. Furthermore, the current estimate of non-cardia gastric cancer attributable to *H. pylori* is 63%, which is based on a relative risk of 5.9 for *H. pylori* strains. However, much higher relative risks observed for certain strains of *H. pylori* suggest that the true attributable fraction may be somewhat higher [21].

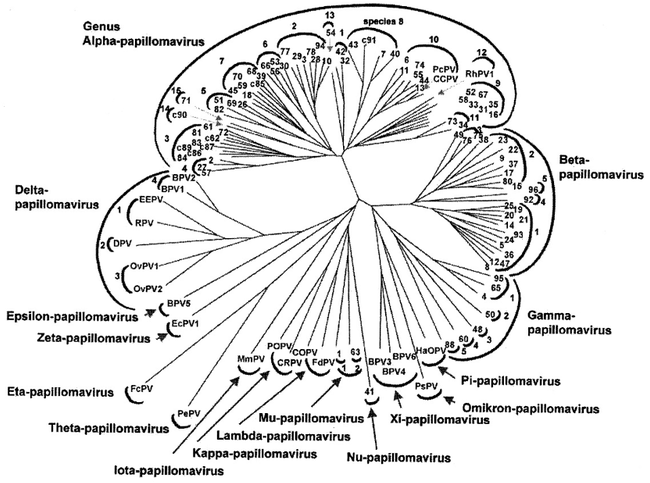


Fig. 2.5.9 *Phylogenetic tree of HPV. The different types of papilloma viruses have been grouped in genera according to similarity in DNA sequence. The most-studied types of HPV associated with cervical cancer are included in genus Alpha. From de Villiers et al. (2004), Virology 324(1):17-27. From de Villiers et al. (2004), Virology 324(1):17-27*

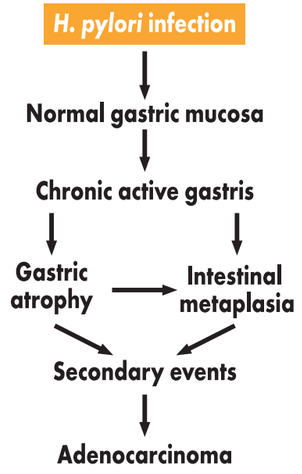


Fig. 2.5.10 *Proposed model of stomach carcinogenesis as progressive process associated with atrophy and intestinal metaplasia with reduced acidity*

HCV or HBV alone. Other cancers associated or suspected to be associated with chronic infections that may occur more frequently among PHIV include cancers of stomach (*H. pylori*), head and neck (HPV), conjunctiva (HPV) and non-melanoma skin cancer (cutaneous HPV), but results from the literature are not quite consistent. Strong evidence for a direct role for HIV-related immune suppression in the development of all these cancers is the similar pattern of excess cancer risk seen among immunosuppressed transplant recipients, who do not share the same behavioural risk factors for viral infection as PHIV [16].

Mechanisms of carcinogenesis

Direct and indirect pathogenic mechanisms have both been implicated for infectious agents involved in human carcinogenesis. HPV, EBV, HTLV1 and HHV8 encode oncoproteins that play a direct role; being able to deregulate fundamental events, e.g. cellular proliferation, DNA repair, apoptosis, chromosomal stability and the immune response. These virus-induced events are explained by the fact that the replication of their DNA is totally dependent on cellular mechanisms. These infectious agents have developed several mechanisms to keep the infected cells alive and in a high proliferative status, even in the presence of cellular stresses that normally lead to exit of cell cycle and/or apoptosis resulting in efficient multiplication of their progeny. In doing so, these viruses facilitate the accumulation of chromosomal abnormalities promoting long-term cellular transformation. A rapid elimination of infected cells by the immune system would drastically decrease the risk of generation of precursor cancer cells. Thus, the carcinogenic potential of these viruses is facilitated by their ability to stimulate cellular proliferation and their efficiency in evading the host immune surveillance.

HPV is one of the best characterised and understood examples of infectious agent with a direct role in carcinogenesis. The products of three early genes, E5, E6 and E7, result in evasion of host immuno-surveillance allowing viral persistence and cellular transformation. Since the integration of viral DNA, which occurs in the majority, if not all, tumour cells, results in a loss of E5 gene expression, it is clear that E5 is involved in early events during the multi-step process of cervical carcinogenesis, and that its function is no longer required after the establishment of the transformed phenotype. In contrast, E6 and E7 are actively expressed in all cervical cancer cells, and inhibition of their transcription leads to a rapid loss of the transformed phenotype. E6 and E7 from the high-risk mucosal HPV types promote cellular transformation targeting several cellular proteins, including the tumour suppressors, p53 and retinoblastoma (pRb), respectively [17].

HPV is a non-lytic virus that is permissive for viral replication only in epidermal keratinocytes. The ability of the virus to influence the immune system is therefore limited to the localised environment of the infected epidermis. It is now clear that several HPV proteins are able to down-regulate the innate and adaptive immunity affecting Toll Like Receptor (TLR)-regulated pathways and antigen presentation [18,19].

Similarly to HPV, EBV, HTLV1 and HHV8 are able to alter the regulation of pathways involved in cellular transformation and/or immune surveillance. The EBV oncoprotein Latent Membrane Protein 1 (LMP1) is an aggregated membrane protein responsible for most of the carcinogenic properties of EBV. LMP1 is expressed in all the EBV-associated malignancies and transform cell *in vitro*, by altering the control of cell cycle and apoptosis. Indeed, LMP1 acts as a constitutively activated tumour necrosis factor receptor (TNFR) mimicking CD40, therefore activating several cellular signalling pathways in a ligand-independent manner, during EBV-induced B-cell immortalization. Hence, LMP1 promotes cell survival and cell proliferation by constitutively activating NF-κB, JNK, p38, STAT and hTERT [22-24]. In addition, LMP1 can down regulate MHC expression, an efficient mechanism for the virus to alter immune surveillance. Other latent EBV genes including EBNA1, LMP2A and the EBV-encoded small RNA EBERs are thought to play a role in EBV-mediated oncogeneis [25].

The oncoprotein Tax from HTLV1, similarly to HPV 16 E6 and E7, targets several tumour suppressors, e.g. p53 and pRb altering the regulation of cellular proliferation and apoptosis. HTLV1 Tax promotes G1/S transition by different mechanisms. For instance, it induces pRb phosphorylation by activating several CDK complexes and directly increasing the intracellular levels of E2F. The TAX mechanism of p53 inactivation is not fully elucidated, but appears to be mediated by targeting the transcriptional co-activator p300/CBP and the NF-κB pathway. Also HHV8 encode proteins that are able to interfere with the regulation of cell cycle and apoptosis. For instance, latency-associated nuclear antigen (LANA) binds pRb and p53 and co-operates with the cellular oncogene H-ras in transformation of primary rat embryo fibroblasts. In addition, HHV8 encodes a viral cyclin (v-cyc) that can bind and activate CDK4/6, which in turn lead to the hyperphosphorylation of pRb. Interestingly the v-cyc/CDK complexes appear to be resistant to $p16^{INK4a}$, a potent inhibitor of the G1-phase CDK complexes, cycDs/CDK4 or 6. As shown for HPV, HHV8 is able to down-regulate the Interferon pathways and down-regulate MHC class I. The virus is also able to promote Th2, thus inhibiting Th1 cell associate responses that are more favourable in an antiviral response. Furthermore, HHV8 encodes a homologue of IL-6 (vIL-6). As IL-6 in the host plays a key role in haematopoiesis, inflammation and oncogenesis, vIL-6 promotes haematopoiesis and acts as an angiogenic factor through the induction of vascular endothelial growth factor.

In contrast, HBV, HCV, *H. pylori* and parasites act via an indirect mechanism inducing tissue damage and chronic inflammation that in turn promote cancer development. The data available so far show that hepatitis viruses do not display *in vitro* transforming activities, but infection may lead to cancer via induction of chronic liver injury and hepatitis. Chronic hepatitis caused by HBV is characterised by chronic liver cell necrosis that stimulates a sustained regenerative response. The inflammatory component includes activated macrophages that are a rich source of free radicals. The cooperation of these mitogenic and mutagenic stimuli has the potential to determine accumulation of chromosomal abnormalities in the infected cells, which may facilitate the multi-step process of liver carcinogenesis. Viral components of HBV (HBx, PreS2, insertion of the viral genome) and HCV (HCV core, NS5A) also play a direct role in liver carcinogenesis by altering several cellular signalling pathways which are important for regulating cell proliferation and apoptosis (Figures 2.5.4 and 2.5.5).

H. pylori infection causes gastritis and atrophy, which in turn alter gastric acid secretion, elevating gastric pH, changing the gastric flora and allowing anaerobic bacteria to colonise the stomach. In addition, *H. pylori* produces active reductase enzymes that transform food nitrate into nitrite, an active molecule capable of reacting with amines, amides and urea generating carcinogenic N-nitroso compounds. (Figure 2.5.9) The carcinogenicity of the different *H. pylori* strains appears to correlate with the presence in the bacterium genome of a region called pathogenicity island, a 40 kb segment that include the cytoxin-associated gene A (cagA). cagA is a protein of 125-145 kDa and is injected by the bacteria into epithelial cells of the gastric mucosa hijacking signal transduction pathways and increasing cellular proliferation, mobility and apotosis. However, the precise role of all these cagA-induced events in carcinogenesis is not entirely elucidated.

REFERENCES

1. Epstein MA (2001). Historical background. *Philos Trans R Soc Lond B Biol Sci* 356: 413-420.

2. zur Hausen H (1996). Roots and perspectives of contemporary papillomavirus research. *J Cancer Res Clin Oncol* 122: 3-13.

3. Ganem D and Prince AM (2004). Hepatitis B virus infection--natural history and clinical consequences. *N Engl J Med* 350: 1118-1129.

4. Ou JH (2006). Hepatitis B, Hepatitis C. and Hepatocellular Carcinoma. In: Warshawsky D, Landolph JR, eds., *Molecular carcinogenesis and the molecular biology of human cancer.* Boca Raton: CRC, Taylor and Francis 151-177.

5. Harris HE, Eldridge KP, Harbour S, et al. (2007). Does the clinical outcome of hepatitis C infection vary with the infecting hepatitis C virus type? *J Viral Hepat* 14: 213-220.

6. Schaefer S (2007). Hepatitis B virus taxonomy and hepatitis B virus genotypes. *World J Gastroenterol* 13: 14-21.

7. Parkin DM (2006). The global health burden of infection-associated cancers in the year 2002. *Int J Cancer* 118: 3030-3044.

8. de Villiers EM, Fauquet C, Broker TR, et al. (2004). Classification of papillomaviruses. *Virology* 324: 17-27.

9. Cogliano V, Baan R, Straif K, et al. (2005). Carcinogenicity of human papillomaviruses. *Lancet Oncol* 6: 204.

10. Munoz N, Bosch FX, de Sanjose S, et al. (2003). Epidemiologic classification of human papillomavirus types associated with cervical cancer. *N Engl J Med* 348: 518-527.

11. Pfister H (2003). Chapter 8: Human papillomavirus and skin cancer. *J Natl Cancer Inst Monogr* 31: 52-56.

12. Epstein MA, Achong BG, Barr YM (1964). Virus particles in cultured lymphoblasts from Burkitt's lymphoma. *Lancet* 1: 702-703.

13. Klein E, Kis LL, Klein G (2007). Epstein-Barr virus infection in humans: from harmless to life endangering virus-lymphocyte interactions. *Oncogene* 26: 1297-1305.

14. UNAIDS, World Health Organization (2006). *AIDS epidemic update; special report on HIV/AIDS, December 2006.* Geneva: UNAIDS.

15. Grulich AE, van Leeuwen MT, Falster MO, et al. (2007). Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis. *Lancet* 370: 59-67.

16. Clifford G and Franceschi S (2007). Immunity, infection, and cancer. *Lancet* 370: 6-7.

17. Tommasino M (2001). Early genes of human papillomaviruses. In: Schwab M, ed., *Encyclopedic Reference of Cancer.* Berlin: Springer. 266-272.

18. Hasan UA, Bates E, Takeshita F, et al. (2007). TLR9 expression and function is abolished by the cervical cancer-associated human papillomavirus type 16. *J Immunol* 178: 3186-3197.

19. O'Brien PM and Campo MS (2003). Papillomaviruses: a correlation between immune evasion and oncogenicity? *Trends Microbiol* 11: 300-305.

20. Raza SA, Clifford GM, Franceschi S (2007). Worldwide variation in the relative importance of hepatitis B and hepatitis C viruses in hepatocellular carcinoma: a systematic review. *Br J Cancer* 96: 1127-1134.

21. Plummer M, van Doorn LJ, Franceschi S, et al. (2007). Helicobacter pylori cytotoxin-associated genotype and gastric precancerous lesions. *J Natl Cancer Inst* 99: 1328-1334.

22. Soni V, Cahir-McFarland E, Kieff E. (2007). LMP1 TRAFficking activates growth and survival pathways. Adv Exp Med Biol.597:173-187.

23. Sylla BS, Hung SC, Davidson DM, et al. (1998). Epstein-Barr virus-transforming protein latent infection membrane protein 1 activates transcription factor NF-kappaB through a pathway that includes the NF-kappaB-inducing kinase and the IkappaB kinases IKKalpha and IKKbeta.

Proc Natl Acad Sci U S A. 95:10106-10111.

24. Terrin L, Dal Col J, Rampazzo E, et al. (2008). Latent membrane protein 1 of Epstein-Barr virus activates the hTERT promoter and enhances telomerase activity in B lymphocytes. J Virol. 82:10175-10187.

25. Young LS, Rickinson AB. (2004). Epstein-Barr virus: 40 years on. Nat Rev Cancer. 4:757-768.

2.6 Alcohol Drinking

Summary

- A causal association has been established between alcohol drinking and cancers of the oral cavity, pharynx, larynx, esophagus, liver, colon, rectum and, in women, breast
- The global burden of alcohol-associated mortality (1 804 000 deaths, or 3.2 % of all deaths) is substantial, according to the WHO Global Burden of Disease project
- In the case of breast and colorectal cancer, a causal association with alcohol drinking has been established only recently, and the public health implications of these associations have not been fully elucidated
- The mechanisms by which alcohol drinking exerts its carcinogenic effects are not fully elucidated, although possible hypotheses include a genotoxic effect of acetaldehyde, an increase in estrogen level, a role as a solvent for other carcinogens, the production of reactive oxygen and nitrogen species and the alteration of folate metabolism
- There is growing evidence that the effect of alcohol is modulated by polymorphisms in genes encoding for enzymes involved in ethanol metabolism, such as alcohol dehydrogenases, aldehyde dehydrogenases and cytochrome P450 2E1, as well as folate metabolism and DNA repair
- Priorities for a research agenda on alcohol-related carcinogenicity would include: (i) the effect of drinking patterns, (ii) investigations on the risk of cancer in suspected target organs and (iii) elucidation of the role of genetic variants

A causal association has been established between alcohol drinking and cancers of the oral cavity, pharynx, larynx, esophagus, liver, colon, rectum and, in women, breast [1]. An association is suspected for lung cancer. Some studies have shown an increased risk of pancreatic cancer with heavy drinking, but the epidemiologic evidence for this is weak.

For squamous-cell carcinomas of the upper aerodigestive tract (oral cavity, pharynx, larynx and esophagus), a causal relationship was first demonstrated in the mid-1950s [2]. In epidemiological studies of this group of tumours, an effect of heavy alcohol intake and a linear relationship with amount of drinking has been consistently shown. A synergism between alcohol drinking and tobacco smoking was demonstrated in the 1970s, and has since become a paradigm of interaction of two environmental factors in human carcinogenesis. A carcinogenic effect of alcohol drinking independent from that of smoking (i.e. an increased risk of head and neck cancers in non-smokers) was first reported in 1961 [2], and replicated in a recent large-scale pooled analysis (Figure 2.6.1) [3].

Heavy alcohol intake increases the risk of hepatocellular carcinoma, with the most likely mechanism through development of liver cirrhosis, although alternative mechanisms such as alteration in the hepatic metabolism of carcinogens may also play a role. Alcoholic liver cirrhosis is probably the most important risk factor for hepatocellular carcinoma in populations with low prevalence of HBV and HCV infection, such as North America and northern Europe. Synergistic interactions on the risk of liver cancer are also thought to occur between tobacco and alcohol, and between HBV/HCV and alcohol [2].

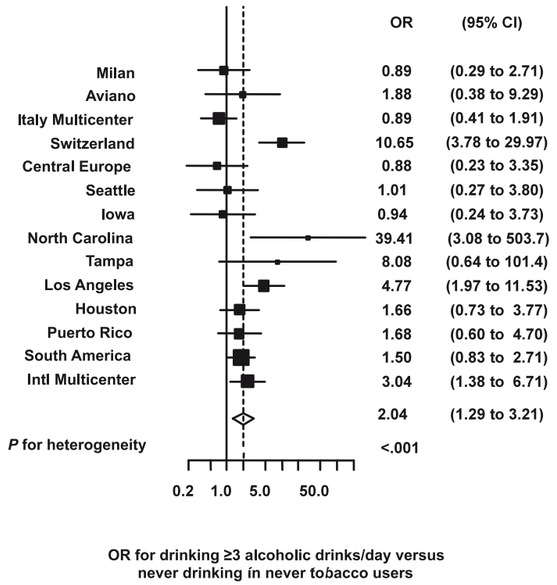


Fig. 2.6.1 *The risk of head and neck cancer, (oral cavity, pharynx and larynx) associated with alcohol drinking in never users of tobacco, overall and by study, using International Head and Neck Cancer Epidemiology consortium pooled data. Odds ratios were adjusted for age, sex, race/ethnicity, education level, and study centre*
From Hashibe et al. [3]

Though the effects may be moderate, there does appear to be a causal relation of alcohol consumption with colorectal and breast cancer risk. Studies on the association of alcohol drinking and adenocarcinoma of the esophagus, stomach cancer, pancreatic cancer and lung cancer have not been consistent. Alcohol drinking does not appear to increase the risk of endometrial, bladder or prostate cancers. In the case of ovarian and kidney cancers, the evidence from epidemiological studies is of a possible protective effect, but further investigation is necessary to clarify the relationships. A reduced risk of non-Hodgkin lymphoma among alcohol drinkers has also been reported. This effect, if real, might differ by lymphoma type, which would contribute to explaining the inconsistencies in results of earlier studies of alcohol and lymphoma.

The major non-neoplastic diseases caused by alcohol drinking include hypertension, haemorrhagic stroke, liver cirrhosis and fibrosis, as well as acute and chronic pancreatitis [1]. In addition, alcohol drinking is a major cause of several types of injuries, and alcohol consumption during pregnancy is associated with various adverse effects including fetal alcohol syndrome, spontaneous abortion, low birth weight, prematurity and intrauterine growth retardation. On the other hand, there is strong evidence that moderate consumption of alcohol reduces the risk of ischaemic heart disease, ischaemic stroke and cholelithiasis.

A global assessment of the burden of alcohol drinking on human health is complicated by several factors, including (i) the background rate of the major diseases, including ischaemic heart disease and liver cirrhosis, (ii) the age distribution of the population, since the incidence of many alcohol-related injuries decreases with age while that of cancer and ischaemic heart disease increases with age and (iii) the pattern of consumption, since the protective effect on ischaemic heart disease is not present at high levels of intake. The most comprehensive estimate of the number of deaths either caused or prevented by alcohol drinking has been conducted within the WHO Global Burden of Disease project [4]. According to this estimate, in 2000 in developed countries the drinking of alcohol was responsible for 185 000 deaths among men, while it prevented 71 000 deaths in men for the same year. For women in developed countries, 277 000 deaths were prevented compared with the 142 000 caused by alcohol. The picture is different in developing countries, because of a lower burden of cardiovascular disease and a greater role of injuries: alcohol drinking is responsible for 1 524 000 extra deaths among men and 301 000 among women. The global burden of alcohol-associated mortality therefore represents 1 804 000 deaths, or 3.2 % of all deaths.

The mechanisms by which alcohol drinking exerts its carcinogenic effects are not fully elucidated: plausible hypotheses include a genotoxic effect of acetaldehyde (the main metabolite of ethanol), an increase in estrogen levels (relevant for breast carcinogenesis), a role as a solvent for other carcinogens, the production of reactive oxygen and nitrogen species and the alteration of folate metabolism. Table 2.6.1 lists the main mechanistic hypotheses, together with our subjective assessment of the strength of the available supporting evidence. The table is restricted to mechanisms known or suspected to operate in cancers with an established association with alcohol drinking.

There is growing evidence that the effect of alcohol is modulated by polymorphisms in genes encoding for enzymes involved in ethanol metabolism, such as alcohol dehydrogenases, aldehyde dehydrogenases and cytochrome P450 2E1, as well as folate metabolism and DNA repair. Alcohol dehydrogenases (ADHs) are enzymes involved in the oxidation of ethanol to acetaldehyde (Figure 2.6.2.) [5]. Subsequent oxidation of acetaldehyde to acetate is catalyzed by the enzyme aldehyde dehydrogenase (ALDH). The efficiency in converting ethanol to acetaldehyde, and subsequent conversion to acetate, is largely determined by the ADH and ALDH gene families, with potential inter-individual

Mechanism	Potential target organs
Strong evidence*	
DNA damage by acetaldehyde	Head and neck, esophagus, liver
Increased estrogen level	Breast
Moderate evidence*	
Solvent for other carcinogens	Head and neck, esophagus
Production of reactive oxygen and nitrogen species	Liver, others?
Alteration of folate metabolism	Colon and rectum, breast, others?
Weak evidence*	
DNA damage by ethanol	Head and neck, esophagus, liver
Nutritional deficiencies (e.g., vitamin A)	Head and neck, others?
Reduced immune surveillance	Liver, others?
Carcinogenicity of constituents other than ethanol	Head and neck, esophagus, liver, others?

Table 2.6.1 *Possible mechanisms of carcinogenicity of alcoholic beverages*
** Subjective assessment of strength of supportive evidence*

differences in acetaldehyde exposure due to the presence of some well-studied common genetic variants with a functional role. Cytochrome P-450 2E1 (CYP2E1) is induced by ethanol, oxidizes ethanol into acetaldehyde, and also activates tobacco procarcinogens including nitrosamines [6]. Methylenetetrahydrofolate reductase (MTHFR) converts 5,10-methylenetetrahydrofolate to 5-methylenetetrahydrofolate, which is important for DNA synthesis and methylation. Sequence variants in DNA repair genes such as those on the nucleotide excision pathway, and on the base excision pathway have been studied as susceptibility factors for various cancers. While the study of genetic variation in alcohol metabolizing genes and their association to cancer is a promising area of research [7], it is unclear at present whether the observed associations are true, and whether they will have clinical or public health relevance.

Alcohol drinking is one of the most important known causes of human cancer. With the exception of aflatoxin, for no single dietary factor is there such a strong and consistent evidence of carcinogenicity. In some populations, namely countries of Central and Eastern Europe, where alcoholic intake is thought to be high (Table 2.6.2), the burden of alcohol-associated cancer (and of other alcohol-associated diseases) is substantial. Alcohol consumption is rapidly increasing in large regions of the world, such as East Asia [8]. In the case of breast and colorectal cancer, two major human neoplasms, a causal association with alcohol drinking has been established only recently, and the public health implications of these associations have not been not fully elucidated. In many countries, people of lower socioeconomic status or education consume more alcohol, which contributes to social inequalities in the cancer burden [9].

Despite its importance in human carcinogenesis, research on alcohol and cancer remains limited in clinical, epidemiological and experimental settings. Priorities for a research agenda on alcohol-related carcinogenicity would include: (i) better epidemiological studies on the effect of drinking patterns (in particular binge drinking, the prevalence of which is increasing in many countries) and of specific alcoholic beverages, (ii) investigations on the risk of cancer in suspected target organs, including pancreatic and kidney cancer, and (iii) elucidation of the role of genetic variants in modifying the risk of alcohol-associated cancer, which would also shed light on possible mechanisms of action.

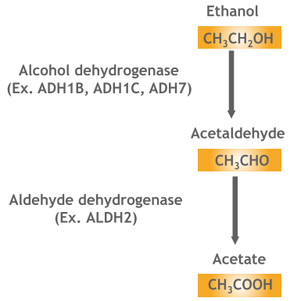


***Fig.* 2.6.2** *The major pathway of alcohol metabolism in humans*

Beer		Wine		Spirits	
Country	**APC**	**Country**	**APC**	**Country**	**APC**
Czech Republic	9.43	Luxembourg	9.43	Republic of Moldova	10.94
Ireland	9.24	France	8.38	Reunion	8.67
Swaziland	7.49	Portugal	7.16	Russian Federation	7.64
Germany	7.26	Italy	6.99	Saint Lucia	7.27
Austria	6.42	Croatia	6.42	Dominica	7.20
Luxembourg	6.16	Switzerland	6.23	Thailand	7.13
Uganda	6.14	Argentina	5.63	Bahamas	7.05
Denmark	6.02	Spain	5.07	Latvia	6.62
The United Kingdom	5.97	Bermuda	4.95	Haiti	6.46
Belgium	5.90	Greece	4.78	Belarus	6.34

***Table* 2.6.2** *Countries with the highest adult per capita (APC) consumption, in litres of pure alcohol by alcoholic beverage type*
** Adapted from the WHO Global Status Report on Alcohol, 2004 [7]*

REFERENCES

1. Boffetta P, Hashibe M (2006). Alcohol and cancer: *Lancet Oncol 7*: 149-156.

2. IARC (1988). *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 44, Alcohol drinking. Lyon, France: International Agency for Research on Cancer.*

3. Hashibe M, P Brennan, S Benhamou, et al. (2007). Alcohol drinking in never users of tobacco, cigarette smoking in never drinkers, and the risk of head and neck cancer: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium. *J Natl Cancer Inst* 99: *777-789.*

4. Rehm J, Room R, Monteiro M, et al. (2004). Alcohol use. In: Ezzati M, Murray C, Lopez AD, Rodgers A (eds). *Comparative Quantification of Health Risks: Global and Regional Burden of Disease Attributable to Selected Major Risk Factors.* Geneva: World Health Organization; 959-1108.

5. Brennan P, Lewis S, Hashibe M, et al. (2004). Pooled analysis of alcohol dehydrogenase genotypes and head and neck cancer: a HuGE review. *Am J Epidemiol* 159: 1-16.

6. Brennan P, Boffetta P (2004). Mechanistic considerations in the molecular epidemiology of head and neck cancer. In: Buffler P, Rice J, Baan R, Bird M, Boffetta P (eds). *Mechanisms of Carcinogenesis: Contributions of Molecular Epidemiology. IARC Sci. Publ. No.157.* Lyon: International Agency for Research on Cancer; 393-414.

7. Hashibe M, McKay JD, Curado MP, et al. (2008). Multiple ADH genes are associated with upper aerodigestive cancers. Nat Genet 40(6):707-709.

8. World Health Organization (2004). *Global Status Report on Alcohol.* Geneva: World Health Organization.

9. Møller H, Tønnesen H (1997). Alcohol drinking, social class and cancer. In: Kogevinas M, Pearce N, Susser M, Boffetta P (eds). *Social Inequalities and Cancer. IARC Sci. Publ. No.138.* Lyon: International Agency for Research on Cancer; 251-63.

2.7 Reproductive Factors and Endogenous Hormones

Summary

> Reproductive factors are strongly involved in the etiology of breast, endometrial and ovarian cancers

> Age at menarche, age at first birth, number of pregnancies, age at last birth and age at menopause have all been associated with cancer risk in women

> Long-term exposure to high levels of endogenous sex steroids increases the risk of breast and endometrial cancers in post-menopausal women

Evidence is accumulating in the literature on the implication of endogenous hormones (particularly sex steroids and growth factors) in the etiology and in the development of several human cancers, especially breast cancer and those of the female reproductive organs (such as ovary and endometrium).

Breast cancer

The incidence of breast cancer is very low in females below the age of 15, and increases very steeply (in the order of about a hundred-fold) by the age of 45. After menopause, the production of estrogens and progesterone from the ovaries ceases, and the increase in breast cancer incidence rates with age slows down compared to pre-menopausal women. This suggests a significant implication of hormones in the etiology/development of breast cancer. *In vitro* experiments have shown that estrogen increases mammary cell proliferation, and *in vivo* experiments in animals have demonstrated that estrogen increases tumour development. Further elements strengthen the association between endogenous sex steroids and breast cancer: an early age at menarche, a late age at menopause and the use of hormone replacement therapy in post-menopausal women have been repeatedly associated with an increase in breast cancer risk [1].

Increases in breast cancer risk are generally explained by the longer lifetime exposure of women to high levels of endogenous sex steroids, especially estradiol, that increase the proliferation and inhibit apoptosis of mammary epithelium (Figure 2.7.1). In addition, overweight and obesity in post-menopausal women not taking exogenous hormones have also been associated with an overall 40% increase in breast cancer risk, and the most widely accepted explanation is again related to the exposure to elevated levels of sex steroids, since in post-menopausal women the ovaries stop producing estrogens, which are instead produced by the aromatisation of androgens in the adipose tissues. Obese women have higher estrogen and lower sex hormone binding globulin (SHBG) levels compared to non-obese women, and therefore increased concentrations of bioavailable estrogens to target tissues.

Early age at first pregnancy, high parity and prolonged breast feeding have been associated with decreased risk of breast cancer (Figure 2.7.2) [1], mainly explained by the differentiation of mammary tissue induced by pregnancy-related hormones. Pregnancy has, however, a double effect on breast cancer risk: a short-term increase and a long-term reduction in risk. The most likely explanation for this double effect is related to the hormone-related differentiation of the cells of the glandular tissues, which reduces the number of susceptible cells (long-term effect), but also stimulates the growth of already existing pre-clinical cancers (short-term effect).

Results from re-analyses and from large-scale prospective epidemiological studies have confirmed a strong implication of endogenous sex steroids in the onset of breast cancer in post-menopausal women (Figure 2.7.3) [2]. Results from these studies showed that women with elevated serum estrogen (estradiol, estrone and free estradiol), as well as androgen (testosterone, free testosterone, androstenedione and dehydrepiandrosterone) concentrations in the upper quintile of the hormones examined were at about two-fold increase in breast cancer risk compared to women in the lowest quintile. SHBG levels were inversely associated with cancer risk. It has also been suggested that the association of circulating sex hormone levels may be stronger with breast cancer positive for estrogen and progesterone receptors. A large prospective study also provided strong evidence of an association of serum endogenous androgens (testosterone, androstenedione, and DHEAS) with breast cancer risk in pre-menopausal women, but no increase in risk was observed for estrogens [3] (Figure 2.7.4).

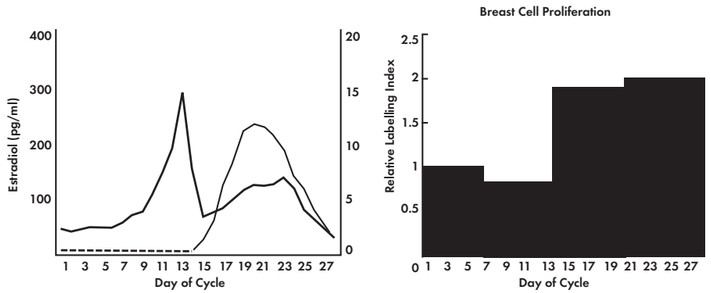


Fig. 2.7.1 *Breast mitotic rate by day of cycle [18]*

Some inconsistencies in the relationship between endogenous estrogens and breast cancer risk in pre-menopausal women across different studies may be due to the difficulty in obtaining accurate estrogen measurements in this population because of the high variability of serum concentrations throughout the menstrual period. It is also plausible that in pre-menopausal women the risk of breast cancer is related to estrogen concentrations in a non-linear manner [3]. A decrease in breast cancer risk among pre-menopausal women was observed with increasing progesterone levels.

Prolactin is a hormone that is involved in the normal development of the normal breast and in lactation. *In vitro*, it promotes cell proliferation and survival, and supports tumour vascularisation. *In vivo*, experiments in animals have shown that prolactin increases tumour growth and proliferation of metastases. A number of case–control studies nested within large cohorts have suggested a positive association between breast cancer incidence and prolactin levels, although results have been more consistent in post-menopausal women than in pre-menopausal women [4].

Insulin-like growth factor-I (IGF-I) is a polypeptide hormone that is involved in several cellular responses related to cell growth, DNA, RNA and protein synthesis. It has mitogenic and anti-apoptotic properties, and co-regulates the proliferation of many cell types, including breast epithelium [5]. Several epidemiological studies have been published on the relationship of circulating IGF-I to breast cancer risk, with different results: preliminary studies reported an overall 2-fold increase in risk with increasing circulating IGF-I levels only in women who had a diagnosis of breast cancer at a relatively young age (before 50 years of age) [6], while more recent studies reported a moderate increase in risk of about 30% in women who had a diagnosis of breast cancer when older than 50 years [7,8].

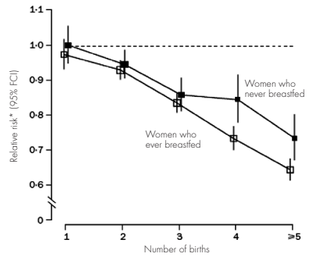


Fig. 2.7.2 *Relative risk of breast cancer in women according to breast feeding history and number of births [19]*

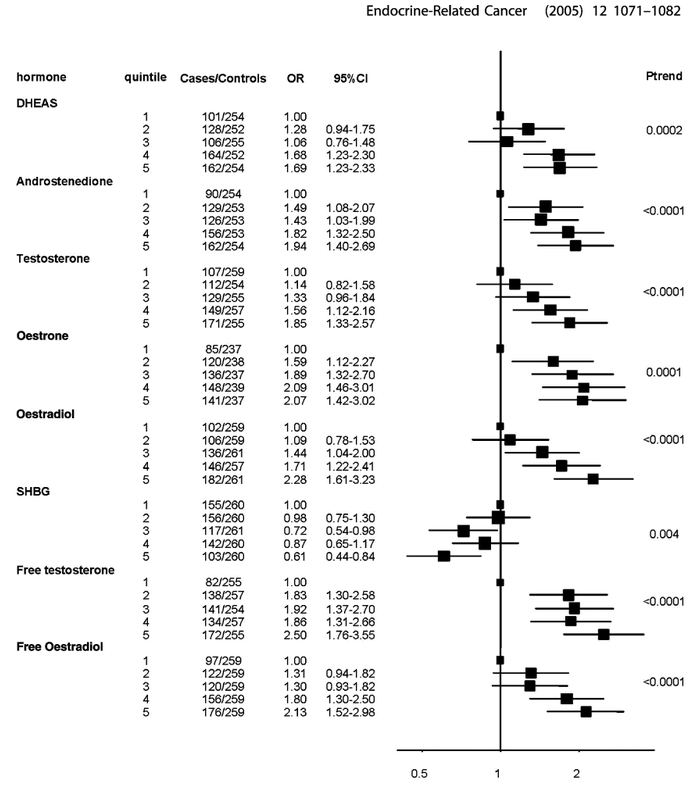


Fig. 2.7.3 *Relative risk of breast cancer among postmenopausal women by quintiles of serum steroid concentrations (the European Prospective Investigation into Cancer and nutrition -EPIC study) [2]*

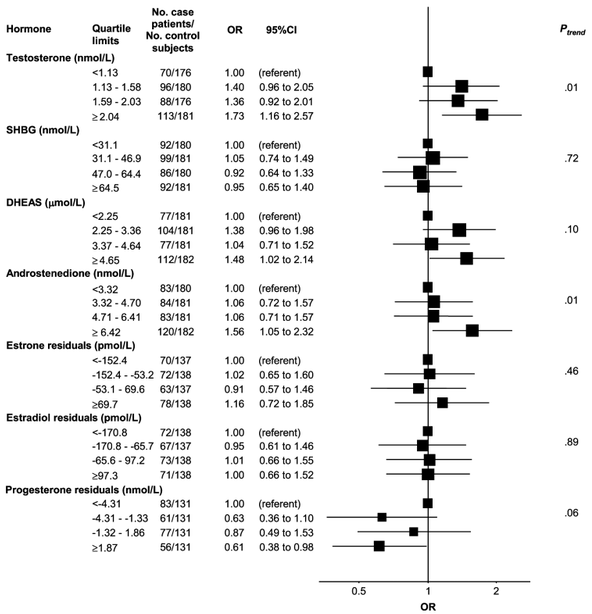


Fig. 2.7.4. *Relative risk of breast cancer among premenopausal women by quintiles of serum steroid concentrations (EPIC study) [3]*

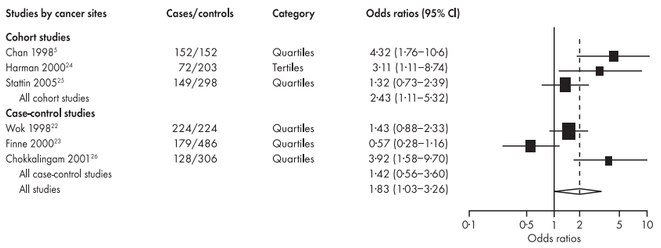


Fig. 2.7.5. *Relative risk of prostate cancer with levels of blood insulin-like growth factor-I. Reanalyses of cohort and case-control studies [17]*

Endometrial cancer

Endometrium is a tissue that is very responsive to hormone stimulation. Risk factors such as an early age at menarche, late age at menopause, nulliparity, hormone replacement therapy (HRT) use and obesity suggest a strong involvement of endogenous hormones in endometrial cancer etiology. The "unopposed estrogen" hypothesis may well explain the relationship between endometrial cancer and sex steroids [9]. This hypothesis states that endometrial cancer risk is increased in women who have relatively high circulating estrogen concentrations that are not counterbalanced by high progesterone concentrations. This theory was mainly developed from the observation that endometrial cells reach their maximum proliferation rates during the follicular phase of the menstrual cycle (a phase in which progesterone concentrations are very low), and from the fact that the use of estrogen-containing only exogenous hormones (without progestagens) increase the risk of endometrial cancer. While estrogen induces the proliferation of the epithelial endometrial cells, progesterone reduces the estrogenic action in the endometrium by stimulating the local synthesis of 17 beta-hydroxysteroid dehydrogenase and by increasing estrogen sulfatase. Progesterone also stimulates the production of insulin-like binding protein-I that lowers the concentration of bioavailable IGF-I.

The "unopposed estrogen" hypothesis can explain most of the risk factors already identified, as early age at menarche, late age at menopause, nulliparity, hormone replacement therapy (HRT) use and obesity. Strong support for the unopposed estrogen hypothesis comes from epidemiological studies, where case–control and prospective studies indicate an increase in risk with increasing circulating estradiol concentrations (Table 2.7.1) [10,11].

While androgens do not seem to have a direct proliferative effect on endometrial cells, they do seem to be involved in endometrial carcinogenesis (possibly through increasing estrogen levels): women with polycystic ovary syndrome (PCOS) (a syndrome associated with increased blood androgen levels, and with infertility, amenorrhea, hirsutism and diabetes), are at higher endometrial cancer risk compared to normal women and tend to develop premenopausal endometrial cancer [10]. Obese women are very often insulin resistant, so they constantly have very high levels of circulating insulin in their blood. Insulin induces endometrial cell proliferation, increases IGF-I activity, stimulates androgen synthesis and down-regulates SHBG concentrations [10], all factors that have been associated with increased risk of endometrial cancer .

Ovarian cancer

Most ovarian malignancies arise from the surface epithelium of the ovary. The epithelium is first trapped within the stroma to form inclusion cysts, which are then transformed into tumour cells. This second step is believed to be hormonally driven. There are already a number of established epidemiological risk factors for ovarian cancer, all suggesting the implication of hormonal factors in the disease aetiology. Infertility, low parity and family history of ovarian cancer increase the risk of ovarian cancer, while the use of oral contraceptives, breast-feeding, hysterectomy or tubal ligation have been shown to decrease the risk [12].

Several hypotheses on the etiology of this cancer have been proposed, including incessant ovulation, excessive gonadotropin stimulation or direct stimulation by steroid hormones [12]. An excessive production of gonadotropins (such as luteinising hormone) can stimulate proliferation and malignant transformations of ovarian epithelium either directly or indirectly through increased ovarian production of androgens. *In vitro* and *in vivo* experiments have shown that ovarian epithelial cell proliferation is stimulated by both androgens and estrogens. Polycystic ovary syndrome (a syndrome associated with increased ovarian androgen secretion) is associated with an increase in ovarian cancer risk, while oral contraceptive use (which suppresses pituitary lutenizing hormone secretion and androgen production) has a strong and long-lasting protective effect [12]. Only a few prospective epidemiological studies have been published so far on the association between endogenous circulating hormones and ovarian cancer risk, with inconsistent results. However, the sample size of these studies was relatively small.

Insulin-like growth factors are involved in steroidogenesis in the ovary, and in the growth and development of ovarian follicles. They have mitogenic and antiapoptotic properties on epithelial ovarian cells. The epidemiological evidence for the implication of IGF-I in ovarian cancer etiology is quite scarce. Recently two case–control studies nested within large cohorts have shown an increase in ovarian risk with increasing circulating IGF-I concentrations in blood in young women (pre- or peri-menopausal age).

Prostate cancer

Most human prostate cancers are very sensitive to androgens and respond to anti-androgen therapies. Surgical and medical castration reduces considerably the risk of metastatic prostate cancers, while some case-reports suggest a causal relationship between the use of androgenic steroids and the development of prostate cancer [13]. Within the prostate, testosterone is reduced to dihydrotestosterone through the activity of 5-alpha reductase, and dihydrotestosterone is metabolised to 3-alpha-androstanediol through the activity of 3-alpha reductase. High intra-prostatic levels of dehydrotestosterone have been associated with an increase in prostate cancer risk. Some studies

Hormone	Quartiles				p for trend
	1	2	3	4	
Estradiol	1.00	1.24 (0.59-2.62)	1.88 (0.88-4.01)	4.13 (1.76-9.72)	0.0008
Estrone	1.00	1.39 (0.66-2.93)	1.81 (0.88-3.71)	3.67 (1.71-7.88)	0.0007
Androstenedione	1.00	1.42 (0.69-2.94)	1.61 (0.75-3.45)	2.15 (1.05-4.40)	0.04
Testosterone	1.00	1.62 (0.82-3.20)	2.30 (1.16-4.55)	1.74 (0.88-3.46)	0.06
DHEAS	1.00	1.49 (0.73-3.02)	2.11 (1.05-4.24)	2.90 (1.42-5.90)	0.002
SHBG	1.00	0.73 (0.38-1.38)	0.41 (0.21-0.81)	0.46 (0.20-1.05)	0.01

Table 2.7.1 *Relative risk of endometrial cancer in postmenopausal women by quartiles of serum steroid concentrations [11]*

suggest a relationship between 5-alfa reductase activity and increased prostate cancer risk. Similarly, experiments in animals showed an increase in epithelial prostate cancer cell proliferation with exposure to androgens. All these data suggest that men exposed to elevated circulating levels of endogenous androgens may be at an increased risk of developing prostate cancer, but for the time being this hypothesis has received only very limited support from epidemiological studies. Results from the Prostate Cancer Prevention Trial showed an approximate 25% reduction in prostate cancer prevalence over the 7-year period of intervention in men taking finasteride (a 5α-reductase inhibitor). With the proportion of high-grade cancers detected in the finasteride group 25% higher than that in the placebo group [14] Updated analysis of the trial has revealed that finasteride reduces the overall risk of prostate cancer by 30% and reduces the risk of clinically significant prostate cancer, including high-grade tumours. For tumours with Gleason scores ≤6, men in the finasteride arm had a relative risk reduction (RRR) of 34% (RR0.66 95% CI 0.55, 0.80). For tumours with Gleason scores ≥7, men in the finasteride arm had an RRR of 27% (RR 0.73 95%CI 0.56, 0.96) [15].

A review of eight prospective studies showed no difference in androgen concentrations between cases and matched controls except for a small increase in androstanediol glucuronide [16]. Studies on circulating estrogens and prolactin showed very little evidence for the implication of these hormones in prostate cancer etiology [16]. IGF-I stimulates proliferation and inhibits apoptosis of prostate cancer cells. In epidemiological studies, evidence is accumulating on the association between circulating endogenous IGF-I concentrations and prostate cancer risk: a meta-analysis suggests an almost 50% increase in cancer risk with high concentrations of IGF-I (Figure 2.7.5) [17]. The increase in prostate cancer seems to be more relevant for aggressive malignancies.

REFERENCES

1. Key TJ, Verkasalo PK, Banks E (2001). Epidemiology of breast cancer. *Lancet Oncol* 2: 133-140.

2. Kaaks R, Rinaldi S, Key TJ, et al. (2005). Postmenopausal serum androgens, oestrogens and breast cancer risk: the European prospective investigation into cancer and nutrition. *Endocr Relat Cancer* 12: 1071-1082.

3. Kaaks R, Berrino F, Key T, et al. (2005). Serum sex steroids in premenopausal women and breast cancer risk within the European Prospective Investigation into Cancer and Nutrition (EPIC). *J Natl Cancer Inst* 97: 755-765.

4. Tworoger SS and Hankinson SE (2006). Prolactin and breast cancer risk. *Cancer Lett* 243: 160-169.

5. Yu H and Rohan T (2000). Role of the insulin-like growth factor family in cancer development and progression. *J Natl Cancer Inst* 92: 1472-1489.

6. Renehan AG, Harvie M, Howell A (2006). Insulin-like growth factor (IGF)-I, IGF binding protein-3, and breast cancer risk: eight years on. *Endocr Relat Cancer* 13: 273-278.

7. Rinaldi S, Peeters PH, Berrino F, et al. (2006). IGF-I, IGFBP-3 and breast cancer risk in women: The European Prospective Investigation into Cancer and Nutrition (EPIC). *Endocr Relat Cancer* 13: 593-605.

8. Baglietto L, English DR, Hopper JL, et al. (2007). Circulating insulin-like growth factor-I and binding protein-3 and the risk of breast cancer. *Cancer Epidemiol Biomarkers Prev* 16: 763-768.

9. Key TJ and Pike MC (1988). The dose-effect relationship between 'unopposed' oestrogens and endometrial mitotic rate: its central role in explaining and predicting endometrial cancer risk. *Br J Cancer* 57: 205-212.

10. Kaaks R, Lukanova A, Kurzer MS (2002). Obesity, endogenous hormones, and endometrial cancer risk: a synthetic review. *Cancer Epidemiol Biomarkers Prev* 11: 1531-1543.

11. Lukanova A, Lundin E, Micheli A, et al. (2004). Circulating levels of sex steroid hormones and risk of endometrial cancer in postmenopausal women. *Int J Cancer* 108: 425-432.

12. Lukanova A and Kaaks R (2005). Endogenous hormones and ovarian cancer: epidemiology and current hypotheses. *Cancer Epidemiol Biomarkers Prev* 14: 98-107.

13. Bosland MC (2000). The role of steroid hormones in prostate carcinogenesis. *J Natl Cancer Inst Monogr* 27: 39-66.

14. Thompson IM, Goodman PJ, Tangen CM, et al. (2003). The influence of finasteride on the development of prostate cancer. *N Engl J Med* 349: 215-224.

15. Sarvis JA and Thompson IM (2008). Prostate cancer chemoprevention: update of the Prostate Cancer Prevention Trial findings and implications for clinical practice. Curr Oncol Rep 10(6): 529-32

16. Eaton NE, Reeves GK, Appleby PN, et al. (1999). Endogenous sex hormones and prostate cancer: a quantitative review of prospective studies. *Br J Cancer* 80: 930-934.

17. Renehan AG, Zwahlen M, Minder C, et al. (2004). Insulin-like growth factor (IGF)-I, IGF binding protein-3, and cancer risk: systematic review and meta-regression analysis. *Lancet* 363: 1346-1353.

18. Pike MC, Pearce CL, Wu AH (2004). Prevention of cancers of the breast, endometrium and ovary. *Oncogene* 23: 6379-6391.

19. Breast cancer and breastfeeding: collaborative reanalysis of individual data from 47 epidemiological studies in 30 countries, including 50302 women with breast cancer and 96973 women without the disease (2002). *Lancet* 360: 187-195.

2.8 Exogenous Hormones and Cancer

Summary

- Oral contraceptive (OC) use reduces the risk of ovarian and endometrial cancer, and this protection persists for at least 20 years after stopping use
- Current OC use is associated with a modest increase in risk of breast and cervical cancer, which however disappears a few years after stopping use
- Hormone replacement therapy (HRT) in menopause is associated with an excess in breast cancer risk that levels off 5–10 years after stopping use
- Unopposed estrogen HRT increases endometrial cancer risk
- HRT may favourably influence colorectal cancer incidence, but the evidence is not conclusive

This chapter considers the cancer risks (and benefits) related to oral contraceptive (OC) and hormone replacement therapy (HRT) use. The use of OCs is associated with a protective effect against ovarian, endometrial and possibly colorectal cancer. However, OC use is associated with excess risk of breast, cervical and liver cancer [1-4]. Benefits and risks of OC use on cancer were reviewed in 1998 and in 2005 by Working Groups at the International Agency for Research on Cancer, which concluded that combined (estrogen-progestin) OCs are carcinogenic to humans based on an increased risk for hepatocellular carcinoma (HCC) [2], breast and cervical cancer [5]. HCC is related to current use of OC, but is extremely rare in young women, and the public health consequences of the association are therefore slight.

Breast cancer

Most information on the relation between breast cancer and OC use is derived from a collaborative reanalysis of individual data including 53 297 women with breast cancer and 100 239 controls from 54 epidemiological studies [6]. This provided definitive evidence that current and recent users of combined OCs have a small increase in the RR of breast cancer (RR 1.24).

However, 10 or more years after stopping use of OC, the RR levels off to approach those of never OC users. The results were similar in women with different background risks of breast cancer. Only women who had begun use before age 20 had an apparent and persistent moderate excess risk (RR 1.22) of breast cancer. Other features of OC use such as duration, dose and type of hormone formulation had little effect on breast cancer risk.

A few additional cohort [7-9] and case–control studies of OC and breast cancer [10-17] have been published after this collaborative reanalysis. In the Royal College of General Practitioners oral contraception study including 46 000 women [9,18], as well as in the Oxford FPA cohort study [19], no relevant association was found between breast cancer incidence mortality and various measures of OC use after more than three decades of follow-up. A cohort study of 426 families of breast cancer probands in Minnesota, USA [8] suggested that ever users of earlier formulations of OC with family history of breast cancer were at high risk for the disease (RR 3.3). That study was based, however, on 38 familial case users only, and contrasted with findings of the collaborative reanalysis [6] which showed no excess risk in users with a family history of breast cancer. A report from the Nurses' Health Study II cohort [20] suggested a favourable effect of physical activity on breast cancer risk in current OC users only, but the data were too limited to adequately assess the interaction between physical activity and OC use. In the Women's Contraception and Reproductive Experiences (CARE) study [21], a population-based case–control study of 1847 postmenopausal women from the USA, previous OC users were not at increased breast cancer risk, and there was a negative interaction between combined hormone replacement therapy (CHRT) use and past OC use. In fact, the excess risk for CHRT use was restricted to never OC users, but it was not observed in past OC users. A few other studies from the USA and Norway [22-24] suggested that use of more recent, low-dose OC is not materially related to breast cancer risk.

Cervical cancer

Cancer of the cervix uteri is relatively rare in developed countries, where cervical screening is widespread, but is still the third most common cancer in women worldwide, with an estimated incidence of about 470 000 cases in 2000, and the second most common in developing countries, where it accounts for about 15% of all cancers in women [25,26]. Also within Europe, the difference in mortality between Western, Central and Eastern European countries was over threefold in the late 1990s, and cervical cancer rates in Eastern Europe have been increasing since the early 1980s [27-29].

Although chronic human papillomavirus (HPV) infection is a necessary cause of cervical cancer [30], other factors are likely to have a role in cervical carcinogenesis. Among these are tobacco smoking and exogenous female hormones, including OCs [31]. Several epidemiological studies have reported an increased risk of invasive cervical carcinoma in relation to ever OC use, and a stronger risk for a longer duration of use. The evidence of an association between OC use and adenocarcinoma of the cervix is based on more limited data [2].

The RR of cervical cancer was significantly elevated among long-term OC users in a study from Morocco [32] and in three studies from the Philippines [33], Thailand [34] and the UK [35]. A study from the USA [36] found no significant association between OC use and invasive or *in situ* cervical carcinoma. In this study, however, an association emerged between long-term OC use and *in situ* adenocarcinoma. In the 35-year follow-up of the Royal College of General Practitioners (RCGP) cohort study, the RR of cervical cancer was 1.33 (95% CI 0.92–1.94, [9]).

Most studies, however, could not take into account HPV infection, and biases related to sexual behaviour or screening could not be ruled out [37]. Given the importance of HPV in cervical carcinogenesis, the relation between OCs and cervical cancer was assessed, restricting the analyses to carriers of HPV DNA. A pooled analysis coordinated by the IARC has been published on the role of OCs in women who tested positive for HPV DNA [38]. This study combined the data of eight case–control studies of invasive cervical cancer and two studies on carcinoma *in situ*, including 1676 cervical cancer cases and 255 controls. No increased risk of cervical cancer was reported for women who had used OCs for less than 5 years, but those who used OCs for 5–9 years had a RR of 2.8, as compared with never users. An even higher risk (RR 4.0) was observed for OC users for 10 or more years. OC use was not associated with HPV positivity among controls, thus suggesting that OCs do not increase the acquisition or persistence of HPV infection, but may facilitate its progression into neoplastic cervical lesions. This finding confirmed the time–risk relation from an Italian case–control study [39] that indicated that OCs have a promoting effect on the process of cervical carcinogenesis, with a fall in risk after stopping use.

In a meta-analysis of 28 cohort and case–control studies of cervical cancer including information on OCs, the overall RR was 1.1 for use of less than 5 years, 1.6 for 5–9 years, and 2.2 for 10 or more years [40]. The data suggest that the risk decreases after OC use has stopped, but the effect of stopping use, independent of duration and other time factors, could not be adequately assessed from published studies.

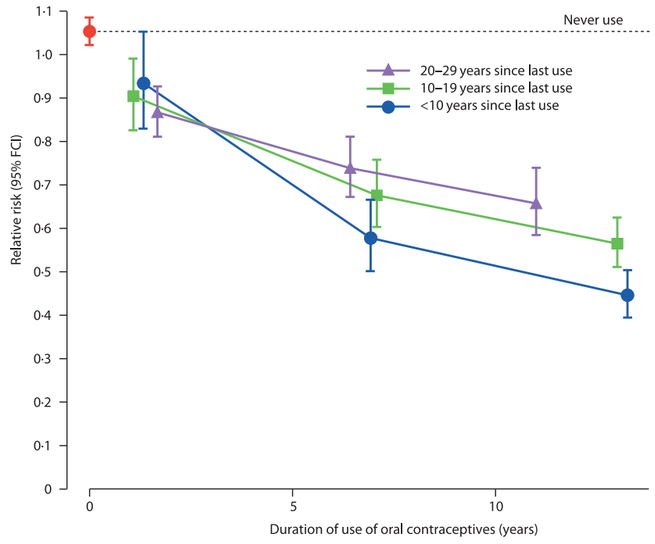


Fig. 2.8.1 *Relative risk* of ovarian cancer by duration and time since last use of oral contraceptives (46)*
**Stratified by study, age, parity, and hysterectomy*

Ovarian cancer

An indication of the favourable impact of OCs on ovarian cancer came from descriptive epidemiology. In several developed countries, young women showed declines in ovarian cancer mortality over the last few decades. Cohort analysis of trends in mortality from ovarian cancer showed that women born after 1920 (i.e. the generations who had used OCs) had reduced ovarian cancer rates, and the downward trends were greater in countries where OCs have been more widely used [2,3]. The protection was similar for newer, low-dose estrogen-progestin pills [41], as well as for various histotypes of ovarian cancer [42], while it is unclear whether the protection is similar for women with hereditary ovarian cancer [43].

The overall estimate of protection for ever use is approximately 30%, and the favourable effect of OCs on epithelial ovarian cancer persists for at least 20 years after stopping use according to the CASH study, and probably continues up to 15–20 years [2,3,5]. The RR was 0.8 up to 20 years after stopping use in a pooled analysis of European studies [44], 0.5 for 15–19 years, and 0.8 for 20 years or more since stopping OC use in a large multicentric US case–control study [45]. The RR was 0.7 for duration >10 years and 20–29 years since last use in the Collaborative Group of Epidemiological Studies of Ovarian Cancer (Figure 2.8.1).In the Oxford Family Planning Association (FPA) cohort study, the RR of death from ovarian cancer was 0.4 at the 30-year follow-up [19], and the RR of ovarian cancer incidence was 0.54 (95% confidence interval, CI 0.40-0.71) for the 35-year follow-up of the RCGP cohort study [9].

Endometrial cancer

OC use also reduces the risk of endometrial cancer by approximately 50% [2,3]. The reduced risk of endometrial cancer persists at least 20 to 30 years after cessation of intake. In the CASH study, the RR was 0.5 for 10–14 years since stopping use; in the WHO study the OR was 0.2 for high progestogen content pills 10 years or more since stopping; in a multicentric US study the OR was 0.3 for 15–19 years and 0.8 for 20 years or more after stopping OC use [2,3]. When duration and recentness of use were evaluated jointly in a case–control study from Washington State [47], longer use (>5 years) was associated with a reduced risk, irrespective of recentness of use. In a Swiss study [48], the RR was 0.4 for 10–19 years after stopping use, and 0.8 for 20 years or more. In a population-based national case–control study from Sweden [49], the RR was 0.2 for 10 or more years of use, and the subsequent use of hormone replacement therapy did not modify the long-term protective effect of OC. The RR of endometrial cancer death was 0.2 in the 30-year follow-up of the Oxford FPA study [19] and that of incidence was 0.58 after 35 years [9]. Endometrial cancer cases were less frequently OC users in a case–control study from China [50].

Colorectal cancer

A role of hormonal and reproductive factors on colorectal carcinogenesis has long been suggested, starting from the observation of an excess of colorectal cancer in nuns [51,52]. A reduction of risk for hormone replacement therapy (HRT) in menopause has also been reported [2,53,54].

Several studies have provided information on OC use and the risk of colorectal cancer. The IARC Monograph 72 [2] reviewed four cohort studies, three of which showed RR for ever OC use below unity. Among 11 case–control studies, the RR was below unity in nine, and significant in two. In a meta-analysis of epidemiological studies on colorectal cancer published up to June 2000, and including quantitative information on OC use, the pooled RR of colorectal cancer for ever OC use was 0.81 from eight case–control studies, 0.84 from four cohort studies, and 0.82 from all studies combined [55]. However, no relation with duration of use was observed. The pattern of risk was similar for colon and rectal cancer. The RR was 0.8 for ever OC use in a recent Swiss case–control study [56]. Only two studies [7,57] included information on recentness of use, and gave some indication that the apparent protection was stronger for women who had used OCs more recently. However, the RR was below unity (RR= 0.79, 95% CI 0.58–0.90) for ever OC users in the 35 years follow-up of the RCGP cohort study [9].

In these analyses, scanty information was available on the type and formulation of OC, but no consistent pattern of trends across calendar year of use (which in several countries is a good proxy of type of preparation) was observed.

Lung cancer

A population-based case–control study of 811 women with lung cancer and 922 controls from Germany [58] showed a reduced lung cancer risk (RR 0.69, 95% CI 0.51–0.92) among ever OC users, in the absence however of any trend in risk with duration of use, age at first use, or calendar year at first use. The RR was non-significantly above unity in the 30-year follow-up of the Oxford FPA cohort study [19] and 1.05 and the 35-year follow-up of the RCGP cohort study [9].

Thus, it is unlikely that any major association is present between OC and lung cancer risk.

Conclusions: OC use

OC use reduces the risk of endometrial and ovarian cancer by approximately 40%; this protection increases with longer use and is long-lasting. The data for colorectal cancer are suggestive of a protective effect of OC, but not conclusive.

With reference to breast cancer, of particular relevance on a public health level is the absence of a persistent excess breast cancer risk in the medium or long term after cessation of OC use, independent of duration of use. In terms of risk assessment for OC use and indications for prescription, these data indicate that any potential increase in risk during OC use, and in the short term after stopping, is of little relevance for younger women whose baseline breast cancer incidence of the disease is extremely low [6,19].

The same line of reasoning applies to cervical cancer. In any case, the association between OC and cervical cancer would be of major relevance in low resource countries, where cervical cancer rates are higher and cervical screening is not adequate [27,29,59,60].

HRT and cancer risk

Menopause has a profound effect on the risk of breast and other female-hormone related cancers, since the slope of incidence for most of these neoplasms levels off after menopause [61]. The most reliable estimate of the influence of menopause on breast cancer risk is given by a collaborative re-analysis of individual data from 51 epidemiological studies including over 52 000 women with breast cancer and 108 000 without breast cancer [62], which estimated an increased risk of 2.8% per year of delayed menopause.

With reference to HRT, in the same data set an elevated risk of breast cancer was reported in current and recent users. The risk increased with longer duration of use by about 2.3% per year, but dropped after cessation of use.

Unopposed estrogen use has been strongly related to endometrial cancer risk in observational studies [2], but cyclic combined estrogen–progestagen risk treatment appears to reduce such an excess risk. Indeed, combined HRT may increase cancer in lean women, but reduce it in overweight ones. However, combined HRT is associated with a higher risk of breast cancer as compared with unopposed estrogens [54,63].

Ovarian cancer risk also appears to be unfavourably influenced by HRT use [64]. Between 1979 and 1998, in the Breast Cancer Detection Demonstration Project (BCDDP) cohort study, 329 cases of ovarian cancer were observed [65]. The RR for estrogen-only HRT was 1.6 (95% confidence interval (CI) 1.2–2.0), for ever users, and rose to 1.8 for 10–19 years of use, and to 3.2 (95% CI 1.7–5.7) for 20 years of use. In the Million Women Study [18], the RR for current HRT users was 1.23 (95% CI 1.09–1.38). The RR increased with duration, and was similar for various types of preparation. There was no excess risk among past users (RR= 0.97).

In contrast, HRT has been related to decreased colorectal cancer risk, the overall RR being about 0.8 among ever users [2,53,54,66].

The most valid evidence on cancer risk in users of combined (estrogen and progestagen) HRT derives, however, from clinical trials, including the Women's Health Initiative (WHI) [67], a randomised controlled primary prevention trial including 8506 women aged 50–70 treated with combined CHRT group and 8102 untreated women. For breast cancer, no difference in risk was apparent during the first 4 years after starting treatment, but an excess risk became evident thereafter, as well as a reduced risk of colorectal cancer. Overall, at 7 years follow-up, 166 breast cancer cases were registered in the CHRT group vs. 124 in the placebo group, corresponding to a RR of 1.24 (95% CI 1.03–1.66).

Data from two other smaller randomised studies are available, one (Heart and Oestrogen/Progestin Replacement Study, HERS) with combined estrogen/progestin therapy [68], and one (Women's Estrogen for Stroke Trial, WEST) with estrogen only [69]. In

	Ever-users*	Duration of use of oral contraceptives			Percent decline in the risk for every 5 years use (95% CI), comparing ever-users
		<5 years	5–9 years	10+ years	
First use before age 20 years					
Relative risk (99% FCI)	0.71 (0.63–0.81)	0.95 (0.80–1.13)	0.65 (0.53–0.81)	0.50 (0.40–0.64)	24.6 (17.0–31.6)
Cases/controls	1009/4381	509/2159	280/1135	169/841	
Mean duration of use	5.4 years	1.9 years	7.0 years	14.2 years	
First use at age 20–24 years					
Relative risk (99% FCI)	0.69 (0.64–0.74)	0.81 (0.73–0.90)	0.68 (0.59–0.78)	0.50 (0.43–0.58)	19.6 (14.4–24.5)
Cases/controls	2051/9384	1166/5063	508/2241	328/1824	
Mean duration of use	5.3 years	1.8 years	6.9 years	13.9 years	
First use at age 25–29 years					
Relative risk (99% FCI)	0.72 (0.66–0.79)	0.84 (0.75–0.95)	0.64 (0.53–0.78)	0.50 (0.41–0.61)	20.4 (14.3–26.0)
Cases/controls	1310/6678	825/3881	249/1376	183/1260	
Mean duration of use	4.8 years	1.6 years	6.8 years	13.6 years	
First use at age 30 years or older					
Relative risk (99% FCI)	0.75 (0.69–0.82)	0.84 (0.76–0.93)	0.63 (0.53–0.74)	0.56 (0.46–0.68)	17.6 (11.6–23.2)
Cases/controls	1740/9337	1131/5583	305/1931	211/1420	
Mean duration of use	4.2 years	1.6 years	6.8 years	12.7 years	

***Table* 2.8.1** *Relative risk of ovarian cancer in ever-users of oral contraceptives compared with that in never users, by age at first use and duration of use of oral contraceptives*
***Never users include 14 703 cases and 51 908 controls with relative risk of 1·00 (99% FCI 0·96–1·04). All relative risks are stratified by study, age, parity, and hysterectomy*
Numbers do not always add to the total, because of missing values

***Fig.* 2.8.2** *Oral contraceptive use reduces the risk of ovarian and endometrial cancer*

a combined analysis of the three randomised trials [70], 205 cases of breast cancer were registered in the HRT groups vs. 154 in the placebo one, corresponding to a pooled RR of 1.27 (95% CI 1.03–1.56). There was however no excess breast cancer risk in the estrogen-only arm of the WHI (RR= 0.77, 95% CI 0.59–1.01, [71]).

Data on endometrial cancer are available from the WHI and the HERS, both based on combined estrogen–progestagen HRT. Overall, 24 cases were observed in the combined HRT groups vs. 30 in the placebo ones, corresponding to a pooled RR of 0.76 (95% CI 0.45–1.31, [70] 2002). This confirms that combined HRT is not related to a material excess risk of endometrial cancer [2,54].

With reference to colorectal cancer, in the WHI 45 cases were observed in the HRT group vs. 67 in the placebo group, corresponding to a RR of 0.63 (95% CI 0.41–0.92). As for breast cancer, the difference in risk between the HRT and the placebo groups became apparent 4 years after starting treatment. Such a time–risk relation gives support to the existence of a real association. There was however no favourable effect on colorectal cancer mortality [66,72]. The combined re-analysis with the HERS data included 56 cases in the combined HRT treatment and 83 cases in the placebo group (pooled RR=0.64, 95% CI 0.45–0.92, [70]).

Observational studies (cohort and case–control) and the limited available evidence from randomised clinical trials do not show any consistent association between HRT and lung cancer risk, as there are similar numbers of studies showing RRs around one (no association) or RRs slightly below one. The absence of any material association between HRT and lung cancer risk is plausible, as it is now apparent that women are not more susceptible to lung cancer than men for a similar level of smoking, thus indicating that female hormones probably do not play an important role in lung carcinogenesis [73]

Conclusions : HRT

Thus, with reference to HRT and cancer risk, the recent findings of the randomised trials are in broad agreement with those of observational (cohort and case–control) studies, and provide convincing evidence that:

(1) HRT, mainly combined estrogen–progestagen HRT, is associated with a moderate excess risk of breast cancer, which becomes evident after a few years of use. The excess risk levels off after 5 to 10 years of stopping use.

(2) Combined HRT is not associated with a material excess risk of endometrial cancer.

(3) HRT has a favourable effect on colorectal cancer risk, which is of interest for any global risk/benefit evaluation of menopause treatment. Its impact on colorectal cancer mortality, if any, remains unclear.

REFERENCES

1. Burkman R, Schlesselman JJ, Zieman M (2004). Safety concerns and health benefits associated with oral contraception. *Am J Obstet Gynecol* 190: S5-22.

2. IARC. (1999). *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 72, Hormonal contraception and post-menopausal hormonal therapy*. Lyon, France: International Agency for Research on Cancer.

3. La Vecchia C, Altieri A, Franceschi S, et al. (2001). Oral contraceptives and cancer: an update. *Drug Saf* 24: 741-754.

4. La Vecchia C and Bosetti C (2004). Benefits and risks of oral contraceptives on cancer. *Eur J Cancer Prev* 13: 467-470.

5. Cogliano V, Grosse Y, Baan R, et al. (2005). Carcinogenicity of combined oestrogen-progestagen contraceptives and menopausal treatment. *Lancet Oncol* 6: 552-553.

6. Breast cancer and hormonal contraceptives: collaborative reanalysis of individual data on 53 297 women with breast cancer and 100 239 women without breast cancer from 54 epidemiological studies. Collaborative Group on Hormonal Factors in Breast Cancer (1996). *Lancet* 347: 1713-1727.

7. Beral V, Hermon C, Kay C, et al. (1999). Mortality associated with oral contraceptive use: 25 year follow-up of cohort of 46 000 women from Royal College of General Practitioners' oral contraception study. *BMJ* 318: 96-100.

8. Grabrick DM, Hartmann LC, Cerhan JR, et al. (2000). Risk of breast cancer with oral contraceptive use in women with a family history of breast cancer. *JAMA* 284: 1791-1798.

9. Hannaford PC, Selvaraj S, Elliott AM, et al. (2007). Cancer risk among users of oral contraceptives: cohort data from the Royal College of General Practitioner's oral contraception study. *BMJ* 335: 651.

10. Levi F, Lucchini F, Pasche C, et al. (1996). Oral contraceptives, menopausal hormone replacement treatment and breast cancer risk. *Eur J Cancer Prev* 5: 259-266.

11. Lipworth L, Katsouyanni K, Stuver S, et al. (1995). Oral contraceptives, menopausal estrogens, and the risk of breast cancer: a case-control study in Greece. *Int J Cancer* 62: 548-551.

12. Magnusson CM, Persson IR, Baron JA, et al. (1999). The role of reproductive factors and use of oral contraceptives in the aetiology of breast cancer in women aged 50 to 74 years. *Int J Cancer* 80: 231-236.

13. Newcomb PA, Longnecker MP, Storer BE, et al. (1996). Recent oral contraceptive use and risk of breast cancer (United States). *Cancer Causes Control* 7: 525-532.

14. Shapiro S, Rosenberg L, Hoffman M, et al. (2000). Risk of breast cancer in relation to the use of injectable progestogen contraceptives and combined estrogen/progestogen contraceptives. *Am J Epidemiol* 151: 396-403.

15. Tryggvadottir L, Tulinius H, Gudmundsdottir GB (1997). Oral contraceptive use at a young age and the risk of breast cancer: an Icelandic, population-based cohort study of the effect of birth year. *Br J Cancer* 75: 139-143.

16. Ursin G, Wu AH, Hoover RN, et al. (1999). Breast cancer and oral contraceptive use in Asian-American women. *Am J Epidemiol* 150: 561-567.

17. Van Hoften C, Burger H, Peeters PH, et al. (2000). Long-term oral contraceptive use increases breast cancer risk in women over 55 years of age: the DOM cohort. *Int J Cancer* 87: 591-594.

18. Beral V, Bull D, Green J, et al. (2007). Ovarian cancer and hormone replacement therapy in the Million Women Study. *Lancet* 369: 1703-1710.

19. Vessey M, Painter R, Yeates D (2003). Mortality in relation to oral contraceptive use and cigarette smoking. *Lancet* 362: 185-191.

20. Colditz GA, Feskanich D, Chen WY, et al. (2003). Physical activity and risk of breast cancer in premenopausal women. *Br J Cancer* 89: 847-851.

21. Norman SA, Berlin JA, Weber AL, et al. (2003). Combined effect of oral contraceptive use and hormone replacement therapy on breast cancer risk in postmenopausal women. *Cancer Causes Control* 14: 933-943.

22. Althuis MD, Brogan DR, Coates RJ, et al. (2003). Hormonal content and potency of oral contraceptives and breast cancer risk among young women. *Br J Cancer* 88: 50-57.

23. Dumeaux V, Alsaker E, Lund E (2003). Breast cancer and specific types of oral contraceptives: a large Norwegian cohort study. *Int J Cancer* 105: 844-850.

24. Marchbanks PA, McDonald JA, Wilson HG, et al. (2002). Oral contraceptives and the risk of breast cancer. *N Engl J Med* 346: 2025-2032.

25. Drain PK, Holmes KK, Hughes JP, et al. (2002). Determinants of cervical cancer rates in developing countries. *Int J Cancer* 100: 199-205.

26. Parkin DM, Bray F, Ferlay J, et al. (2001). Estimating the world cancer burden: Globocan 2000. *Int J Cancer* 94: 153-156.

27. Levi F, Lucchini F, Negri E, et al. (2000). Cervical cancer mortality in young women in Europe: patterns and trends. *Eur J Cancer* 36: 2266-2271.

28. Levi F, Lucchini F, Franceschi S, et al. (2001). Inequalities in health in Europe. *BMJ* 322: 798.

29. Levi F, Lucchini F, Negri E, et al. (2004). Trends in cancer mortality in the European Union and accession countries, 1980-2000. *Ann Oncol* 15: 1425-1431.

30. Walboomers JM, Jacobs MV, Manos MM, et al. (1999). Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. *J Pathol* 189: 12-19.

31. Schiffman MH, Brinton LA, Devesa SS, et al. (1996). Cervical cancer. In: Schottenfeld D, Fraumeni JF, eds., *Cancer epidemiology and prevention*. New York: Oxford University Press 1090-1116.

32. Chaouki N, Bosch FX, Munoz N, et al. (1998). The viral origin of cervical cancer in Rabat, Morocco. *Int J Cancer* 75: 546-554.

33. Ngelangel C, Munoz N, Bosch FX, et al. (1998). Causes of cervical cancer in the Philippines: a case-control study. *J Natl Cancer Inst* 90: 43-49.

34. Chichareon S, Herrero R, Munoz N, et al. (1998). Risk factors for cervical cancer in Thailand: a case-control study. *J Natl Cancer Inst* 90: 50-57.

35. Deacon JM, Evans CD, Yule R, et al. (2000). Sexual behaviour and smoking as determinants of cervical HPV infection and of CIN3 among those infected: a case-control study nested within the Manchester cohort. *Br J Cancer* 83: 1565-1572.

36. Lacey JV, Brinton LA, Abbas FM, et al. (1999). Oral contraceptives as risk factors for cervical adenocarcinomas and squamous-cell carcinomas. *Cancer Epidemiol Biomarkers Prev* 8: 1079-1085.

37. Deligeoroglou E, Michailidis E, Creatsas G (2003). Oral contraceptives and reproductive system cancer. *Ann N Y Acad Sci* 997: 199-208.

38. Moreno V, Bosch FX, Munoz N, et al. (2002). Effect of oral contraceptives on risk of cervical cancer in women with human papillomavirus infection: the IARC multicentric case-control study. *Lancet* 359: 1085-1092.

39. Parazzini F, Chatenoud L, La Vecchia C, et al. (1998). Time since last use of oral contraceptives and risk of invasive cervical cancer. *Eur J Cancer* 34: 884-888.

40. Smith JS, Green J, Berrington de Gonzalez A, et al. (2003). Cervical cancer and use of hormonal contraceptives: a systematic review. *Lancet* 361: 1159-1167.

41. Ness RB, Grisso JA, Klapper J, et al. (2000). Risk of ovarian cancer in relation to estrogen and progestin dose and use characteristics of oral contraceptives. SHARE Study Group. Steroid Hormones and Reproductions. *Am J Epidemiol* 152: 233-241.

42. Tung KH, Goodman MT, Wu AH, et al. (2003). Reproductive factors and epithelial ovarian cancer risk by histologic type: a multiethnic case-control study. *Am J Epidemiol* 158: 629-638.

43. Modan B, Hartge P, Hirsh-Yechezkel G, et al. (2001). Parity, oral contraceptives, and the risk of ovarian cancer among carriers and noncarriers of a BRCA1 or BRCA2 mutation. *N Engl J Med* 345: 235-240.

44. Narod SA, Risch H, Moslehi R, et al. (1998). Oral contraceptives and the risk of hereditary ovarian cancer. Hereditary Ovarian Cancer Clinical Study Group. *N Engl J Med* 339: 424-428.

45. Bosetti C, Negri E, Trichopoulos D, et al. (2002). Long-term effects of oral contraceptives on ovarian cancer risk. *Int J Cancer* 102: 262-265.

46. Rosenberg L, Palmer JR, Zauber AG, et al. (1994). A case-control study of oral contraceptive use and invasive epithelial ovarian cancer. *Am J Epidemiol* 139: 654-661.

47. Voigt LF, Deng Q, Weiss NS (1994). Recency, duration, and progestin content of oral contraceptives in relation to the incidence of endometrial cancer (Washington, USA). *Cancer Causes Control* 5: 227-233.

48. Levi F, La Vecchia C, Gulie C, et al. (1991). Oral contraceptives and the risk of endometrial cancer. *Cancer Causes Control* 2: 99-103.

49. Weiderpass E, Adami HO, Baron JA, et al. (1999). Use of oral contraceptives and endometrial cancer risk (Sweden). *Cancer Causes Control* 10: 277-284.

50. Xu WH, Xiang YB, Ruan ZX, et al. (2004). Menstrual and reproductive factors and endometrial cancer risk: Results from a population-based case-control study in urban Shanghai. *Int J Cancer* 108: 613-619.

51. Fernandez E, Bosetti C, La Vecchia C, et al. (2000). Sex differences in colorectal cancer mortality in Europe, 1955-1996. *Eur J Cancer Prev* 9: 99-104.

52. Fraumeni JF, Lloyd JW, Smith EM, et al. (1969). Cancer mortality among nuns: role of marital status in etiology of neoplastic disease in women. *J Natl Cancer Inst* 42: 455-468.

53. Hebert-Croteau N (1998). A meta-analysis of hormone replacement therapy and colon cancer in women. *Cancer Epidemiol Biomarkers Prev* 7: 653-659.

54. La Vecchia C, Brinton LA, McTiernan A (2001). Menopause, hormone replacement therapy and cancer. *Maturitas* 39: 97-115.

55. Fernandez E, La Vecchia C, Balducci A, et al. (2001). Oral contraceptives and colorectal cancer risk: a meta-analysis. *Br J Cancer* 84: 722-727.

56. Levi F, Pasche C, Lucchini F, et al. (2003). Oral contraceptives and colorectal cancer. *Dig Liver Dis* 35: 85-87.

57. Fernandez E, La Vecchia C, Franceschi S, et al. (1998). Oral contraceptive use and risk of colorectal cancer. *Epidemiology* 9: 295-300.

58. Kreuzer M, Gerken M, Heinrich J, et al. (2003). Hormonal factors and risk of lung cancer among women? *Int J Epidemiol* 32: 263-271.

59. Franceschi S, Herrero R, La Vecchia C (2000). Cervical cancer screening in Europe. What next? *Eur J Cancer* 36: 2272-2275.

60. Skegg DC (2002). Oral contraceptives, parity, and cervical cancer. *Lancet* 359: 1080-1081.

61. La Vecchia C and Franceschi S (2003). Hormone replacement therapy and cancer: an update. *Eur J Cancer Prev* 12: 3-4.

62. Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 women without breast cancer. Collaborative Group on Hormonal Factors in Breast Cancer (1997). *Lancet* 350: 1047-1059.

63. Schairer C, Lubin J, Troisi R, et al. (2000). Menopausal estrogen and estrogen-progestin replacement therapy and breast cancer risk. *JAMA* 283: 485-491.

64. Bosetti C, Negri E, Franceschi S, et al. (2001). Relationship between postmenopausal hormone replacement therapy and ovarian cancer. *JAMA* 285: 3089.

65. Lacey JV, Mink PJ, Lubin JH, et al. (2002). Menopausal hormone replacement therapy and risk of ovarian cancer. *JAMA* 288: 334-341.

66. La Vecchia C, Gallus S, Fernandez E (2005). Hormone replacement therapy and colorectal cancer: an update. *J Br Menopause Soc* 11: 166-172.

67. Rossouw JE, Anderson GL, Prentice RL, et al. (2002). Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. *JAMA* 288: 321-333.

68. Hulley S, Furberg C, Barrett-Connor E, et al. (2002). Noncardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/progestin Replacement Study follow-up (HERS II). *JAMA* 288: 58-66.

69. Viscoli CM, Brass LM, Kernan WN, et al. (2001). A clinical trial of estrogen-replacement therapy after ischemic stroke. *N Engl J Med* 345: 1243-1249.

70. Beral V, Banks E, Reeves G (2002). Evidence from randomised trials on the long-term effects of hormone replacement therapy. *Lancet* 360: 942-944.

71. Anderson GL, Limacher M, Assaf AR, et al. (2004). Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA* 291: 1701-1712.

72. Chlebowski RT, Wactawski-Wende J, Ritenbaugh C, et al. (2004). Estrogen plus progestin and colorectal cancer in postmenopausal women. *N Engl J Med* 350: 991-1004.

73. La Vecchia C (2006). Hormone replacement therapy in menopause and lung cancer: an update. *Eur J Cancer Prev* 15: 283-284.

CANCER INSTITUTE PROFILE: Instituto Nacional de Enfermedades Neoplásicas (INEN)

The Instituto Nacional de Enfermedades Neoplásicas "Eduardo Cáceres Graziani", better known by the acronym INEN, is the most important cancer hospital in Peru and perhaps can be placed among the best in South America. The outpatient services of INEN saw more than 170 000 patients last year and 10 000 were admitted. Of these 1400 had cervical cancer, 1000 breast cancer, 300 malignant lymphoma, 200 acute leukaemia in adults and 100 in children. Stomach, prostate and lung cancer, in that order, were the most prevalent malignancies in men. Beside the important role in the management of this large number of patients, INEN plays two other roles of great relevance: education of oncologists through a residency program that started in 1952 and has already graduated close to 500 specialists, including some from neighbouring countries, and carrying out research protocols in association with important groups in the United States and Europe.

website: www.inen.sld.pe

2.9 Diet, Obesity and Physical Activity

Summary

> There were great expectations that epidemiological studies would discover the dietary habits associated with increased or decreased risk of cancer

> Results from large prospective cohort studies and randomised trials provided evidence that apart from some specific cancers (e.g., stomach cancer) diet accounted for at best a minority of cancers. In particular, intakes of fat, of fruit and vegetables and of meat were either not associated or only slightly associated with colorectal, breast and prostate cancer occurrence

> New promising research avenues investigate combinations of dietary patterns and of lifestyle (e.g. the Mediterranean pattern), and make greater use of biomarkers of exposure to specific nutrients

Epidemiological studies have found strong associations between diet and cardiovascular disease that have been largely reproduced in laboratory experiments. These findings have led to the development of efficient primary prevention of ischemic cardiovascular diseases and the discovery of pharmaceuticals that can be used for both primary prevention and treatment of these diseases. In contrast to cardiovascular diseases, diet and cancer remains at present a most difficult and complicated area of study [1].

In the 1960s, ecological observations pointed at several intriguing relationships between intake of fats and mortality from colorectal cancer or breast cancer. Figure 2.9.1 is an example of such a correlation often found between a diet component and a cancer. Additionally, studies in migrants showed that subjects moving from areas with a low incidence of several cancers, including colorectal and breast cancer, tend to acquire the cancer incidence levels of the host populations [2-5].

The incidence of and mortality from stomach cancer have declined dramatically over the past 50 years in most industrialised countries. This decline is deemed to be partly due to changes in food preservation (e.g. refrigeration instead of salting or smoking) and nutritional habits (e.g. greater availability of fresh fruits and vegetables). A decline in *Helicobacter pylori* colonisation of the stomach due to antibiotic treatment for other diseases or specific eradication of this bacterium has probably also contributed to the decrease in the stomach cancer burden [5].

All these observations led to the hypothesis that nutrition was the predominant non-genetic factor responsible for cancer. In their seminal work on cancer mortality in the USA, Doll and Peto in 1981 estimated that 35% of cancer deaths could be attributable to dietary and nutritional practices, while 30% could be attributable to tobacco smoking. However, the 35% estimate was within a wide "range of acceptable estimates" ranging between 10% and 70%. This estimate of 35% has been widely quoted and used without comment, usually without quoting the wide range of acceptable estimates. Most of the evidence available at the time of Doll and Peto's report was based on case–control studies, and selection and recall biases have been found to be particularly influential in nutrition-related case–control studies. More recently, Doll and Peto offered new estimates of which 25% of cancer deaths could be due to "diet", with a range of acceptable estimates of 15 to 35% [5,7]. As for their 1981 estimates, Doll and Peto provided little detail on how these estimates were computed.

Because ecological and case–control studies are well-known to be prone to biases and difficult to control for confounding factors, more robust study designs were needed in order to establish more firmly the possible links between dietary patterns and cancer. Prospective cohort studies were mounted in the 1980s mainly in the USA, and later in other parts of the world. Several randomised trials were also organized in the USA, e.g. on fibre intake and colorectal cancer. Contrary to all expectations, these well-conducted large-scale cohort studies and randomised trials have provided evidence against a major direct role of nutritional factors in cancer occurrence.

Diet, lifestyle and colorectal, breast and prostate cancer

Table 2.9.1 provides a brief overview of the main results of prospective cohort and randomised trials on the diet-cancer association, and on overweight/obesity and lack of physical activity on three major cancers: colorectal, breast and prostate. Randomised trials provide the strongest scientific evidence, but such trials testing the impact of modification of dietary habits on cancer risk are complex and expensive. Also, for ethical and practical reasons, many questions cannot be addressed with trials. Systematic review with meta-analysis of prospective cohort studies is the second best source of evidence. In the absence of meta-analysis, the prospective cohort studies themselves are the next best source of evidence, and several reviews (without meta-analysis) have summarised key findings from cohort studies. Case–control studies are not to be taken into account when studies with more robust designs exist. References in the table are intended to guide the reader to useful publications for more detailed literature searches.

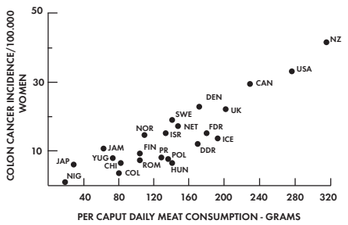


Fig. 2.9.1 *Correlation between incidence of colon cancer in women and mean individual daily meat consumption in 23 countries [6]*

Fig. 2.9.2 *Regular physical exercise appears to be correlated with decreased risk of cancer*

"Small increase" in risk in the table means a risk of cancer occurrence increased by 20 to 30% between groups of subjects with highest versus lowest intakes (groups often defined as quartiles or quintiles). In this case, about 5 to 10% of all cancers may be attributable to high intakes, and thus drastic changes in dietary habits are unlikely to substantially decrease the cancer incidence rate.

The associations between dietary factors and colorectal cancer are of particular interest since this organ may be influenced by foodstuffs in transit through the large bowel, by biological substances absorbed by the colorectal epithelium and by substances circulating in the bloodstream. Prospective cohort studies and clinical trials failed to find evidence for an association between the intake of fibre, of fat and of fruits and vegetables and colorectal cancer. Preserved meat and red meat probably increase the risk of colorectal cancer, but relative risks found so far are of the order of a 30% increase for very high versus very low intakes of red meat. Higher consumption of milk and calcium is associated with a small decreased risk of colorectal cancer, with the inverse association probably limited to cancers of the distal colon and the rectum.

For breast cancer, systematic reviews with meta-analysis have shown no evidence for a protective effect of fruits and vegetables. For fat intake, prospective cohort studies found no association between fat intake and breast cancer, but a randomised trial organized within the Women's Health Initiative trial suggested a small reduction (9%) of borderline significance in breast cancer occurrence with decreased fat intakes [5,8,9].

No association between dietary patterns and prostate cancer has been discovered. The small increase in prostate cancer risk sometimes found with intake of dairy products is probably linked to high calcium intakes rather than to fat intakes. Alcoholic beverages are part of the diet, and have been repeatedly found to be risk factors for colorectal and for breast cancer, but not for prostate cancer (see *Alcohol Drinking*, Chapter 2.6).

For the three major cancers considered in this section, results from prospective studies and randomised trials have yielded results showing no association or associations of much smaller magnitude than were anticipated by results of ecological and case–control studies. As a consequence, drastic changes in some important components of the diet (e.g. a major decrease in fat intake or a significant increase in intakes of fruits and vegetables) are not likely to result in significant change in the incidence of these three frequent cancers.

The case for fruits and vegetables

On the basis of a considerable number of laboratory findings, mechanistic biological hypotheses, and ecological and case–control studies, it was long thought that high intakes of fruits and vegetables would be one of the most efficient primary prevention methods against cancer. The evidence linking high intakes of fruit and vegetables to lower cancer risk has been reviewed by an IARC Working Group [10]: there were no cancers for which the evidence was evaluated as sufficient to conclude that higher fruit or vegetable intake had a preventive effect. Subsequently, major analyses of prospective studies have continued to demonstrate consistently a lack of association between intake of fruits and vegetables and risk of several cancers.

The World Cancer Research Fund has sponsored systematic reviews on diet and cancer. A decade after its original report [11], the current report [12] presents considerably weaker conclusions for the strength of evidence of a protective effect of high intakes of fruits and vegetables against several common epithelial

Fig. 2.9.3 *"There is sufficient evidence in humans for a cancer-preventive effect of physical activity" for cancers of the colon and breast*

Fig. 2.9.4 *"There are no cancers for which the evidence was evaluated as sufficient to conclude that higher fruit or vegetable intake has a preventive effect'*

cancers. The association was downgraded from "convincing" in the first WCRF report in 1997 to "probable" in the second WCRF report of 2007.

Overweight and obesity

The body mass index (BMI) is the weight (in kg) divided by the square of the height (in metres) of an individual. According to international standards, male and female adults with a BMI between 25 and 29.9 kg/m^2 are considered overweight, while those with a BMI equal to or greater than 30 kg/m^2 are obese. Overweight and obesity represent risk factors of considerable importance for cardiovascular diseases, diabetes mellitus and arthritis. An IARC Working Group [13] found that overweight and obesity were consistently associated with:

- in both men and women: adenocarcinoma or the esophagus, kidney cancer;
- men: colon cancer;
- women: breast and endometrial cancer in post-menopausal women.

The IARC systematic review concluded that there was not sufficient evidence for an association of overweight or obesity with prostate cancer (Table 2.9.1). More recent cohort studies [14] and a meta-analysis [15] confirmed findings from the IARC review, and added evidence for a role of obesity in gallbladder cancer in women.

In most industrialised countries, overweight and obesity are increasing, which will contribute to steadily increasing numbers of several cancers in the future. In the coming decades, if there is no reversal in the currently observed trends, obesity and overweight will significantly contribute to further increases in cancer incidence.

Physical activity

The evidence for a cancer-preventive effect of physical activity was evaluated by an IARC Working Group [13] which concluded that "there is sufficient evidence in humans for a cancer-preventive effect of physical activity" for cancers of the colon and breast, and preventive effects increase with increasing physical activity in terms of duration and intensity. This protective effect was independent of the effect of body weight. Conversely, physical inactivity is a risk factor for cancer (Table 2.9.1).

To the best of our knowledge, no study has yet tried to estimate the optimal level of physical activity for cancer prevention. However, for colon cancer, the IARC Working Group on physical activity noted that "at least 30 minutes per day of more than moderate level of physical activity might be needed to see the greatest effect in risk reduction" [13]. For breast cancer, the "risk reduction begins at levels of 30–60 minutes per day of moderate-intensity to vigorous activity in addition to the usual levels of occupational and household activity of most women" [13].

New approaches in the lifestyle-diet-cancer association

Disease occurrence among people following a strict vegetarian diet (i.e. implying no meat, very low-fat diet, and sometimes no animal products at all) has been extensively studied. The most striking observation is that the incidence of breast and prostate cancer is similar among vegetarians than in the background population, while the incidence of colorectal cancer is about half that of the background population [16]. Of interest also, was the finding that the magnitude of decrease in cancer risk (e.g. the colorectal cancer risk) was substantially more associated with a lean body mass index and regular physical exercise than with vegetarian status. These observations prompted the working hypothesis that what really matters is not a particular nutrient or class of nutrients, but rather the combination of dietary pattern and lifestyle habits that influences the likelihood of disease, and of cancer in particular.

The scientific relevance of this working hypothesis has been demonstrated by recent cohort studies that showed decreased risk in overall mortality, and in cancer and cardiovascular, and non-cancer, non-cardiovascular mortality in subjects who had a diet close to the "Mediterranean dietary pattern": rich in carbohydrates, vegetal oil, fish, fruits and vegetables, and poor in meat and animal fat [17-19]. Each single dietary item typically part of or typically at odds with the Mediterranean dietary pattern had no or little association with disease or death occurrence, but it is the combination of dietary items that contributed to lowering cancer and cardiovascular diseases. Conversely, the absence of such a combination would contribute to increasing the risk of cancer and cardiovascular diseases. Furthermore, adherence to a Mediterranean diet was also associated with less smoking, less obesity, more physical activity. Hence, a Mediterranean diet can be considered as usually associated with healthier lifestyle, which also contributes to health benefits associated with this dietary pattern.

Also in line with the working hypothesis, another prospective study showed that the combination of physical activity, absence of smoking and of obesity, low alcohol intake and higher serum vitamin C levels was associated with lower death rates [20].

Another promising research area is the use of biomarkers of exposure, which are likely to provide more reliable reflects of exposures to a variety of food items and behaviours than questionnaires. For instance, the plasma phospholipid elaidic acid level is a good biomarker of dietary intakes of manufactured foods. Results from a cohort study have suggested a strong association between plasma levels of the phospholipid elaidic acid and breast cancer occurrence [21].

	Colorectal cancer (CRC)			Breast cancer			Prostate cancer		
Increases in intakes of	Change in risk	Type of studies	References	Change in risk	Type of studies	References	Change in risk	Type of studies	References
Fruits and vegetables	No change	Review	[22]	No change	RCT	[23]	No change	Cohorts	[24]
	No change	RCT on polyps	[25]	No change	MetaA	[26]			
	No change	MetaA on CRC	[27]						
Fibres	No change	RCT on polyps	[25]	No sufficient data	Review	[12]	No sufficient data	Review	[12]
	No change	MetaA on CRC	[28]						
Fat	No change	RCT on CRC	[29]	Small increase	RCT	[9]	No sufficient data	Review	[12]
	No change	Cohorts	[30]	No change	MetaA	[31]			
Red meat, processed meat	Small increase	Review and cohorts	[22,32,33]	No sufficient data	Review	[12]	No change	Cohorts	[12]
Fish	No change	Review	[22]	No change	Review	[34,35]	No change	Review	[35]
Dairy products, including calcium	Small decrease of polyps	RCT on polyps	[36]	No change in postmenopausal women, possible small decrease in risk in pre-menopausal women	Cohorts	[37]	No change, but possible increased risk with high calcium intakes	Cohorts	[38-42]
	Small decrease of CRC incidence	Cohorts	[41]						
Alcohol	Small increase	Review, MetaA	[43]	Increased risk	MetaA	[31]	No change	Review	[43]
Lifestyle factors									
Overweight/ obesity	Increase	MetaA, Review	[13,15]	Increase after menopause	MetaA, Review	[13,15,31]	No change	MetaA, Review	[13,15]
Lack of physical activity	Increase (for colon cancer)	Review	[13,44]	Increase, mainly after menopause	Review	[13,44]	Small increase	Review	[13]

Table 2.9.1 *Summary of main findings from cohort studies and randomised trials on foodstuffs, lifestyle habits and colorectal, breast and prostate cancer*
MetaA: systematic review with meta-analysis of prospective cohort studies - RCT: randomized controlled trial - Review: exhaustive review of prospective cohort studies, but without meta-analysis
CRC: colorectal cancer

REFERENCES

1. Boyle P, Boffetta P, Autier P (2008). Diet, nutrition and cancer: public, media and scientific confusion. *Ann Oncol* 19: 1665-1667.

2. Maskarinec G and Noh JJ (2004). The effect of migration on cancer incidence among Japanese in Hawaii. *Ethn Dis* 14: 431-439.

3. McCredie M, Williams S, Coates M (1999). Cancer mortality in East and Southeast Asian migrants to New South Wales, Australia, 1975-1995. *Br J Cancer* 79: 1277-1282.

4. McCredie M, Williams S, Coates M (1999). Cancer mortality in migrants from the British Isles and continental Europe to New South Wales, Australia, 1975-1995. *Int J Cancer* 83: 179-185.

5. Tomatis L, Aitio A, Day NE, et al. (1990). *IARC Scientific Publications, Volume 100, Cancer: causes, occurrence and control.* Lyon, France: International Agency for Research on Cancer.

6. Armstrong B and Doll R (1975). Environmental factors and cancer incidence and mortality in different countries, with special reference to dietary practices. *Int J Cancer* 15: 617-631.

7. Doll R and Peto R (1981). The causes of cancer: quantitative estimates of avoidable risks of cancer in the United States today. *J Natl Cancer Inst* 66: 1191-1308.

8. Prentice RL, Caan B, Chlebowski RT, et al. (2006). Low-fat dietary pattern and risk of invasive breast cancer: the Women's Health Initiative Randomized Controlled Dietary Modification Trial. *JAMA* 295: 629-642.

9. Prentice RL and Anderson GL (2008). The women's health initiative: lessons learned. *Annu Rev Public Health* 29: 131-150.

10. IARC (2003). *IARC Handbooks of Cancer Prevention, Volume 8, Fruits and vegetables*. Lyon, France: International Agency for Research on Cancer.

11. World Cancer Research Fund / American Institute for Cancer Research (1997). *Food, Nutrition and the Prevention of Cancer: a Global Perspective*. Washington, DC: AICR.

12. World Cancer Research Fund / American Institute for Cancer Research (2007). *Food, Nutrition, Physical Activity and the Prevention of Cancer: a Global Perspective*. Washington, DC: AICR.

13. IARC (2002). *IARC Handbooks of Cancer Prevention, Volume 6, Weight control and physical activity*. Lyon, France: International Agency for Research on Cancer.

14. Reeves GK, Pirie K, Beral V, et al. (2007). Cancer incidence and mortality in relation to body mass index in the Million Women Study: cohort study. *BMJ* 335: 1134.

15. Renehan AG, Tyson M, Egger M, et al. (2008). Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *Lancet* 371: 569-578.

16. Willett W (2003). Lessons from dietary studies in Adventists and questions for the future. *Am J Clin Nutr* 78: 539S-543S.

17. Mitrou PN, Kipnis V, Thiebaut AC, et al. (2007). Mediterranean dietary pattern and prediction of all-cause mortality in a US population: results from the NIH-AARP Diet and Health Study. *Arch Intern Med* 167: 2461-2468.

18. Trichopoulou A, Costacou T, Bamia C, et al. (2003). Adherence to a Mediterranean diet and survival in a Greek population. *N Engl J Med* 348: 2599-2608.

19. Trichopoulou A, Lagiou P, Kuper H, et al. (2000). Cancer and Mediterranean dietary traditions. *Cancer Epidemiol Biomarkers Prev* 9: 869-873.

20. Khaw KT, Wareham N, Bingham S, et al. (2008). Combined impact of health behaviours and mortality in men and women: the EPIC-Norfolk prospective population study. *PLoS Med* 5: e12 DOI:10.1371/journal.pmed.0050012.

21. Chajes V, Thiebaut AC, Rotival M, et al. (2008). Association between serum trans-monounsaturated fatty acids and breast cancer risk in the E3N-EPIC Study. *Am J Epidemiol* 167: 1312-1320.

22. Marques-Vidal P, Ravasco P, Ermelinda CM (2006). Foodstuffs and colorectal cancer risk: a review. *Clin Nutr* 25: 14-36.

23. Pierce JP, Natarajan L, Caan BJ, et al. (2007). Influence of a diet very high in vegetables, fruit, and fiber and low in fat on prognosis following treatment for breast cancer: the Women's Healthy Eating and Living (WHEL) randomized trial. *JAMA* 298: 289-298.

24. Kirsh VA, Peters U, Mayne ST, et al. (2007). Prospective study of fruit and vegetable intake and risk of prostate cancer. *J Natl Cancer Inst* 99: 1200-1209.

25. Schatzkin A, Lanza E, Corle D, et al. (2000). Lack of effect of a low-fat, high-fiber diet on the recurrence of colorectal adenomas. Polyp Prevention Trial Study Group. *N Engl J Med* 342: 1149-1155.

26. Smith-Warner SA, Spiegelman D, Yaun SS, et al. (2001). Intake of fruits and vegetables and risk of breast cancer: a pooled analysis of cohort studies. *JAMA* 285: 769-776.

27. Koushik A, Hunter DJ, Spiegelman D, et al. (2007). Fruits, vegetables, and colon cancer risk in a pooled analysis of 14 cohort studies. *J Natl Cancer Inst* 99: 1471-1483.

28. Park Y, Hunter DJ, Spiegelman D, et al. (2005). Dietary fiber intake and risk of colorectal cancer: a pooled analysis of prospective cohort studies. *JAMA* 294: 2849-2857.

29. Beresford SA, Johnson KC, Ritenbaugh C, et al. (2006). Low-fat dietary pattern and risk of colorectal cancer: the Women's Health Initiative Randomized Controlled Dietary Modification Trial. *JAMA* 295: 643-654.

30. Giovannucci E, Rimm EB, Stampfer MJ, et al. (1994). Intake of fat, meat, and fiber in relation to risk of colon cancer in men. *Cancer Res* 54: 2390-2397.

31. Michels KB, Mohllajee AP, Roset-Bahmanyar E, et al. (2007). Diet and breast cancer: a review of the prospective observational studies. *Cancer* 109: 2712-2749.

32. Cross AJ, Leitzmann MF, Gail MH, et al. (2007). A prospective study of red and processed meat intake in relation to cancer risk. *PLoS Med* 4: e325 DOI:10.1371/journal.pmed.0040325.

33. Norat T, Bingham S, Ferrari P, et al. (2005). Meat, fish, and colorectal cancer risk: the European Prospective Investigation into cancer and nutrition. *J Natl Cancer Inst* 97: 906-916.

34. Engeset D, Alsaker E, Lund E, et al. (2006). Fish consumption and breast cancer risk. The European Prospective Investigation into Cancer and Nutrition (EPIC). *Int J Cancer* 119: 175-182.

35. Terry P, Rohan TE, Wolk A, et al. (2002). Fish consumption and breast cancer risk. *Nutr Cancer* 44: 1-6.

36. Baron JA, Beach M, Mandel JS, et al. (1999). Calcium supplements for the prevention of colorectal adenomas. Calcium Polyp Prevention Study Group. *N Engl J Med* 340: 101-107.

37. Shin MH, Holmes MD, Hankinson SE, et al. (2002). Intake of dairy products, calcium, and vitamin d and risk of breast cancer. *J Natl Cancer Inst* 94: 1301-1311.

38. Ahn J, Albanes D, Peters U, et al. (2007). Dairy products, calcium intake, and risk of prostate cancer in the prostate, lung, colorectal, and ovarian cancer screening trial. *Cancer Epidemiol Biomarkers Prev* 16: 2623-2630.

39. Giovannucci E, Liu Y, Stampfer MJ, et al. (2006). A prospective study of calcium intake and incident and fatal prostate cancer. *Cancer Epidemiol Biomarkers Prev* 15: 203-210.

40. Park SY, Murphy SP, Wilkens LR, et al. (2007). Calcium, vitamin D, and dairy product intake and prostate cancer risk: the Multiethnic Cohort Study. *Am J Epidemiol* 166: 1259-1269.

41. Park Y, Mitrou PN, Kipnis V, et al. (2007). Calcium, dairy foods, and risk of incident and fatal prostate cancer: the NIH-AARP Diet and Health Study. *Am J Epidemiol* 166: 1270-1279.

42. Rodriguez C, McCullough ML, Mondul AM, et al. (2003). Calcium, dairy products, and risk of prostate cancer in a prospective cohort of United States men. *Cancer Epidemiol Biomarkers Prev* 12: 597-603.

43. Boffetta P and Hashibe M (2006). Alcohol and cancer. *Lancet Oncol* 7: 149-156.

44. Kruk J (2007). Physical activity in the prevention of the most frequent chronic diseases: an analysis of the recent evidence. *Asian Pac J Cancer Prev* 8: 325-338.

CANCER INSTITUTE PROFILE: Prof. N. N. Petrov Research Institute of Oncology

The Research Institute was established on the 15th of March 1927 in Leningrad (now St. Petersburg, Russia) within the framework of the multidisciplinary hospital named after I. I. Mechnikov. Professor N. N. Petrov, the founder and initiator of oncology in Russia,, was appointed as its first Director; in 1966, his name was given to the Institute.

The Institute has the state license on performing research, clinical and experimental activities in the field of oncology as well as educational, international and editorial work. The main issues of the investigations are as follows: etiology and pathogenesis of cancer, new methods of prevention and detection of cancer, surgery, radiotherapy, chemotherapy and combined treatment of adult and paediatric cancer patients, as well as their follow-up and rehabilitation.

The Institute's hospital consists of 405 beds and is able to treat all principal malignancies. Many tumours can be cured by the endoscopic methods; conservative, organ-saving surgery is being carried out on the early stages of cancer.

Our Institute is associated with many international organisations such as the International Agency for Research on Cancer (IARC), International Union Against Cancer (UICC), World Health Organization (WHO), and the United Nations Environment Program (UNEP). Some Institute scientists are members of different international scientific and social organizations as well (ASCO, ESMO, ESO, ESSO, ESTRO, EORTC, Reach to Recovery, etc.).

Our current areas of specific research interest include:

- study of carcinogenesis mechanisms, and the roles of endo- and exogenous factors influencing cancer development and indicating means for its prevention;
- investigation of biochemical, molecular and immunological factors that allow assessment of cancer risk and greater understanding of its development;
- development of methods of biotherapy of solid tumours (dendrite cell vaccines, genotherapy, cytokines);
- elaboration and introduction of new highly-effective drugs and high-quality methods, based on the latest scientific achievements, and complex usage of new and standard techniques of cancer treatment;
- study and introduction of new drugs and methods for improving tolerance of anti-cancer therapy, reducing its toxicity and increasing the quality of cancer patients' lives;
- improvement of organ-saving surgery aimed at better quality of life for cancer patients; and improvement of methods for accurate estimation and correct planning of cancer control activities in Russia by studying different kinds of indices in cancer (mortality, morbidity, demography, etc.) as well as dynamic prognostication of these indices in the future by using Cancer Registry data.

2.10 Ionising Radiation

Summary

> Exposure to ionizing radiation from natural as well as from industrial, medical and other sources can increase the risk of a variety of neoplasms, including leukaemia, breast cancer and thyroid cancer

> Over 20 years have passed since the nuclear accident at Chernobyl, and it is now estimated that by 2065 there will be 16 000 cases of thyroid cancer and 28 000 cases of other cancers in Europe as a result of this accident

Natural and man-made sources generate radiant energy in the form of electromagnetic waves. Their interaction with biological systems is principally understood at the cellular level. Electromagnetic waves are characterised by their wavelength, frequency or energy. Effects on biological systems are determined by the intensity of the radiation, the energy in each photon and the amount of energy absorbed by the exposed tissue.

The electromagnetic spectrum extends from waves at low frequency (low energy), referred to as "electric and magnetic fields", to those at very high frequencies, which are often called "electromagnetic radiation" (Figure 2.10.1). The highest-energy electromagnetic radiation is X- and gamma-radiation, which have sufficient photon energy to produce ionization (i.e. create positive and negative electrically-charged atoms or parts of molecules) and thereby break chemical bonds. Other forms of ionizing radiation are the sub-atomic particles (neutrons, electrons (beta-particles) and alpha-particles) that make up cosmic rays and are also emitted by radioactive atoms. Non-ionizing radiation is a general term for that part of the electromagnetic spectrum which has photon energies too weak to break chemical bonds, and includes ultraviolet radiation, visible light, infrared radiation, radiofrequency and microwave fields, extremely low frequency (ELF) fields, as well as static electric and magnetic fields.

Ionizing radiation

Exposure to ionizing radiation is unavoidable [1]. Humans are exposed both to X-rays and gamma-rays from natural sources (including cosmic radiation and radioactivity present in rocks and soil) and typically, to a much lower extent, from man-made sources (Figure 2.10.2).

On average, for a member of the general public, the greatest contribution comes from medical X-rays and the use of radiopharmaceuticals, with lower doses from fallout from weapons testing, nuclear accidents (such as Chernobyl) and accidental and routine releases from nuclear installations. Medical exposures occur both in the diagnosis (e.g. radiography) of diseases and injuries and in the treatment (e.g. radiotherapy) of cancer and of some benign diseases. Occupational exposure to ionizing radiation occurs in a number of jobs, including the nuclear industry and medicine. Airline pilots and crew are exposed to cosmic radiation. The risk projections suggest that (by 2006) Chernobyl may have caused about 1000 cases of thyroid cancer and 4000 cases of other cancers in Europe, representing about 0.01% of all incident cancers since the accident. Models predict that by 2065 about 16 000 (95% CI 3400–72 000) cases of thyroid cancer and 25 000 (95% CI 11 000–59 000) cases of other cancers may be expected due to radiation from the accident, whereas several hundred million cancer cases are expected from other causes [2-4].

Although these estimates are subject to considerable uncertainty, they provide an indication of the order of magnitude of the possible impact of the Chernobyl accident. It is unlikely that the cancer burden from the largest radiological accident to date could be detected by monitoring national cancer statistics. Indeed, results of analyses of time trends in cancer incidence and mortality in Europe do not at present indicate any increase in cancer rates—other than of thyroid cancer in the most contaminated regions—that can be clearly attributed to radiation from the Chernobyl accident.

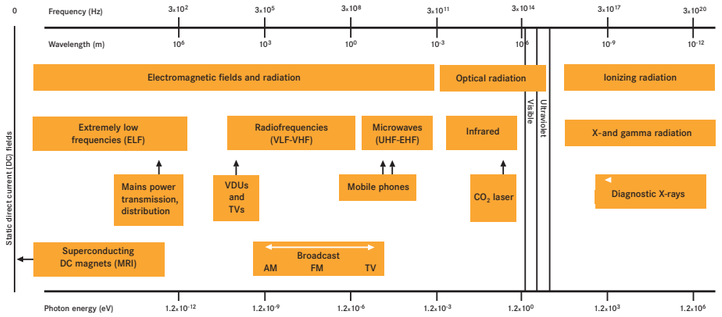


Fig. 2.10.1 *The spectrum of electromagnetic fields and their use in daily life*

Cancer causation

Ionizing radiation is one of the most intensely studied carcinogens [5-7]. Knowledge of associated health effects comes from the epidemiological study of hundreds of thousands of exposed persons, including the survivors of the atomic bombings in Hiroshima and Nagasaki, patients irradiated for therapeutic purposes, populations with occupational exposures and people exposed as a result of accidents. These data are complemented by findings from large-scale animal experiments carried out to evaluate the effects of different types of radiation, taking account of variation in dose and exposure pattern, and with reference to cellular and molecular endpoints. Such experiments are designed to characterise the mechanisms of radiation damage, repair and carcinogenesis.

Survivors of the atomic bombings in Hiroshima and Nagasaki were exposed primarily to gamma rays. Among these people, dose-related increases in the risk of leukaemia, breast cancer, thyroid cancer and a number of other malignancies have been observed. Increased frequency of these same malignancies has also been observed among cancer patients treated with X-rays or gamma rays. The level of cancer risk after exposure to X-rays or gamma rays is modified by a number of factors in addition to radiation dose, and these include the age at which exposure occurs, the length of time over which radiation is received and the sex of the exposed person. Exposure to high-dose radiation increases the risk of leukaemia by over five-fold. Even higher relative risks have been reported for thyroid cancer following irradiation during childhood.

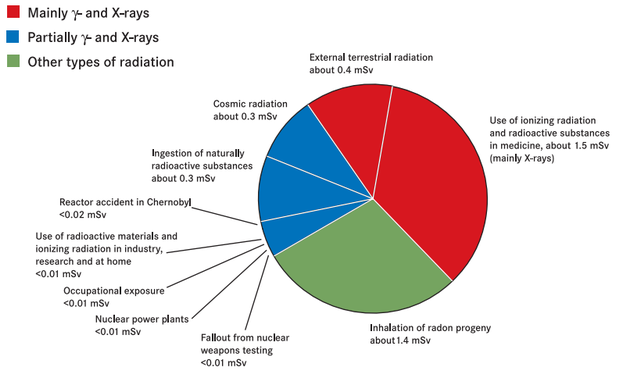


Fig. 2.10.2 *Estimated annual dose of ionizing radiation received by a member of the general public*

	Lifetime risk		Number of years of life lost per case	
	0.2 Sv	1 Sv	0.2 Sv	1 Sv
Solid cancers	2.4%	10.9%	11.2	11.6
Leukaemia	0.14%	1.1%	31	31

Table 2.10.1 *Estimated risk of cancer following acute whole-body exposure to gamma-radiation at two dose levels*

In a study of nuclear industry workers from 15 countries, 1–2% of cancer-related deaths other than leukaemia may be attributable to protracted low-dose radiation exposure while on the job [8]. Other than leukaemia, associations were the most significant for lung cancer and multiple myeloma [9].

Internalised radionuclides that emit alpha-particles and beta-particles are carcinogenic to humans. For most people, exposure to ionizing radiation from inhaled and tissue-deposited radionuclides is mainly from naturally-occurring radon-222. Exposure to thorium-232, which occurs in soil, is less common. Cancers associated with exposure to particular nuclides, usually in an occupational context, include lung cancer, bone sarcomas, liver cancer, leukaemia and thyroid cancer.

The United Nations Scientific Committee on the Effects of Atomic Radiation [10] has estimated the lifetime risk of solid cancers and of leukaemia following an acute whole-body exposure to gamma-radiation, together with the corresponding estimated numbers of years of life lost per radiation-induced case. The current recommendations of the International Commission for Radiological Protection are to limit exposures to the general public to 1 mSv per year, and doses to workers to 100 mSv over 5 years [11] (1 Sievert equals 1 joule per kilogram).

Another source of ionizing radiation to the public and workers is from accidents and releases from nuclear power plants. The largest nuclear accident in history occurred on April 26, 1986 at the Chernobyl nuclear plant in northern Ukraine. The Chernobyl accident resulted in a large release of radionuclides, which were deposited over a very wide area, particularly in Europe. In 2003, the WHO convened an Expert Group on Health (EGH) that produced a comprehensive technical report on the health effects of the Chernobyl accident. The main long-term health effect of radiation exposure as a result of the accident is expected to be cancer [12]. To date, a dramatic risk in the incidence of thyroid cancer has been observed among those who were

exposed as children and adolescents in the most heavily contaminated areas following the accident. There has been anecdotal evidence of rises in other cancers, but such increases could not be differentiated from improvement in registration, diagnosis and reporting [12].

A large increase in the incidence of childhood thyroid cancer was reported in contaminated areas. Most of the radiation exposure to the thyroid was from iodine isotopes, especially I-131. Cardis et al. [13] studied 276 case patients with thyroid cancer through 1998 and 1300 matched control subjects, all aged younger than 15 years at the time of the accident. Individual doses were estimated for each subject based on their whereabouts and dietary habits at the time of the accident and in the following days, weeks and years; their likely stable iodine status at the time of the accident was also evaluated. A strong dose-response relationship was observed between radiation dose to the thyroid received in childhood and thyroid cancer risk (P<.001). For a dose of 1 Gy, the estimated odds ratio of thyroid cancer varied from 5.5 (95% CI= 3.1–9.5) to 8.4 (95% CI= 4.1–17.3), depending on the risk model. A linear dose-response relationship was observed up to 1.5–2 Gy.

The risk of radiation-related thyroid cancer was three times higher in iodine-deficient areas (relative risk [RR]= 3.2, 95% CI = 1.9–5.5) than elsewhere. Administration of potassium iodide as a dietary supplement reduced this risk of radiation-related thyroid cancer by a factor of 3 (RR = 0.34, 95% CI = 0.1–0.9 for consumption of potassium iodide versus no consumption).

Exposure to I-131 in childhood is associated with an increased risk of thyroid cancer. Both iodine deficiency and iodine supplementation appear to modify this risk. These results have important public health implications: stable iodine supplementation in iodine-deficient populations may substantially reduce the risk of thyroid cancer related to radioactive iodines in the case of exposure to radioactive iodines in childhood that may occur after radiation accidents or during medical diagnostic and therapeutic procedures.

It has taken longer to estimate the impact of the accident on the risk of other cancers in Europe. An IARC Working Group was established to estimate the human cancer burden in Europe as a whole from radioactive fallout from the accident [14].

Fig. 2.10.3 *The Chernobyl nuclear power plant*

Agent or substance	Cancer site/cancer
IARC Group 1: Carcinogenic to humans	
X-rays and gamma-radiation	Various – all sites
Solar radiation	Skin
Radon-222 and its decay products	Lung
Radium-224, -226, -228 and their decay products	Bone
Thorium-232 and its decay products	Liver, including haemangiosarcoma; leukaemia
Radioiodines (including iodine-131)	Thyroid
Plutonium-239 and its decay products (aerosols)	Lung, liver, bone
Phosphorus-32	Leukaemia
Neutrons	Various
Alpha (a) particle-emitting radionuclides	Various
Beta (b) particle-emitting radionuclides	Various
IARC Group 2A: Probably carcinogenic to humans	
Sunlamps and sun beds, use of	Skin
Ultraviolet radiation	Skin

Table 2.10.2 *Various forms and sources of radiation that are carcinogenic to humans (IARC Group 1) or probably carcinogenic to humans (IARC Group 2A)*

REFERENCES

1. IARC (2000). *IARC monographs on the evaluation of carcinogenic risks to humans, Volume 75, Ionizing Radiation, Part 1: X- and Gamma-radiation and Neutrons*. Lyon, France: International Agency for Research on Cancer.

2. Cardis E, Howe G, Ron E, et al. (2006). Cancer consequences of the Chernobyl accident: 20 years on. *J Radiol Prot* 26: 127-140.

3. Cardis E, Kesminiene A, Ivanov V, et al. (2005). Risk of thyroid cancer after exposure to 131I in childhood. *J Natl Cancer Inst* 97: 724-732.

4. Cardis E, Krewski D, Boniol M, et al. (2006). Estimates of the cancer burden in Europe from radioactive fallout from the Chernobyl accident. *Int J Cancer* 119: 1224-1235.

5. United Nations Scientific Committee on the Effects of Atomic Radiation (2000). *Sources and effects of Ionizing radiation: 2000 Report*. Vienna: UNSCEAR.

6. US National Academy of Sciences (1990). *Health effects on populations of exposure to low levels of ionizing radiation (BEIR V Report)*. Washington, DC: National Academy of Sciences.

7. US National Academy of Sciences (1998). *Health effects of radon and other internally deposited Alpha-emitters (BEIR IV Report)*. Washington, DC: National Academy of Sciences.

8. Cardis E, Vrijheid M, Blettner M, et al. (2005). Risk of cancer after low doses of ionising radiation: retrospective cohort study in 15 countries. *BMJ* 331: 77.

9. Cardis E, Vrijheid M, Blettner M, et al. (2007). The 15-Country Collaborative Study of Cancer Risk among Radiation Workers in the Nuclear Industry: estimates of radiation-related cancer risks. *Radiat Res* 167: 396-416.

10. United Nations Scientific Committee on the Effects of Atomic Radiation (1994). *Sources and Effects of Ionizing Radiation: 1994 Report*. Vienna: UNSCEAR.

11. International Commission on Radiological Protection (1991). *Recommendations of the International Commission on Radiological Protection*. Oxford: Pergamon Press.

12. Lahkola A, Auvinen A, Raitanen J, et al. (2007). Mobile phone use and risk of glioma in 5 North European countries. *Int J Cancer* 120: 1769-1775.

13. Schoemaker MJ, Swerdlow AJ, Ahlbom A, et al. (2005). Mobile phone use and risk of acoustic neuroma: results of the Interphone case-control study in five North European countries. *Br J Cancer* 93: 842-848.

14. Lonn S, Ahlbom A, Christensen HC, et al. (2006). Mobile phone use and risk of parotid gland tumor. *Am J Epidemiol* 164: 637-643.

2.11

Sunlight and Ultraviolet Radiation

Summary

> Sunlight is by far the most significant source of ultraviolet irradiation and causes several types of skin cancer, particularly in highly-exposed populations with fair skin, e.g. Australians of Caucasian origin

> Sunlight is recognised as the cause of squamous and basal cell cancer, and of cutaneous melanoma

> Genetically determined sensitivity to sunlight is associated with high propensity to sunburn, poor tanning ability, red hair and freckles.

> Artificial sources of ultraviolet radiation have become common in many countries, mainly as sunlamps for indoor tanning purposes. Indoor tanning is associated with increased risk of cutaneous melanoma and of squamous cell cancer when exposure started before 30 years old

> Sun protection should be based on seeking shade, clothes and hat wearing. Sunscreens should be applied only on body parts that cannot be protected with clothes or hats

Exposure to sunlight has been shown to be the main cause of skin cancer, including cutaneous melanoma (CM), basal skin cancer (BCC) and squamous skin cancer (SCC), and since 1992 solar radiation has been classified as a Group I carcinogenic agent by the IARC [1]. Approximately 5% of the total solar radiation received at the surface of the earth is in ultraviolet range, and the sun is the main source of exposure to UVR for most individuals. Sufficient evidence shows that the ultraviolet radiation (UVR) is the main environmental cause of SCC and BCC. This radiation is also deemed to be the main environmental cause of CM in humans. There are currently no recommendations for "safe doses" for human skin, i.e. there is no threshold UVR dose below which there would not be increased risk of skin cancer. Sunlight and UVR are also suspected to play a role in ocular melanoma, but further evidence of a possible causal association is needed.

Sunlight consists of visible light (400–700 nm), infrared radiation (>700 nm) and UVR. UVR belongs to the non-ionizing part of the electromagnetic spectrum and ranges from 100 nm to 400 nm; 100 nm has been chosen arbitrarily as the boundary between non-ionizing and ionizing radiation. UV radiation is conventionally categorised into 3 regions: UVA (>315–400 nm), UVB (>280–315 nm) and UVC (>100–280 nm). The quality (spectrum) and quantity (intensity) of sunlight are modified during its passage through the atmosphere. The ozone contained in the stratosphere (10–50 km above the earth's surface) stops almost all UV radiation <290 nm (UVC) as well as 70 to 90% of the UVB.

On the Mediterranean coast at noon in the summer, the UVR radiation from sunlight consists of about 95% UVA and about 5% UVB. UVB has long been recognised as the carcinogenic component of UVR. Since the end of the 1990s, both UVA and UVB have been known as having carcinogenic effects, but much more UVA is needed to achieve carcinogenic effects (e.g. DNA damage) similar to those observed with UVB. Also, UVA penetrates deeper into the skin than UVB, and causes biological damage that is qualitatively different from that induced by UVB, and which might also be implicated in skin carcinogenesis.

An individual's level of exposure to UV varies with latitude, altitude, time of year, time of day, clouding of the sky and other atmospheric components such as air pollution. At the Earth's surface, compared to UVA, UVB irradiation is more related to latitude (highest around the equator and lowest around the poles), season (highest in hot seasons, lowest in colder seasons), time of day (highest around 10 AM–2 PM solar hours), altitude (higher at altitude than at sea level), and earth surface cover (e.g. UVB is reflected by snow or by water).

Ozone depletion

Ozone depletion has been caused by substances released in the atmosphere that destroy the ozone (ozone-depleting substances (ODS)), for instance the chlorofluorocarbons (CFC) that were used as spray propellants until 1992, when an international ban known as the revised Montreal Protocol was applied to use of these substances [2]. The stratospheric ozone levels have decreased annually since the 1970s, especially in the southern hemisphere. Because the atmosphere in thinner at the poles, the ozone depletion is maximal at the most Northern and most Southern areas, and lowest at the equator. Thus the Nordic countries, Australia, New Zealand, Canada, and Russia, all generally populated with light-skinned people, are at higher risk of increased SCC and cutaneous melanoma because of ozone depletion [3].

In the past few years, the ozone layer seems to have stabilised, and current prospects of recovery of the ozone layer are also linked to the evolution of global climate change [4,5].

Acute effects of exposure to sunlight and other sources of UVR

The most common acute skin reaction induced by exposure to sunlight and other sources of UVR is an inflammatory process at skin level expressed as an erythema (i.e. skin reddening in light-skinned individuals). With increasing UVR dose, skin erythema develops as sunburn that is often painful and may sometimes be complicated with blisters. The minimal erythemal dose (MED) was the first way to biologically quantify exposure to UVR in humans, and is defined as the minimal amount of energy from sunlight (or other UVR sources) required for producing a qualifying erythemal response, usually after 24h.

Acquisition of a suntan is the other acute affect. But contrary to many beliefs, an acquired tan offers little protection against DNA damage induced by UVR. An acquired tan is mainly triggered by UVR-induced DNA damage itself, and is thus more an indicator of carcinogenic skin damage than a protection against this damage. It is the constitutive pigmentation that represents a real protection against the damaging effects of UVR.

UVB is far more efficient than UVA in inducing the synthesis of melanin, and for producing a deep, persistent tan. UVB is also one thousand times more potent than UVA for inducing sunburn.

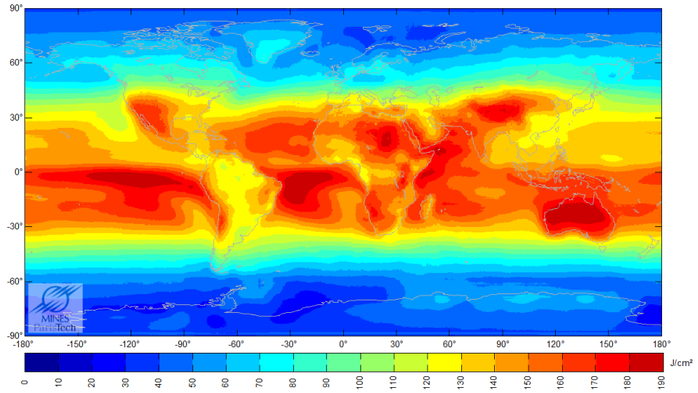


Fig. 2.11.1 *Yearly mean of daily UV (280-400 nm) irradiation in the world (Joules/cm2, 1990-2004)*

Individual susceptibility to skin carcinogenic damage due to sunlight and UVR

Susceptibility to carcinogenic effects of sunlight and UVR is highly genetically determined. The most susceptible individuals are those with very pale skin who always burn and never tan when in the sun. Red hair and numerous freckles (or solar lentigines) on the face, arms or shoulders are other host characteristics indicative of high sun sensitivity. The latter characteristics are sometimes termed the "Celtic phenotype", which has been discovered to be associated with mutations in the MC1R gene. This gene regulates the formation of eumelanin (that is brown or black and photoprotective) by melanocytes and also the capacity of the melanocyte to resist UVR-induced DNA damage. The MC1R gene is highly polymorphic, and about 80 mutations of this gene have been described [6]. These mutations may induce functional defects resulting in variable increases in the susceptibility to UVR-induced skin lesions [7]. These mutations also lead to the synthesis of pheomelanin (instead of eumelanin) that is red or yellow and is suspected to also play a role in skin cancer occurrence [8].

Individuals with light skin but low propensity to sunburn and who tan easily are much less susceptible to carcinogenic effects of sunlight and UVR. Individuals with naturally pigmented skin (i.e. constitutive pigmentation) have a very low susceptibility to carcinogenic effects of sunlight or UVR. As a result, skin cancer is rare in dark-skinned populations. The rare cutaneous melanoma occurring in individuals with naturally pigmented skin will often develop on the soles of feet or under toenails, as a result of skin insult due to barefoot walking.

Individual susceptibility may be greatly increased by inherited or acquired diseases or by treatments. For instance, subjects with rare inherited deficits in DNA repair (e.g. *xeroderma pigmentosum*) develop hundreds of times more skin cancers. African albino subjects are at high risk of developing multiple SCC. Psoriasis patients treated with PUVA (oral psoralens combined with sessions of UVA irradiation) have a higher risk of developing SCC as well as BCC. Patients under immune suppression therapy for organ transplant have a high risk of developing skin cancer.

Age and susceptibility to sunlight and UVR

A large body of data shows that in light-skinned populations, susceptibility to carcinogenic effects of sunlight and UVR relevant to cutaneous melanoma (and probably also to BCC) are greater during childhood and adolescence. Studies in migrants indicate that the younger the age at exposure, the greater the risk of cutaneous melanoma in later life [9]. Also, sun exposure during adult life is associated with cutaneous melanoma occurrence only if sun exposure took place during childhood [10]. This age-related susceptibility is most probably related to the immaturity of the skin, it being more vulnerable to UVR-induced damage in younger populations.

Gender and anatomical differences in susceptibility to sunlight and UVR

Sharp gender contrast exists for the body distribution of cutaneous melanoma: in males, most cutaneous melanoma occur on the trunk and shoulders, then on the upper arms and on the face, while in women, most cutaneous

melanoma occur on the lower limbs, and then on the upper limbs [11]. The number of acquired nevi is the strongest individual predictor of cutaneous melanoma, and the body distribution of nevi in young children parallels the body distribution of CM in adults [12]. These findings further underline the importance of childhood exposure to sunlight for the development of CM during adult life. They also illustrate that different body parts have different susceptibility to sunlight and UVR that this also varies with gender.

BCC usually occurs on the head and the neck, but recent data show increasing BCC incidence on body sites that are only intermittently sun-exposed, e.g. the trunk [13]. SCC occurs nearly always on chronically sun-exposed areas, such as the head and the neck.

Sunlight, artificial sources of UVR and human behaviours

Exposure to sunlight or to other sources of UVR encompasses a large variety of behaviours. In the 1980s, epidemiological studies evidenced that SCC was more associated with the chronic sun exposure pattern, i.e. lifetime accumulation of exposure to sunlight (e.g. outdoor workers, farmers), while cutaneous melanoma was associated with the so-called intermittent sun exposure pattern, i.e. subjects spending most of their time indoors and having brutal acute sun exposures during holidays in sunny areas, with often the pursuit of tanned skin or of a "healthy look" [1,14,15]. BCC was associated with both exposure patterns.

More recently, it has been suggested that all these behaviours can be grouped into two broad categories distinguishing between non-intentional and intentional sun exposure [16,17]. Non-intentional sun exposure (NISE) represents sun exposure during daily activities, without willingly acquiring a tan or intentionally spending a long time in the sun. During NISE, skin areas most usually sun exposed are the head and neck, the hands, the forearms, and in subjects wearing short trousers or skirts, the lower legs and the dorsum of feet. Examples of NISE are outdoor activities such as gardening or work on building sites or in farming fields, as well as sport activities like skiing.

Intentional sun exposure (ISE) is essentially motivated by the acquisition of a tan or by the possibility or going uncovered in the sun. During ISE, significant portions of the trunk, shoulders and of the upper parts of limbs are frequently uncovered.

Cutaneous melanoma occurrence is more associated with ISE situations, while SCC occurrence is more associated with NISE situations. BCC occurrence is most probably associated with both types of sun exposure.

Non-intentional exposures to sunlight and other sources of UVR (NISE)

Artificial sources of UVR are used in numerous industrial processes, and also in research laboratories. UVR is part of the treatment of many diseases, such as psoriasis and dermatitis. The type and spectrum of UVR lamps may be different from one condition to another. In some diseases, like psoriasis, the cumulative exposure to UVR can be substantial, can be accompanied by use of oral photocarcinogens (the PUVA therapy combining UVA and oral 8-methoxypsoralen) and is sometimes supplemented with sunbed use. In these patients, higher rates of SCC and BCC than in the general population are usually observed.

Lighting through use of fluorescent tubes contains a small proportion of UV radiation. These small amounts could represent a hazard, as fluorescent lighting is widely distributed. Epidemiological studies have not however produced data consistent with an effect of fluorescent lighting on melanoma occurrence.

Intentional exposure to sunlight or to artificial sources of UVR (ISE)

The most common ISE behaviour is sunbathing. The tanned skin fashion started in the 1930s in light-skinned populations after popularisation of the healthy effects of sunlight, e.g. for prevention of rickets [18].

Since the end of the 1980s, in countries populated with light-skinned people, deliberate exposure to artificial sources of UVR has become common through the use of sunbeds, mainly for the acquisition of a tanned skin. This new fashion has been largely facilitated by ungrounded beliefs such as the putative lower carcinogenic potential of sunbeds (as compared to sunlight), the psychological benefits of UVR exposure during the winter, and more recently, the maintenance of so-called "optimal vitamin D status".

In large, powerful tanning units, the UVR intensity may be 10 to 15 times higher than that of the midday sun [19], and UVA doses per unit of time received by the skin during a typical sunbed session are well above what is experienced during daily life or during sunbathing. Annual UVA doses received by frequent indoor tanners may be 1.2 to 4.7 times that received from the sun, and in addition to those received from the sun. Such powerful sources of UVA radiation probably do not exist on the Earth's surface, and repeated exposures to high doses of UVA constitute a new phenomenon in humans. Health hazards associated with repeated exposures to powerful indoor tanning devices remain largely unknown, as this fashion developed quite recently, and the full health

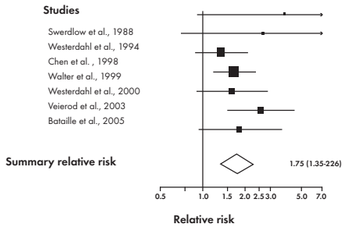


Fig. 2.11.2 *Relative risk for cutaneous melanoma associated with first use of indoor tanning equipment at age < 35 years : estimates of 7 studies and summary estimate*

impact of such exposure may not be seen for another one or two decades.

A systematic review carried out by an IARC Working Group in 2006 has shown that the risk of cutaneous melanoma is increased by 70% when sunbed use starts before about 30 years of age (Figure 2.11.2) [19,20]. This finding is in line with known susceptibility to carcinogenic effects of UVR at younger ages. Recent surveys have revealed that substantial numbers of teenagers use sunbeds; with respect to this, priority for the prevention of damage caused by sunbed use should concentrate on limiting sunbed use by adolescents and young adults [19-21].

Sun protection

The main goal of sun protection is to decrease the incidence of SCC, BCC and cutaneous melanoma through methods that have in common the reduction of exposure to sunlight and to other sources of UVR. Avoidance of sunshine or exposure to UVR sources, and seeking of shade are the most straightforward sun protection methods. When in the sun, barriers to UVR usually consist of wearing a hat and clothing, and use of sunscreens. Hats should be broad-brimmed so that the scalp, the face, the ears and the neck are protected. Common fabrics represent efficient barriers against UVR transmission to the skin. Dark colours are more protective than light colours, and wet clothes are less protective than dry clothes. Some fabrics and clothes have been specifically devised to protect the skin against sun damage, and are recommended for individuals highly susceptible to the damaging effects of UVR (e.g. red-haired people, patients under photosensitising treatment). The ability of a fabric to block UVR is called the ultraviolet protection factor (UPF), but there is no international standardisation of its measurement.

The sun protection factor (SPF) of sunscreens provides an internationally standardised estimate of the ability of a *thick* layer of sunscreen to delay the occurrence of a sun-induced skin erythemal reaction. The higher the SPF, the longer the time needed to develop an erythema. Because sunburn occurrence is associated with greater risk of skin cancer, the SPF has been thought to be an indicator of the ability of sunscreens to protect against sun-induced skin carcinogenic phenomena. However, the causal link between sunburn and melanoma is questioned, as this association may simply reflect the genetically determined propensity to sunburn [22,23]. Also, UVR can induce biological damage (such as immune suppression or oxidative damage) at doses lower than those needed to induce an erythema [19].

Observational and randomized studies have provided evidence that during NISE, reduction of amounts of UVR reaching skin surface through clothing, sunscreen use or reduction of time spent in the sun can decrease the occurrence of SCC, and also of sunburns and of skin precursor lesions of SCC (e.g. skin keratoses). [24-27].

During ISE, however, observational and randomised studies have demonstrated that sunscreen use may have the consequence of increasing the time spent in the sun, mainly because tan acquisition is longer when a sunscreen is used, and also because it takes more

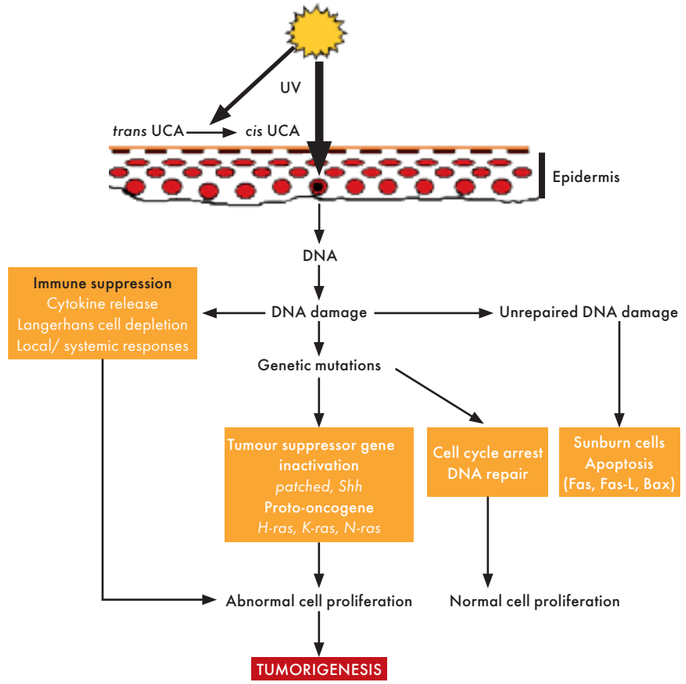


Fig. 2.11.3 *Pathways implicated in the induction of non-melanoma skin cancer by ultraviolet radiation (UCA= urocanic acid)*

time to get a sunburn [24,28,29]. So, sunscreen use during ISE may actually increase the risk of cutaneous melanoma (and probably also of BCC) [17] Sunscreen use during ISE does not decrease sunburn occurrence and allows suntan seekers to adopt more hazardous sun exposure behaviours, such as sunbathing around noon, when UVB irradiation is maximal [10,24,28,30]. In contrast, during ISE situations, clothing protects against melanoma occurrence and nevi development in children [31].

Hence, sunscreens should be rather used during NISE, and in these situations, application onto the skin should be liberal, as the usual tendency is to apply too small a quantity of sunscreen, which results in an actual SPF 3 to 5 times lower than indicated on the bottle.

In this respect, generous application of SPF 15 sunscreen is better than parsimonious application of a sunscreen of higher SPF. If one cannot refrain from intentional sun exposure (essentially for tan acquisition), it is better to avoid using a sunscreen in order to avoid staying in the sun longer than if a sunscreen was not used. It is also better not to sunbathe during the hottest hours of the day, when UVB irradiation is maximal. Suntan seeker should start with short sunbathing sessions, depending on natural sun sensitivity, and then gradually increase time spent in the sun as their tan gets deeper. Individuals who do not tan or tan only after burning should by no means engage in sunbathing and should not have recourse to a sunscreen for increasing their ability to stay in the sun.

Sun protection of children should be based on seeking shade, hat wearing and clothing. If sunscreen is used, it should only be applied on skin areas that cannot be protected with hats and clothes. So, by definition, sunscreen should never be applied on the trunk of a child, as sun protection of the trunk should be done with clothes.

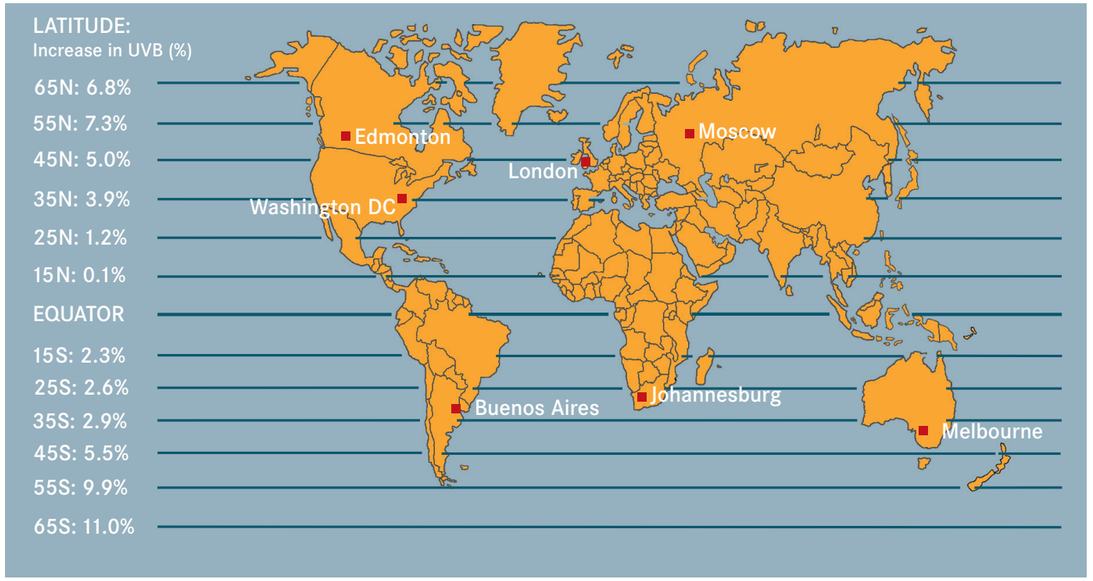


Fig. 2.11.4 *Satellite-based analyses (1996) demonstrate increases in average annual levels of ultraviolet B (UVB) radiation reaching the Earth's surface over the past ten years. These changes are strongly dependent on latitude*

REFERENCES

1. IARC. (1992). *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 55, Solar and ultraviolet radiation*. Lyon, France: International Agency for Research on Cancer.

2. Rowland FS (2006). Stratospheric ozone depletion. *Philos Trans R Soc Lond B Biol Sci* 361: 769-790.

3. de Gruijl FR, Longstreth J, Norval M, et al. (2003). Health effects from stratospheric ozone depletion and interactions with climate change. *Photochem Photobiol Sci* 2: 16-28.

4. Velders GJ, Andersen SO, Daniel JS, et al. (2007). The importance of the Montreal Protocol in protecting climate. *Proc Natl Acad Sci U S A* 104: 4814-4819.

5. Weatherhead EC and Andersen SB (2006). The search for signs of recovery of the ozone layer. *Nature* 441: 39-45.

6. Gerstenblith MR, Goldstein AM, Fargnoli MC, et al. (2007). Comprehensive evaluation of allele frequency differences of MC1R variants across populations. *Hum Mutat* 28: 495-505.

7. Raimondi S, Sera F, Gandini S, et al. (2008). MC1R variants, melanoma and red hair color phenotype: a meta-analysis. *Int J Cancer* 122: 2753-2760.

8. Rouzaud F, Kadekaro AL, Abdel-Malek ZA, et al. (2005). MC1R and the response of melanocytes to ultraviolet radiation. *Mutat Res* 571: 133-152.

9. Whiteman DC, Whiteman CA, Green AC (2001). Childhood sun exposure as a risk factor for melanoma: a systematic review of epidemiologic studies. *Cancer Causes Control* 12: 69-82.

10. Autier P and Dore JF (1998). Influence of sun exposures during childhood and during adulthood on melanoma risk. EPIMEL and EORTC Melanoma Cooperative Group. European Organisation for Research and Treatment of Cancer. *Int J Cancer* 77: 533-537.

11. Elwood JM and Gallagher RP (1998). Body site distribution of cutaneous malignant melanoma in relationship to patterns of sun exposure. *Int J Cancer* 78: 276-280.

12. Autier P, Boniol M, Severi G, et al. (2004). Sex differences in numbers of nevi on body sites of young European children: implications for the etiology of cutaneous melanoma. *Cancer Epidemiol Biomarkers Prev* 13: 2003-2005.

13. de Vries E, Louwman M, Bastiaens M, et al. (2004). Rapid and continuous increases in incidence rates of basal cell carcinoma in the southeast Netherlands since 1973. *J Invest Dermatol* 123: 634-638.

14. Armstrong BK (1988). Epidemiology of malignant melanoma: intermittent or total accumulated exposure to the sun? *J Dermatol Surg Oncol* 14: 835-849.

15. Elwood JM, Gallagher RP, Hill GB, et al. (1985). Cutaneous melanoma in relation to intermittent and constant sun exposure--the Western Canada Melanoma Study. *Int J Cancer* 35: 427-433.

16. Vainio H, Miller AB, Bianchini F (2000). An international evaluation of the cancer-preventive potential of sunscreens. *Int J Cancer* 88: 838-842.

17. IARC (2001). *IARC Handbooks of Cancer Prevention, Volume 5, Sunscreens*. Lyon, France: International Agency for Research on Cancer.

18. Albert MR and Ostheimer KG (2003). The evolution of current medical and popular attitudes toward ultraviolet light exposure: part 2. *J Am Acad Dermatol* 48: 909-918.

19. International Agency for Research on Cancer Working Group on artificial ultraviolet (UV) light and skin cancer (2007). The association of use of sunbeds with cutaneous malignant melanoma and other skin cancers: A systematic review. *Int J Cancer* 120: 1116-1122.

20. IARC (2006). *IARC Working Group Reports, Volume 1, Exposure to Artificial UV Radiation and Skin Cancer*. Lyon, France: International Agency for Research on Cancer.

21. Autier P and Boyle P (2008). Artificial ultraviolet sources and skin cancers: rationale for restricting access to sunbed use before 18 years of age. *Nat Clin Pract Oncol* 5: 178-179.

22. Marks R and Whiteman D (1994). Sunburn and melanoma: how strong is the evidence? *BMJ* 308: 75-76.

23. Whiteman D and Green A (1994). Melanoma and sunburn. *Cancer Causes Control* 5: 564-572.

24. Autier P, Boniol M, Dore JF (2007). Sunscreen use and increased duration of intentional sun exposure: still a burning issue. *Int J Cancer* 121: 1-5.

25. Green A, Williams G, Neale R, et al. (1999). Daily sunscreen application and betacarotene supplementation in prevention of basal-cell and squamous-cell carcinomas of the skin: a randomised controlled trial. *Lancet* 354: 723-729.

26. Naylor MF, Boyd A, Smith DW, et al. (1995). High sun protection factor sunscreens in the suppression of actinic neoplasia. *Arch Dermatol* 131: 170-175.

27. Thompson SC, Jolley D, Marks R (1993). Reduction of solar keratoses by regular sunscreen use. *N Engl J Med* 329: 1147-1151.

28. Autier P, Dore JF, Negrier S, et al. (1999). Sunscreen use and duration of sun exposure: a double-blind, randomized trial. *J Natl Cancer Inst* 91: 1304-1309.

29. Autier P, Dore JF, Reis AC, et al. (2000). Sunscreen use and intentional exposure to ultraviolet A and B radiation: a double blind randomized trial using personal dosimeters. *Br J Cancer* 83: 1243-1248.

30. Autier P, Dore JF, Cattaruzza MS, et al. (1998). Sunscreen use, wearing clothes, and number of nevi in 6- to 7-year-old European children. European Organization for Research and Treatment of Cancer Melanoma Cooperative Group. *J Natl Cancer Inst* 90: 1873-1880.

31. Autier P (2005). Cutaneous malignant melanoma: facts about sunbeds and sunscreen. *Expert Rev Anticancer Ther* 5: 821-833.

2.12 Electromagnetic Radiation

Summary

> Extremely low frequency electromagnetic fields generated by electrical power transmission have been associated with an increased risk of childhood leukaemia, but the findings are not conclusive. Even if this association is real, the number of excess cases is likely to be very small

> Radiofrequency radiation emitted by mobile telephones has been investigated in a number of studies. There is some evidence that long-term and heavy use of mobile/cellular phones may be associated with moderate increased risks of gliomas, parotid gland tumours, and acoustic neuromas; however, evidence is conflicting and a role of bias in these studies cannot be ruled out

> With reference to radio frequency, available data do not show any excess risk of brain cancer and other neoplasms associated with the use of mobile phones

> With reference to ELF fields, available data allow us to exclude any excess risk of (childhood) leukaemia and other cancers at the levels of exposure likely to be encountered by most (>99%) of the population)

> To date there is no convincing biological or biophysical support for a possible association between exposure to ELF fields and the risk of leukaemia or any other cancer

Although a source of exposure to man for many decades, electromagnetic fields (EMF) have seen an unprecedented increase in the number and diversity of sources in recent years [1], principally extremely low frequency and radiofrequency fields. Such sources include all equipment using electricity, television, radio, computers, mobile telephones, microwave ovens, anti-theft gates in large shops, radars and equipment used in industry, medicine and commerce. Static fields and extremely low frequency fields occur naturally, and also arise as a consequence of the generation and transmission of electrical power and through the operation of a range of industrial devices and domestic appliances, the latter often at a greater field intensity. Exposure to extremely low frequency fields is mainly from human-made sources for the generation, transmission and use of electricity. Occupational exposure occurs, for example, in the electric and electronics industry, in welding and in the use and repair of electrical motors. Environmental exposure to extremely low frequency fields occurs in residential settings due to proximity to electricity transmission lines and use of electrical appliances. Levels of exposure from many environmental sources are typically low [2].

Exposure to radiofrequency radiation can occur in a number of ways. The primary natural source of radiofrequency fields is the sun. Manmade sources, however, are the main source of exposure. Radiofrequency fields are generated as a consequence of commercial radio and television broadcasting and from telecommunications facilities. Radiofrequency fields in the home are generated by microwave ovens and burglar alarms. However, mobile telephones are now the greatest source of radiofrequency exposure for the general public.

A major obstacle in conducting epidemiological studies of EMF is the difficulty in accurately measuring the dose and exposure pattern. This is particularly true in the case of mobile telephones, where the dose emitted by phones has been changing between models and over time, and the use pattern of left or right side also varies within individuals. Measuring exposure to total EMF is also fraught with difficulty, and estimating the exposure to individual components of the spectrum involved is extremely difficult to the point of being impossible.

The INTERPHONE study is an ambitious project aiming at assessing the risk of cancer from the use of mobile phones. A number of the individual components have been published [3].

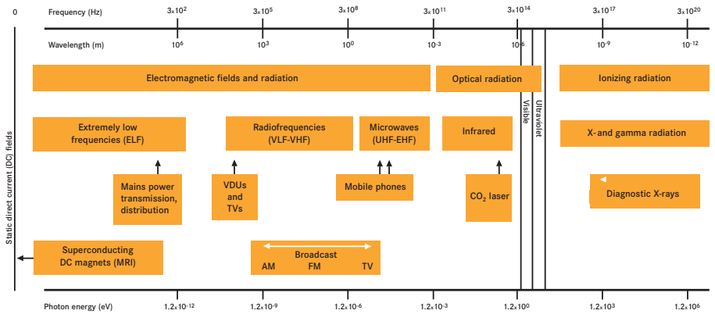


***Fig.* 2.12.1** *The spectrum of electromagnetic fields and their use in daily life*

Separate studies have been carried out for acoustic neurinoma, glioma, meningioma and tumours of the parotid gland. The studies used a common core protocol and were carried out in Australia, Canada, Denmark, Finland, France, Germany, Israel, Italy, Japan, New Zealand, Norway, Sweden and the UK. Details of the study protocol and procedures have been published [4]. The overall study includes approximately 2600 gliomas, 2300 meningiomas, 1100 acoustic neurinomas, 400 parotid gland tumours and their respective controls. This is by far the largest epidemiological study of these tumours to date. A number of methodological issues have been addressed including study design, participation bias, recall error and exposure assessment that are essential in the interpretation of results from the study.

Results of national analyses of the relation between mobile phone use and risk of specific tumour types in some of the participating countries have indicated that in most studies, the OR related to ever having been a regular mobile phone user was below 1, in some instances statistically significantly. This possibly reflects participation bias or other methodological limitations.

For glioma, although results by time since start of use and amount of phone use vary, the number of long-term users is small in individual countries and results are therefore compatible. Pooling of data from Nordic countries and part of the UK yielded a significantly increased risk of glioma related to use of mobile phones for a period of 10 years or more on the side of the head where the tumour developed [5]. This finding could either be causal or artifactual, related to differential recall between cases and controls.

For meningioma and acoustic neurinoma, most National studies provided little evidence of an Increased risk. The numbers of long-term heavy users in individual studies were even smaller than for glioma, however, and prevent any definitive conclusion about a possible association between mobile telephone use and the risk of these tumours. A pooled analysis of data from Nordic countries and the UK found a significantly increased risk of acoustic neurinoma related to duration of use of 10 years or more on the side of tumour [6]. Again, this finding could either be causal or artifactual, related to differential recall between cases and controls.

For parotid gland tumours, no increased risk was observed overall for any measure of exposure investigated. In a combined analysis of data from Sweden and Denmark [7], a nonsignificantly increased risk of benign tumours was observed for ipsilateral use of 10 years or more, while a decreased risk was seen for contralateral use, possibly reflecting differential recall between cases and controls. In the Israeli study, where study subjects tended to report substantially heavier use of mobile phones, results suggest a possible relation between heavy mobile phone use and risk of parotid gland tumours. Additional investigations of this association, with longer latency periods and large numbers of heavy users, are needed to confirm these findings. In respect of the work environment, employees working in close proximity to radiofrequencyemitting systems may receive high levels of exposure. This includes workers

***Fig.* 2.12.2** *Child and cellphone*

Frequency	Class	Type of device or service
30 - 300 kHz	LF (low)	LF broadcast and long-range radio
300 - 3,000 kHz	MF (medium)	AM radio, radio navigation, ship-to-shore
3 - 30 MHz	HF (high)	CB radio, amateurs, HF radio communications and broadcast
30 - 300 MHz	VHF (very high)	FM radio, VHF TV, emergency services
300 - 3,000 MHz	UHF (ultra high)	UHF TV, paging, mobile telephones, amateur radios
3 - 30 GHz	SHF (super high)	Microwaves, satellite communications, radar, point to point microwave communications
30 - 300 GHz	EHF (extremely high)	Radar, radioastronomy, short-link microwave communications

***Table* 2.12.1** *Radiofrequency range: class and type of device or service*

***Fig.* 2.12.3** *Power line*

in the broadcasting, transport and communication industries, and in antenna repair, military personnel (e.g. radar operators) and police officers (utilising traffic control radars). There are also industrial processes that use radiofrequency fields, including dielectric heaters for wood lamination and sealing of plastics, industrial induction heaters and microwave ovens, medical diathermy equipment to treat pain and inflammation of body tissues, and electrosurgical devices for cutting and welding tissues.

Cancer causation

Several expert groups have recently reviewed the scientific evidence concerning the carcinogenicity of extremely low frequency fields [8-10]. A number of epidemiological studies on childhood leukaemia indicate a possible relationship between risk and exposure to extremely low frequency fields. Studies of adult cancers following occupational or environmental exposures to extremely low frequency fields are much less clear. There is little experimental evidence that these fields can cause mutations in cells. Mechanistic studies and animal experiments do not show any consistent positive results, although sporadic findings concerning biological effects (including increased cancers in animals) have been reported. IARC has classified extremely low frequency fields as possibly causing cancer in humans (Group 2B), based on childhood leukaemia findings [11].

The evidence for the carcinogenicity of radiofrequency fields is even less clear. A few epidemiological studies in occupational settings have indicated a possible increase in the risk of leukaemia or brain tumours, while other studies indicated decreases. These studies suffer from a number of limitations. The experimental evidence is also limited, but suggests that radiofrequency fields cannot cause DNA mutations. The lack of reproducibility of findings limits the conclusions that can be drawn.

REFERENCES

1. Bernhardt JH, Matthes R, Repacholi M (1997). *Nonthermal effects of RF electromagnetic Fields: Proceedings of the International Seminar on Biological Effects of RF Electromagnetic Fields and Related Health Risks - Munich, Germany, 20-21 November 1996*. Geneva: International Commission on Non-Ionizing Radiation Protection.

2. Bernhardt JH, Matthes R, Repacholi M (1998). *Static and extremely low frequency electric and magnetic fields*. Geneva: International Commission on Non-Ionizing Radiation Protection.

3. *INTERPHONE Study - Latest results update*. Available from: http://www.iarc.fr/en/content/download/8384/61101/file/Interphone8oct08.pdf Date Accessed: October 27, 2008.

4. Cardis E, Richardson L, Deltour I, et al. (2007). The INTERPHONE study: design, epidemiological methods, and description of the study population. *Eur J Epidemiol* 22: 647-664.

5. Lahkola A, Auvinen A, Raitanen J, et al. (2007). Mobile phone use and risk of glioma in 5 North European countries. *Int J Cancer* 120: 1769-1775.

6. Schoemaker MJ, Swerdlow AJ, Ahlbom A, et al. (2005). Mobile phone use and risk of acoustic neuroma: results of the Interphone case-control study in five North European countries. *Br J Cancer* 93: 842-848.

7. Lonn S, Ahlbom A, Christensen HC, et al. (2006). Mobile phone use and risk of parotid gland tumor. *Am J Epidemiol* 164: 637-643.

8. US National Institute of Environmental Health Sciences. *Electric & Magnetic Fields*. Available from: http://www.niehs.nih.gov/health/topics/agents/emf/ Date Accessed: October 27, 2008.

9. Royal Society of Canada (2000). *A Review of the Potential Health Risks of Radiofrequency Fields from Wireless Telecommunication Devices*. Ottawa: Royal Society of Canada.

10. Independent Expert Group on Mobile Phones (Great Britain), Stewart WD (2000). *Mobile Phones and Health*. Didcot, Oxon: National Radiological Protection Board.

11. IARC (2002). *IARC monographs on the evaluation of carcinogenic risks to humans, Volume 80, non-ionizing radiation, Part 1: static and extremely low-frequency (ELF) electric and magnetic fields*. Lyon, France: International Agency for Research on Cancer.

2.13 Occupational Exposures

Summary

> Twenty-nine occupational agents, as well as 15 exposure circumstances are carcinogenic to humans

> Exposure is still widespread for several important carcinogens such as asbestos, polycyclic aromatic hydrocarbons, heavy metals and silica

> The burden of occupational cancer among exposed subjects may be substantial

> Prevention of occupational cancer is feasible and has taken place in industrialized countries during recent decades

> Limited data on occupational cancer risk are available from low-income countries

It has been known for over 200 years that exposures encountered at the workplace are a cause of cancer. Occupational cancers were initially detected by clinicians. From the early findings of Pott of scrotal cancer among chimney sweeps in 1775 [1] to Creech and Johnson's identification of angiosarcoma of the liver among vinyl chloride workers two centuries later [2], unusual cancers among persons with unusual occupations were sufficient evidence to judge that the occupational exposure caused the cancer. The era of initial identification of occupational cancer by a clinician has extended into the last quarter of the 20th century. The period of formal epidemiological assessment of the occurrence of cancer in relation to workplace exposures started after World War II. Knowledge of the occupational and other environmental causes of cancer grew rapidly in the 1950s and 1960s. Cancer hazards in the workplace in the earlier decades of this century were substantial, causing, in extreme cases, all of the most heavily exposed to develop cancer, as occurred in some groups of manufacturers of 2-naphtylamine and benzidine, while coal-tar fumes and asbestos have been so widespread that tens of thousands of skin and lung cancers have developed. While the remaining hazards are now starting to disappear through elimination of these substances and of exposures to them, some of the consequences of the earlier exposures still exist. Estimates of the burden of occupational cancer in high-resource countries are in the order of 2–5% [3].

At present, there are 29 chemicals, groups of chemicals and mixtures for which exposures are mostly occupational, that are established human carcinogens (Table 2.13.1). While some agents such as asbestos, benzene, and heavy metals, are currently widely used in many countries, other agents have mainly a historical interest (e.g. mustard gas and 2-naphthylamine). An additional 28 occupational agents are classified as probably carcinogenic to humans (Group 2A): these are listed in Table 2.13.2, and include exposures that are currently prevalent in many countries, such as diesel engine exhaust and trichloroethylene. A large number of important occupational agents are classified as possible human carcinogens (Group 2B): e.g. acetaldehyde, carbon black, chloroform, chlorophenoxy herbicides, DDT, dichloromethane, glass wool, polychlorophenols and styrene. The complete list can be found on the IARC web site (http://monographs.iarc.fr).

The distinction between occupational and environmental carcinogens is not always straightforward. Several of the agents listed in Tables 2.13.1 and 2.13.2 are also present in the general environment, although exposure levels tend to be higher at the workplace. This is the case for the examples of 2,3,7,8-TCDD, diesel engine exhaust, radon and asbestos. On the other hand, there are agents that have been evaluated in IARC groups 1 or 2A, for which exposure is not primarily occupational, but which often encountered in the occupational environment. They include drugs such as cyclophosphamide and cyclosporin (occupational exposure can occur in pharmacies and during their administration by nursing staff); food contaminants such as aflatoxins, to which food processors can be exposed; biological agents, such as Hepatitis B virus, Hepatitis C virus and Human Immunodeficiency virus, to which medical personnel can be exposed; environmental agents, in particular solar radiation (exposure in agriculture, fishing and other outdoor occupations); and lifestyle factors, in particular secondhand tobacco smoke in bars and other public settings.

Polycyclic aromatic hydrocarbons (PAHs) represent a specific problem in the identification of occupational carcinogens. This group of chemicals includes several potent experimental carcinogens, such as benzo[*a*]pyrene, benz[*a*]anthracene and dibenz[*a,h*]anthracene. However, humans are always exposed to mixtures of PAHs (several of which are listed in Tables 2.13.1 and 2.13.2: e.g. coal-tars, soots, creosotes), and an assessment of the carcinogenicity of individual PAHs in humans is difficult.

Current understanding of the relationship between occupational exposures and cancer is far from complete; in fact, for many experimental carcinogens no definitive evidence is available from exposed workers. In some cases, there is considerable evidence of increased risks associated with particular industries and occupations, although no specific agents can be identified as etiological factors. Table 2.13.3 reports occupations and industries that entail (or are suspected to entail) a carcinogenic risk on the basis of the IARC Monographs programme. Fifteen occupations and industries are listed in IARC Group 1 and four in Group 2A.

Fig. 2.13.1 *Coal mine*

Constructing and interpreting lists of chemical or physical carcinogenic agents and associating them with specific occupations and industries is complicated by a number of factors. Information on industrial processes and exposures is frequently poor, not allowing a complete evaluation of the importance of specific carcinogenic exposures in different occupations or industries. In addition, exposures to well-known carcinogenic exposures, such as vinyl chloride and benzene, occur at different intensities in different occupational situations. Furthermore, changes in exposure occur over time in a given occupational situation, either because identified carcinogenic agents are substituted by other agents or (more frequently) because new industrial processes or materials are introduced. Finally, any list of occupational exposures can only refer to the relatively small number of chemical exposures that have been investigated with respect to the presence of a carcinogenic risk.

The same factors complicate the estimates of the burden of cancer attributable to occupation. Figures in the order of 4–5% of total cancer deaths have been proposed in the past [4], but estimates based on systematic evaluations of relative risks and data on exposure prevalence have resulted in lower estimates, in the order of 2–3% [5,6]. A single figure on the proportion of cancers due to occupations might be misleading as exposure concentrates on subgroups of the population, namely male blue-collar workers, among whom the burden can be substantial.

Exposure	Target organ	Main industry or use
4-Aminobiphenyl	Bladder	Rubber
Arsenic and arsenic compounds	Lung, skin	Glass, metals, pesticides
Asbestos	Lung, pleura	Insulation, construction
Benzene	Leukemia	Solvent, fuel
Benzidine	Bladder	Pigment
Beryllium and beryllium comp.	Lung	Aerospace, metals
Bis(chloromethyl)ether*	Lung	Chemical
1,3-Butadiene	Leukemia	Plastic, rubber
Chloromethyl methyl ether*	Lung	Chemical
Cadmium and cadmium comp.	Lung	Pigment, battery
Chromium[VI] compounds	Nasal cavity, lung	Metal plating, pigment
Coal-tar pitches	Skin, lung, bladder	Construction, electrodes
Coal-tars	Skin, lung	Fuel
Ethylene oxide	NA**	Chemical, sterilant
Formaldehyde	Nasopharynx	Plastic, textile
Gallium arsenide	NA**	Semiconductors
Mineral oils, untreated and mildly treated	Skin	Lubricant
Mustard gas (sulphur mustard)*	Pharynx, lung	War gas
2-Naththylamine*	Bladder	Pigment
Nickel compounds	Nasal cavity, lung	Metal, alloy
Radon-222 and its decay products	Lung	Mining
Shale-oils	Skin	Lubricant, fuel
Silica, crystalline	Lung	Construction, mining
Soots	Skin, lung	Pigment
Strong-inorganic-acid mists containing sulphuric acid	Larynx, lung	Chemical
Talc containing asbestiform fibers	Lung	Paper, paint
2,3,7,8-Tetrachlorodibenzo-p-dioxin	NA**	Chemical
Vinyl chloride	Liver	Plastic
Wood dust	Nasal cavity	Wood

Table 2.13.1 *Agents, groups or agents and mixtures classified as established human carcinogens [9], for which exposure is mainly occupational*
** Agent mainly of historical interest*
*** Not applicable (agent classified in Group 1 on the basis of mechanistic evidence).*

Exposure	Suspected target organ	Main industry or use
Acrylamide	-	Plastic
Benzidine-based dyes	Bladder	Pigment, leather
Captafol	-	Pesticide
α-Chlorinated toluenes (benzal chloride, benzotrichloride, benzyl chloride, benzoyl chloride)	-	Pigment, chemical
4-Chloro-o-toluidine	Bladder	Pigment, textile
Cobalt metal with tungsten carbide	Lung	Hard metal production
Creosotes	Skin	Wood
Diesel engine exhaust	Lung	Transport, mining
Diethyl sulfate	-	Chemical
Dimethylcarbamoyl chloride	-	Chemical
1,2-Dimethylhydrazine	-	Research
Dimethyl sulfate	-	Chemical
Epichlorohydrin	-	Plastic
Ethylene dibromide	-	Fumigant
Indium phosphide	-	Semiconductors
Lead compounds, inorganic	Lung, stomach	Metals, pigments
Methyl methanesulfonate	-	Chemical
4-4′-Methylene-bis-2-chloroaniline (MOCA)	Bladder	Rubber
Non-arsenical insecticides	Leukemia	Agriculture
Polychlorinated biphenyls	Liver, lymphoma	Electrical components
Styrene-7,8-oxide	-	Plastic
Tetrachloroethylene	Oesophagus, lymphoma	Solvent
o-Toluidine	Bladder	Pigment
Trichloroethylene	Liver, lymphoma	Solvent, dry cleaning
1,2,3-Trichloropropane	-	Solvent
Tris(2,3-dibromopropyl)phosphate	-	Plastic, textile
Vinyl bromide	-	Plastic, textile
Vinyl fluoride	-	Chemical

Table 2.13.2 *Agents, groups or agents and mixtures classified as probable human carcinogens [9], for which exposure is primarily occupational*

While the study of occupational cancer has concentrated on specific jobs, industries and agents, it is likely that indirect effects of occupation have become more important. For example, the increasing employment of women in jobs outside the home has probably contributed to changes in reproductive habits, which may entail an increased risk of hormone-related cancers. Recently, shiftwork that involves circadian disruption has been classified as a probable human carcinogen by the IARC Monographs Programme, on the basis of limited evidence of an increased risk of breast cancer [7].

Occupational cancer is likely to be a more important problem in medium- and low-resource countries than in high-resource countries because of the importance of the informal sector, the lack of stringent implementation of existing regulations, the low level of attention paid by management and the workforce to industrial hygiene, and the presence of child labour [8]. However, detailed information on prevalence of exposure and of cancer risk is currently lacking.

Fig. 2.13.2 *Asbestos insulation is common in buildings and presents a hazard when disturbed during demolition. Protective clothing must be worn to avoid contact with asbestos fibres.*

Industry/occupation	Target organs*
Group 1	
Aluminium production	Lung, bladder
Auramine, manufacture of	Bladder
Boot and shoe manufacture and repair	Nasal cavity, leukaemia
Chimney sweeping	Skin, lung
Coal gasification	Skin, lung, bladder
Coal-tar distillation	Skin
Coke production	Skin, lung, kidney
Furniture and cabinet making	Nasal cavity
Haematite mining (underground) with exposure to radon	Lung
Iron and steel founding	Lung
Isopropanol manufacture (strong-acid process)	Nasal cavity
Magenta, manufacture of	Bladder
Painter	Lung, bladder
Paving and roofing with coal-tar pitch	Lung
Rubber industry	Bladder, leukaemia
Group 2A	
Art glass, glass containers and pressed ware, manufacture	(Lung, stomach)
Carbon electrode manufacture	(Lung)
Hairdresser or barber	(Bladder, lung)
Petroleum refining	(Leukaemia, skin)

Table 2.13.3 *Industrial processes and occupations evaluated in IARC Monographs* Volumes 1-98 [9]
** Suspected target organs are given in parentheses*

REFERENCES

1. Pott P (1775). Chirurgical observations relative to the cataract, the polypus of the nose, the cancer of the scrotum, the different kinds of ruptures, and the mortification of the toes and feet. London: T.J. Carnegy.

2. Creech JL and Johnson MN (1974). Angiosarcoma of liver in the manufacture of polyvinyl chloride. *J Occup Med* 16: 150-151.

3. Siemiatycki J, Richardson L, Boffetta P (2006). Occupation. In: Schottenfeld D, Fraumeni JF, eds., *Cancer epidemiology and prevention*. New York: Oxford University Press. 322-354.

4. Doll R, Peto R (1981). *The causes of cancer quantitative estimates of avoidable risks of cancer in the United States today*. Oxford: Oxford University Press.

5. IARC (2007). *IARC Working Group Reports, Volume 3, Attributable Causes of Cancer in France in the Year 2000*. Lyon, France: International Agency for Research on Cancer.

6. Dreyer L, Andersen A, Pukkala E (1997). Avoidable cancers in the Nordic countries. Occupation. *APMIS* 105 Suppl: 68-79.

7. Straif K, Baan R, Grosse Y, et al. (2007). Carcinogenicity of shift-work, painting, and fire-fighting. *Lancet Oncol* 8: 1065-1066.

8. Pearce N, Matos E, Vainio H, et al. (1994). *IARC Scientific Publications, Volume 129, Occupational cancer in developing countries*. Lyon, France: International Agency for Research on Cancer.

9. IARC (1972-2007). *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volumes 1 - 98*. Lyon, France: International Agency for Research on Cancer.

Fig. 2.13.3 *Asphalt road-workers are exposed to polycyclic aromatic hydro-carbons*

2.14 Environmental Pollution

Summary

> Environmental pollution contributes to the world's cancer burden in a limited way

> Many known, probable and possible carcinogens can be found in the environment, and all people carry traces of these pollutants in their bodies

> Some environmental pollutants are widely dispersed, and others are concentrated in small geographic areas

> There are wide disparities in exposure, and pollution levels can be high in newly-industrialised countries with less stringent regulations

> Much environmental pollution can be prevented

In a broad sense, environmental factors are implicated in the causation of the majority of human cancers [1]. "Environmental factors" is generally understood to encompass everything that is not specifically genetic in origin. This includes many significant causes of cancer that are considered discretionary (although marketing and societal influences are also important): tobacco smoking, alcohol consumption and dietary habits. Evidence for the role of environmental factors comes from a variety of sources: from geographic variations in the distribution of the world cancer burden, from time trends showing increases or decreases in different forms of cancer, from studies of people migrating from one country to another, and from studies of twins raised in different environments.

There is a prominent subset of environmental factors, however, over which the individual has little control: environmental pollution, which includes the chemical contamination of the air we breathe, the water we drink, the food we eat, and the soil, sediment, surface waters and groundwater that surround the places we live. Many carcinogens can be found in the environment, and all people carry traces of environmental pollutants in their bodies.

The cancer risks from environmental pollution are difficult to study. People are exposed to hundreds, if not thousands, of chemicals and other agents through their environment, and environmental exposure assessment can be exceedingly complex. Some environmental pollutants are widely dispersed across the globe while others are concentrated in small geographic areas near specific industrial sources. This results in wide disparities in the level of exposure to environmental pollutants, and some population groups may face high risks that do not have a noticeable impact on national cancer incidence statistics. Nonetheless, there are several examples to indicate that the carcinogens that pollute our environment do contribute to the world cancer burden (Table 2.14.1).

Asbestos

Asbestos is one of the best characterised causes of human cancer in the workplace (see *Occupational exposures*, Chapter 2.13). The carcinogenic hazard associated with asbestos fibres has been recognized since the 1950s [1,2]. Non-occupational exposure to asbestos may occur domestically and as a consequence of localised pollution. People who live with asbestos workers may be exposed to asbestos dust brought home on clothes. The installation, degradation, removal and repair of asbestos-containing products in the context of household maintenance represent another mode of residential exposure. Whole neighbourhoods may be exposed to asbestos as a result of local asbestos mining or manufacturing. Some parts of the world also experience asbestos exposure as a result of the erosion of asbestos or asbestiform rocks.

In common with occupational exposure, exposure to asbestos due to residential circumstances results in an increased risk of mesothelioma, a rare tumour derived from the cells lining the peritoneum, pericardium or pleura [3]. Likewise, non-occupational exposure to asbestos may cause lung cancer, particularly among smokers [4]. A very high incidence of mesothelioma as a consequence of neighbourhood exposure is evident among inhabitants of villages in Turkey where houses and natural surroundings contain the mineral erionite.

Outdoor air pollution

Ambient air pollution has been implicated as a cause of various health problems, including cancer, and in particular as a cause of lung cancer. Air pollution entails a complex mixture of different gaseous and particulate components whose concentrations vary greatly with place and time. Human exposure to air pollution is therefore difficult to quantify. It may be possible, however, to attribute some carcinogenic risk to specific atmospheric pollutants, including benzo[a]pyrene, benzene, 1,3-butadiene, some metallic compounds, particulate matter (especially finer particles) and possibly ozone.

Emissions of traditional industrial air pollutants such as sulphur dioxide and particulate matter have decreased in developed countries, but high exposures still remain. Motor vehicle exhaust remains a continuing or even increasing problem as the number of vehicles increases. In a study based on air monitoring and population data for 100 western European urban areas, a high proportion of the population was exposed at levels above the WHO's air quality guidelines [5]. In the United States, modelled concentrations of hazardous air pollutants sometimes exceeded applicable reference concentrations [6].

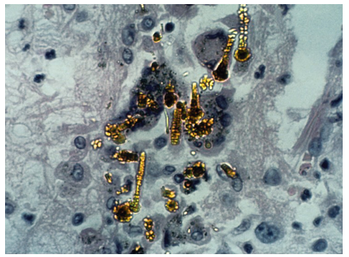


Fig. 2.14.1 *Lung tissue with infiltrate of asbestos fibres*

In developing countries, outdoor air pollution is likely to represent a greater public health problem than in more developed countries. In addition to vehicle emissions and industrialization, there may be poorly regulated use of coal, wood and other biomass (e.g. animal dung, crop residues) for electricity production, cooking, and heating. Although the proportion of global energy derived from biomass fuels has decreased from 50% in 1900 to about 13% in 2000, use of such fuels is increasing in some impoverished regions [7].

Numerous studies have compared residence in urban areas, where air is considered to be more polluted, to residence in rural areas as a risk factor for lung cancer [8]. In general, lung cancer rates were higher in urban areas, and in some studies were correlated with levels of specific pollutants such as benzo[a]pyrene, metallic compounds and particulate matter, or with mutagenicity in bacterial assay systems of particulate extracts. Other studies have attempted to address exposure to specific components of outdoor air, providing risk estimates in relation to quantitative or semi-quantitative exposure to pollutants. In general, these studies have provided evidence for an increased risk of lung cancer among residents in areas with higher levels of air pollution.

Localised air pollution may be a hazard in relation to residence near to specific sources of pollution, such as coal-fired power plants, petroleum refineries, metal manufacturing plants, iron foundries, incinerators and smelters. In general, an increased risk of lung cancer in the proximity of pollution sources has been demonstrated. In three Scottish towns, for example, increased lung cancer mortality occurred in the vicinity of foundries from the mid-1960s to the mid-1970s and later subsided in parallel with emission

Agent	Cancer site/Cancer
IARC Group I	
Aflatoxins	Liver
Arsenic and arsenic compounds*	Lung, skin
Asbestos	Lung, pleura, peritoneum
Benzene	Leukaemia
1,3-Butadiene	Leukaemia, lymphoma
Chromium[VI] compounds	Lung, nasal cavity
Erionite	Lung, pleura
Environmental tobacco smoke	Lung
Ethylene oxide	Leukaemia
Formaldehyde	Nasopharynx
Radon and its decay products	Lung
Solar radiation	Skin
Silica, crystalline	Lung
2,3,7,8-Tetrachlorodibenzo-para-dioxin (TCDD)	Several organs
IARC Group 2A	
Diesel engine exhaust	Lung, bladder
Ultraviolet radiation A	Skin
Ultraviolet radiation B	Skin
Ultraviolet radiation C	Skin
Polychlorinated biphenyls	Liver, bile ducts, leukaemia, lymphoma
Tetrachloroethylene	Esophagus, lymphoma
Trichloroethylene	Kidney, liver, lymphoma

Table 2.14.1 *Some carcinogens that are found in the environment*

reductions [9]. Similar results were obtained in studies focusing on industrial emissions of arsenic from coal burning and non-ferrous metal smelting. The evidence for an increased risk of cancers other than lung cancer from outdoor air pollution is inconclusive at present.

Air pollution by chlorofluorocarbons (CFCs) is believed to be indirectly responsible for increases in skin cancers around the globe. These chemicals, including halons, carbon tetrachloride and methyl chloroform, are emitted from home air conditioners, foam cushions and many other products. CFCs are carried by winds into the stratosphere, where the action of strong solar radiation releases chlorine and bromine atoms that react with, and thereby eliminate, molecules of ozone. Depletion of the ozone layer is believed to be responsible for global increases in UVB radiation (see Chapter 2.11).

Indoor air pollution

About half of the world's population, mostly in low-resource and medium-resource countries, uses solid fuels for cooking or heating, often in poorly ventilated spaces. The WHO identified indoor smoke from combustion of solid fuels as one of the top ten risks for the global burden of disease. Very high lung cancer rates occur among non-smoking women who use solid fuels in some parts of China and other Asian countries. Young children who are home for most of the day are also highly exposed. The components of this indoor smoke include coarse, fine, and ultrafine particles and many organic compounds, including carcinogens such as benzo[a]pyrene, formaldehyde and benzene. There is also strong epidemiologic and experimental evidence that cooking-oil emissions from high-temperature frying may pose a cancer hazard [10].

Tobacco smoke is an important source of indoor air pollution (see *Passive smoking*, Chapter 2.3). Environmental exposure to tobacco smoke has been linked to lung cancer and heart disease in adults and respiratory disease, middle ear disease, asthma and sudden infant death syndrome in children [11,12].

Among the most prominent pollutants of indoor air are radon and formaldehyde. Outdoor air pollutants can also accumulate indoors when buildings are not well ventilated. This problem can be exacerbated by efforts to weatherproof buildings to make them more energy-efficient.

Water and soil pollution

Access to clean water is one of the basic requirements of human health. Water quality is influenced by seasons, geology of the soil and discharges from agriculture and industry. The greatest concern relates to infectious disease. Microbiological contamination of water is controlled by disinfection methods based on chlorine, hypochlorite, chloramine or ozone. As a result of the interaction of chlorine with organic chemicals already present, drinking water may contain chlorination by-products, some of which are potentially carcinogenic [13]. Chloroform and other trihalomethanes are among those most commonly found. Studies of bladder cancer have suggested an increased risk associated with consumption of chlorinated drinking water [14], although doubts remain as to whether such associations are causal because of the way in which the studies measured exposure [15]. Given the large number of people exposed to chlorination by-products, however, even a small increase in risk, if real, would result in a substantial number of cases attributable to this factor. It is desirable to reduce such by-products without reducing the effectiveness of disinfection procedures.

Arsenic causes cancer in the skin, lung, bladder and other organs [13,16]. The main source of environmental exposure to arsenic for the general population is through ingestion of contaminated drinking water. High exposure to arsenic from drinking water is found in several areas of Argentina, Bangladesh, Chile, India, Mexico, Mongolia, Taiwan and the USA. There is strong evidence of an increased risk of bladder, skin, and lung cancers following consumption of water with high arsenic contamination [13,15]. The data on other cancers, such as those of the liver and kidney, are less clear but suggestive of a systemic effect. The studies have been conducted in areas of high arsenic content (typically above 200 ug/L). The risks at lower arsenic concentrations (e.g., above 5 ug/L) are not established, but an increased risk of bladder cancer in the order of 50% is plausible.

Several other groups of pollutants of drinking water have been investigated as possible sources of cancer risk in humans [15]. These include organic compounds (such as chlorinated solvents and pesticides) derived from industrial, commercial, and agricultural activities, and in particular from waste sites. Organic pollutants that persist in the environment and accumulate in fish (such as polychlorinated dibenzo-p-dioxins, polychlorinated biphenyls (PCBs), and organochlorine pesticides) are of particular concern, as well as nitrates and nitrites, radionuclides, hormonally-active compounds, and asbestos. For most pollutants, the epidemiological studies are inconclusive; however, an increased risk of stomach cancer has been repeatedly reported in areas with high nitrite levels in drinking water and an increased risk of leukaemia has been observed among residents in areas with elevated levels of radium in drinking water.

Estimating cancer risks from environmental pollution

Many of the carcinogens in our environment were first recognized as such through studies in experimental animals or through studies of highly-exposed workers (see *Identifying human carcinogens*, Chapter 2.1). Accordingly, the total cancer burden from environmental exposure in the general population can only be estimated by mathematical models. Several analyses have attributed only a small percentage of cancers to environmental pollution [2,17]. These reviews generally considered only known human carcinogens, most of which were identified through occupational studies several decades ago and are less present in today's environment thanks to government regulation. Environmental pollution levels may be higher in newly-industrialised countries with less stringent regulations or enforcement, and there is not as much information about cancer risks in less-studied groups such as women, children, and the elderly.

Also important is the potential cancer burden from exposure to hundreds of probable and possible human carcinogens that have been identified and from thousands of new chemicals that have not been tested for their cancer potential. Little is known about risks from combinations of exposures at levels found in the environment or from exposures during critical time windows of development or in susceptible populations. Cancers may have multiple causes, so that environmental factors may contribute to cancers that are attributed to occupational or lifestyle factors. The known interactions between radon and smoking or between asbestos and smoking support the idea that individual cancers may have multiple causes.

Finally, it is important to remember that environmental pollution is not only a cancer problem. Much environmental pollution can be prevented, and reducing environmental pollution can contribute to reductions in diseases other than cancer and to increases in aesthetics and in the overall quality of life.

REFERENCES

1. Tomatis L, Aitio A, Day NE, et al. (1990). *IARC Scientific Publications, Volume 100, Cancer: causes, occurrence and control*. Lyon, France: International Agency for Research on Cancer.

2. Doll R and Peto R (1981). The causes of cancer: quantitative estimates of avoidable risks of cancer in the United States today. *J Natl Cancer Inst* 66: 1191-1308.

3. Boffetta P (2006). Human cancer from environmental pollutants: the epidemiological evidence. *Mutat Res* 608: 157-162.

4. Health Effects Institute, Asbestos Literature Review Panel (1991). *Asbestos in public and commercial buildings : a literature review and synthesis of current knowledge*. Cambridge, MA: Health Effects Institute-Asbestos Research.

5. WHO European Center for Environment and Health (1995). Air Pollution. In: *Concern for Europe's tomorrow: health and the environment in the WHO European region* Stuttgart, Germany: Wissenschaftliche Verlagsgesellschaft. 139-175.

6. Woodruff TJ, Caldwell J, Cogliano VJ, et al. (2000). Estimating cancer risk from outdoor concentrations of hazardous air pollutants in 1990. *Environ Res* 82: 194-206.

7. Bruce N, Perez-Padilla R, Albalak R (2000). Indoor air pollution in developing countries: a major environmental and public health challenge. *Bull World Health Organ* 78: 1078-1092.

8. Katsouyanni K and Pershagen G (1997). Ambient air pollution exposure and cancer. *Cancer Causes Control* 8: 284-291.

9. Williams FL and Lloyd OL (1988). The epidemic of respiratory cancer in the town of Armadale: the use of long-term epidemiological surveillance to test a causal hypothesis. *Public Health* 102: 531-538.

10. Straif K, Baan R, Grosse Y, et al. (2006). Carcinogenicity of household solid fuel combustion and of high-temperature frying. *Lancet Oncol* 7: 977-978.

11. United States Environmental Protection Agency (1992). *Respiratory health effects of passive smoking: lung cancer and other disorders*. Washington, DC: Office of Health and Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Report No. EPA/600/6-90/006F.

12. IARC. (2004). *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 83, Tobacco smoke and involuntary smoking*. Lyon, France: International Agency for Research on Cancer.

13. IARC. (2004). IIARC Monographs on the Evaluation of Carcinogenic Risks to Humans, *Volume 82, Some drinking-water disinfectants and contaminants, including arsenic*. Lyon, France: International Agency for Research on Cancer.

14. Morris RD, Audet AM, Angelillo IF, et al. (1992). Chlorination, chlorination by-products, and cancer: a meta-analysis. *Am J Public Health* 82: 955-963.

15. Cantor KP (1997). Drinking water and cancer. *Cancer Causes Control* 8: 292-308.

16. IARC. (1987). *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Supplement 7, Overall evaluations of carcinogenicity: an updating of IARC Monographs volumes 1 to 42*. Lyon, France: International Agency for Research on Cancer.

17. Boffetta P, Tubiana M, Hill C, et al. *The causes of cancer in France*. Available from: http://annonc.oxfordjournals.org/cgi/content/full/mdn597 Date Accessed: September 2, 2008.

WEBSITES

United States Environmental Protection Agency: http://www.epa.gov/

Health Effects Institute (jointly funded by the U.S. Environmental Protection Agency and the motor vehicle manufacturing industry): http://www.healtheffects.org/

***Fig.* 2.14.2** *Industrial atmospheric emissions may include carcinogens*

2.15 Genetic Susceptibility

Summary

> Cancer genetic susceptibility is due to inheritance of specific sequence variants in cancer susceptibility genes that confer increased risk of cancer

> Cancer susceptibility genes may be oncogenes, tumour suppressor genes or risk modifier genes

> Genetic risk is a continuous variable. Susceptibility genes, and pathogenic sequence variants in them, fall into a spectrum from high-risk through intermediate-risk to modest-risk

> The field of high-risk susceptibility genes, especially for common cancers such as breast cancer and colon cancer, is fairly well explored; many and perhaps most such genes (i.e. BRCA1, BRCA2, APC, MLH1 and MSH2) are already known

> Intermediate-risk and modest-risk susceptibility genes are known to exist, but their identities and genetics are much less thoroughly understood. This is an extremely active research area

Cancer genetics comprices of two main subfields: genetic susceptibility and somatic cell genetics. Genetic susceptibility focuses on inherited (constitutional or germline) genetic variation in cancer susceptibility genes, and the effects of that inherited variation on an individual's lifetime cancer risk. In contrast, somatic cell genetics focuses on mutations that arise in an individual's cells during their lifetime and the role that those mutations play during tumour initiation and progression.

What kinds of genes can be cancer susceptibility genes? In a grand biochemical sense, cancer genes are largely organised into three groups: oncogenes, tumour suppressor genes and risk modifiers. The unifying characteristic of oncogenes is that their normal function tends to drive a process required for tumour initiation, progression, invasion, or metastasis forward. From a genetics point of view, this means that oncogenes are genes where either over-expression or gain of function mutations contribute to tumorigenesis. Classic examples include the RAS and MYC families of oncogenes. Tumour suppressor genes are the opposite; their normal function tends to inhibit a process required for tumorigenesis. Thus, from a genetics point of view, tumour suppressors are genes where either under-expression or loss of function mutations contribute to tumorigenesis. Classic examples include the retinoblastoma predisposition gene RB and the melanoma predisposition gene CDKN2A (p16). Within the tumour suppressors, there is a special subclass termed caretaker genes. Caretakers are involved in detection or repair of DNA damage, and loss of function of caretaker genes results in problems such as loss of cell cycle arrest that should be triggered by DNA damage, loss of apoptosis that should be triggered by DNA damage, and/or reduced DNA repair efficiency. Classic examples of caretakers include the Li-Fraumeni susceptibility gene TP53 and the breast/ovarian cancer susceptibility gene BRCA1. Finally, risk modifier genes are not main-effect oncogenes or tumour suppressors but rather genes whose normal function can modify the risk due to a carcinogenic exposure (either environmental or genetic). Examples include the alcohol dehydrogenases and acetaldehyde dehydrogenases (ADHs and ALDHs) that modify risk of head and neck cancer attributable to heavy alcohol consumption but have little effect on cancer risk in non-drinkers [1] and RAD51, which can modify the risk of breast cancer in BRCA2 carriers but has little effect on risk in non-carriers [2].

Evidence for a genetic component of risk for common cancers dates back at least to breast cancer pedigree studies carried out in the 1860s by Paul Broca [3]. Since that time, pedigree analyses have been complemented with linked genealogy/cancer registry studies, twin studies, segregation analyses, and a panoply of molecular genetic approaches. In a descriptive sense, these classes of studies have delivered three important pieces of information about genetic susceptibility: (i) For most of the common cancers, about 25% of the difference in risk between individuals is attributable to genetic susceptibility [4]. This measurement places a lower limit on the genetic population attributable fraction (gPAF)—the proportion of disease burden among the individuals in a population that is caused by that genetic variant—of these cancers, but the upper limit of gPAF could approach 100% [5]. (ii) The ratio of familial relative risk (FRR) experienced by first-degree relatives of breast cancer cases, colon cancer cases and prostate cancer cases versus unselected cases is ~2.0–2.5, and considerable evidence is consistent with the idea that the majority of this FRR is due to inherited susceptibility rather than, for example, shared environment [6-8]. (iii) Excess familial risk is most evident among the relatives of early onset cases for these cancers [7].

At this time, genetic susceptibility to breast cancer and colon cancer are better understood than genetic susceptibility for any of the other common cancers. For breast cancer, molecular studies have revealed that the FRR attributable to the ensemble of known susceptibility genes BRCA1, BRCA2, ATM, CHEK2, TP53, and PTEN is about 1.25, and their combined gPAF is about 5% [9,10]. For colon cancer, risks attributable to the ensemble of known susceptibility genes APC, MLH1, MSH2, MSH6, and MYH appear to be comparable to the known breast cancer susceptibility genes [11-13]. Thus we generally conclude that these genes are responsible for 5% of the attributable fraction and 20–25% of the familial relative risk of breast cancer and colon cancer. What categories of genes, and what classes of sequence variants in those genes, are responsible for the yet unexplained risk?

To assist this discussion of cancer susceptibility genes and deleterious sequence variants, we have prepared two graphs of genotype relative risk by carrier frequency. The first, Figure 2.15.1, is annotated with contour lines of gPAF, providing a frame of reference familiar to molecular epidemiologists. The second, Figure 2.15.2, is annotated with contour lines of FRR, a reference frame more familiar to genetic epidemiologists. On these graphs, risk and frequency are both divided into three strata. On the risk axes, high-risk refers to sequence variants with odds ratios ≥5.0, intermediate-risk refers to odds ratios in the range of 2.0<OR<5.0, and modest-risk refers to OR≤2.0, as annotated. On the frequency axes, common refers to sequence variant carrier frequencies ≥10%; uncommon refers to variants with frequencies in the range of 1% to 10%, and rare refers to variants with frequencies of <1%. Used this way, the 3x3 stratifications define 9 sectors. A question that we would eventually like to answer is what fraction of the risk of the common cancers is attributable to each of these categories of genes/sequence variants?

High risk genes/variants. For the common cancers, any high-risk variants with carrier frequencies above 1% in the general population (sectors 2 and 3) would have been found long ago by linkage analysis; it appears that none exist. While linkage analyses followed by positional cloning led to the discovery of susceptibility genes, such as APC, MSH2, BRCA1, and BRCA2, that harbour many rare, high-risk variants (sector 1) [14-22], lack of clear positional cloning successes since 1996 and failure to find strong evidence of new linkages in the very large breast cancer and prostate cancer genome scans recently reported by Smith et al. and Xu et al., respectively [23,24], has led some to argue that few genes harbouring high-risk breast, colon, or prostate cancer susceptibility alleles remain to be identified. While it remains possible that homogenous family selection through close attention to tumour phenotype will lead to identification of more genes harbouring true high-risk sequence variants, it seems at least as likely that the deleterious variants in remaining susceptibility genes will confer lower risk than those in the already established high-risk breast cancer susceptibility genes and therefore lie at or below the conceptual border with the intermediate risk stratum.

Intermediate risk genes/variants. Linkage analysis provides a systematic route to localising high-risk susceptibility genes, and genomewide SNP association studies provide a systematic route to localizing common, modest-risk genetic variants. However, current technology does not provide an economical genomewide approach to that which logically lies in-between: intermediate-risk susceptibility genes harbouring pathogenic sequence variants that are individually uncommon or rare. Nonetheless, studies of individual genes have demonstrated that these exist. Perhaps the three best-understood intermediate-risk susceptibility genes are ATM, CHEK2 and MC1R. Inheritance of a heterozygous truncating variant in ATM or CHEK2 confers an approximately 2-fold risk of breast cancer plus increased risks of a number of other cancers [28,29]. Similarly, inheritance of a heterozygous reduced function missense substitution in the melanocortin receptor MC1R can confer twofold to fourfold increased risks of melanoma; interestingly, these MC1R genotypes are also associated with easily visible melanoma prone phenotypes such as very fair skin, freckling and red hair [30].

Modest risk genes/variants. The disequilibrium structure of the human genome and gene pool is such that there tend to be few common SNP patterns (or haplotypes or SNP groups) at any given locus. This feature dramatically reduces the number of markers required to carry out genomewide SNP association studies as well as the degree of multiple testing inherent in such studies [31]. The result is that recently conducted genomewide SNP association studies had >80% power to detect associations at carrier frequencies of 10% for ORs of 1.5, and studies that use early-onset or familial cases should achieve sufficient power at ORs of 1.25. Although we do not currently know how much risk is attributable to variants in this frequency range (sectors 4&5), large-scale association studies are beginning to find and replicate evidence of risk association for some SNPs [32,33], and the optimistic view is that most common main effect genotype associations with risk of breast cancer, colon cancer, prostate cancer and some of the less common cancers should be found in the next few years.

The contour lines of gPAF and FRR plotted in Figures 2.15.1 and 2.15.2 provide another view of both potential importance and likelihood of the nine risk x frequency sectors. Individual deleterious sequence variants can be repre-

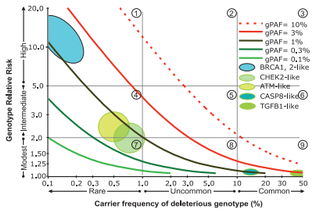


Fig. 2.15.1 *Genetic population attributable fraction contour lines. Calculations from [25-27]*

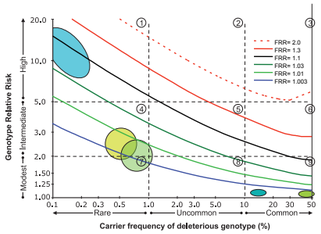


Fig. 2.15.2 *Familial relative risk contour lines. Calculations from [25-27]*

sented as a point on the graph. Alternatively, the pooled characteristic of a class of mutations in a susceptibility gene, for instance all of the high-risk mutations in BRCA1, can also be represented as a point on the graph. At some future time when most of the genetic basis of the common cancers is understood, the risk conferring genes could all be plotted on the graph, resulting in some kind of cloud of points. But what will the shape and density distribution of that cloud of points be? Under the common disease/common variant (CD/CV) hypothesis, we would expect the density distribution to be skewed towards the high-frequency end of the graph, at or above a carrier frequency of 10%, unless most of the risk is in minor allele homozygotes. In contrast, the common disease/rare variant (CD/ RV) hypothesis predicts a density distribution that peaks at lower carrier frequencies.

One relationship revealed by examination of these two graphs is that high-risk genes (e.g. BRCA 1 & 2) contribute to FRR relatively more efficiently than they contribute to gPAF; conversely, modest-risk SNPs (e.g. Caspase-8, TGFB1, FGFR2 [32,33]) contribute to gPAF more efficiently than they contribute to FRR [25,26]. We can deduce an interesting consequence from this relationship. On the one hand, the missing genetic component of breast cancer risk cannot be explained entirely by high-risk susceptibility genes. For example, an ensemble of high-risk genes, each with OR=10 and a pooled deleterious variant carrier frequency of 0.1%, could account for all of the unexplained familial relative risk and yet not account for the unexplained gPAF. Not to mention that linkage studies exclude the possibility of enough unidentified high-risk genes to account for the missing FRR. On the other hand, the missing genetic component of breast cancer risk cannot be explained entirely by modest-risk susceptibility genes either. For example, an ensemble of common modest-risk SNP with OR=1.25 and carrier frequency of 20% could have a gPAF far in excess of 100% without accounting for the missing FRR. Therefore, while we cannot yet specify the shape and density distribution of the aforementioned cloud of points in risk-frequency space, we can exclude the possibility that most of the risk (as measured by FRR) is accounted for by either rare, high-risk genes or common modest-risk SNPs.

Since the first major susceptibility genes for the common cancers were found in the early 1990s, we have learned a considerable amount about genetic cancer susceptibility, underlying susceptibility genes, and the biochemical pathways in which they function. For the known high-risk susceptibility genes, our growing understanding has led to genetic tests and to medical and surgical interventions that can add years to the lives of gene mutation carriers (see *Genetic testing*, Chapter 4.14). Whether improved understanding of intermediate-risk and modest-risk susceptibility genes will lead to similar medical utility remains a question for the future.

REFERENCES

1. Hashibe M, Boffetta P, Zaridze D, et al. (2006). Evidence for an important role of alcohol- and aldehyde-metabolizing genes in cancers of the upper aerodigestive tract. *Cancer Epidemiol Biomarkers Prev* 15: 696-703.

2. Antoniou AC, Sinilnikova OM, Simard J, et al. (2007). RAD51 135G->C modifies breast cancer risk among BRCA2 mutation carriers: results from a combined analysis of 19 studies. *Am J Hum Genet* 81: 1186-1200.

3. Broca PP (1866). *Traité des tumeurs*. Paris: Asselin.

4. Lichtenstein P, Holm NV, Verkasalo PK, et al. (2000). Environmental and heritable factors in the causation of cancer--analyses of cohorts of twins from Sweden, Denmark, and Finland. *N Engl J Med* 343: 78-85.

5. Rothman KJ, Greenland S (1998). *Modern epidemiology*. Philadelphia, PA: Lippincott-Raven.

6. Amundadottir LT, Thorvaldsson S, Gudbjartsson DF, et al. (2004). Cancer as a complex phenotype: pattern of cancer distribution within and beyond the nuclear family. *PLoS Med* 1: e65.

7. Goldgar DE, Easton DF, Cannon-Albright LA, et al. (1994). Systematic population-based assessment of cancer risk in first-degree relatives of cancer probands. *J Natl Cancer Inst* 86: 1600-1608.

8. Kerber RA and O'Brien E (2005). A cohort study of cancer risk in relation to family histories of cancer in the Utah population database. *Cancer* 103: 1906-1915.

9. Pharoah PD, Dunning AM, Ponder BA, et al. (2004). Association studies for finding cancer-susceptibility genetic variants. *Nat Rev Cancer* 4: 850-860.

10. Thompson D and Easton D (2004). The genetic epidemiology of breast cancer genes. *J Mammary Gland Biol Neoplasia* 9: 221-236.

11. Dunlop MG, Farrington SM, Nicholl I, et al. (2000). Population carrier frequency of hMSH2 and hMLH1 mutations. *Br J Cancer* 83: 1643-1645.

12. Ilyas M, Straub J, Tomlinson IP, et al. (1999). Genetic pathways in colorectal and other cancers. *Eur J Cancer* 35: 1986-2002.

13. Southey MC, Jenkins MA, Mead L, et al. (2005). Use of molecular tumor characteristics to prioritize mismatch repair gene testing in early-onset colorectal cancer. *J Clin Oncol* 23: 6524-6532.

14. Aaltonen LA, Peltomaki P, Leach FS, et al. (1993). Clues to the pathogenesis of familial colorectal cancer. *Science* 260: 812-816.

15. Bodmer WF, Bailey CJ, Bodmer J, et al. (1987). Localization of the gene for familial adenomatous polyposis on chromosome 5. *Nature* 328: 614-616.

16. Hall JM, Lee MK, Newman B, et al. (1990). Linkage of early-onset familial breast cancer to chromosome 17q21. *Science* 250: 1684-1689.

17. Leppert M, Dobbs M, Scambler P, et al. (1987). The gene for familial polyposis coli maps to the long arm of chromosome 5. *Science* 238: 1411-1413.

18. Miki Y, Swensen J, Shattuck-Eidens D, et al. (1994). A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1. *Science* 266: 66-71.

19. Peltomaki P, Aaltonen LA, Sistonen P, et al. (1993). Genetic mapping of a locus predisposing to human colorectal cancer. *Science* 260: 810-812.

20. Tavtigian SV, Simard J, Rommens J, et al. (1996). The complete BRCA2 gene and mutations in chromosome 13q-linked kindreds. *Nat Genet* 12: 333-337.

21. Wooster R, Neuhausen SL, Mangion J, et al. (1994). Localization of a breast cancer susceptibility gene, BRCA2, to chromosome 13q12-13. *Science* 265: 2088-2090.

22. Wooster R, Bignell G, Lancaster J, et al. (1995). Identification of the breast cancer susceptibility gene BRCA2. *Nature* 378: 789-792.

23. Smith P, McGuffog L, Easton DF, et al. (2006). A genome wide linkage search for breast cancer susceptibility genes. *Genes Chromosomes Cancer* 45: 646-655.

24. Xu J, Dimitrov L, Chang BL, et al. (2005). A combined genomewide linkage scan of 1,233 families for prostate cancer-susceptibility genes conducted by the international consortium for prostate cancer genetics. *Am J Hum Genet* 77: 219-229.

25. Goldgar DE (2002). Population aspects of cancer genetics. *Biochimie* 84: 19-25.

26. Hemminki K and Bermejo JL (2007). Constraints for genetic association studies imposed by attributable fraction and familial risk. *Carcinogenesis* 28: 648-656.

27. Lilienfeld AM, Lilienfeld DE (1980). *Foundations of epidemiology*. New York: Oxford University Press.

28. CHEK2*1100delC and susceptibility to breast cancer: a collaborative analysis involving 10,860 breast cancer cases and 9,065 controls from 10 studies (2004). *Am J Hum Genet* 74: 1175-1182.

29. Renwick A, Thompson D, Seal S, et al. (2006). ATM mutations that cause ataxia telangiectasia are breast cancer susceptibility alleles. *Nat Genet* 38: 873-875.

30. Hayward NK (2003). Genetics of melanoma predisposition. *Oncogene* 22: 3053-3062.

31. A haplotype map of the human genome (2005). *Nature* 437: 1299-1320.

32. Cox A, Dunning AM, Garcia-Closas M, et al. (2007). A common coding variant in CASP8 is associated with breast cancer risk. *Nat Genet* 39: 352-358.

33. Easton DF, Pooley KA, Dunning AM, et al. (2007). Genome-wide association study identifies novel breast cancer susceptibility loci. *Nature* 447: 1087-1093.

2.16 Medical and Iatrogenic Causes

Summary

> Chronic inflammation has been associated with excess risk of lung cancer, mesothelioma, oesophageal, colorectal, bladder and several other cancers

> Chronic pancreatitis has been related to a gross excess risk of pancreatic cancer

> Subjects with cirrhosis have an over tenfold excess risk of primary liver cancer

> Diabetes is associated with excess risk of endometrial, colorectal, liver and possibly pancreatic cancer

> Excess cancer risk has been reported in subjects treated with chemotherapy, radiotherapy, HRT, phenacetin and selective other drugs

Inflammation

The association between chronic inflammation and several malignancies has been recognised for many years. As early as 1863, the German pathologist Rudolf Virchow noted leucocytes in neoplastic tissues and made a connection between inflammation and cancer. Most of the early data were derived from descriptions of chronic cutaneous lesions, such as ulcers, burn scars or draining sinus tract [1,2]. Since then, the association between chronic inflammation and subsequent cancer has been recognised in many conditions (bladder cancer after schistosomiasis, ovarian cancer after pelvic inflammatory disease, esophageal cancer after Barrett's metaplasia, colorectal cancer after inflammatory bowel disease, ulcerative colitis and Crohn's disease, lung cancer and mesothelioma after silicosis, asbestosis or COPD and pancreas cancer after chronic pancreatitis). Inflammatory process is also an important cofactor in viral carcinogenesis (gastric cancer and MALT hlymphoma after *H. pylori*, cervical cancer after human papillomavirus, liver cancer after hepatitis B and C virus and Kaposi sarcoma after human herpes virus type 8 infection) [3].

Chronic pancreatitis and pancreatic cancer

Chronic pancreatitis has several causes, but the most common in western countries is heavy alcohol consumption. The frequency of chronic pancreatitis is low in light and moderate drinkers (i.e. less than about 20 units of alcohol per week); most patients with chronic alcoholic pancreatitis have consumed six or more drinks per day for a period of 20 years. Several studies have now linked chronic pancreatitis with an increased risk of pancreatic cancer [4]. The evidence comes from different types of studies, with case–control studies being the most frequent. Most of these studies have shown that compared to control subjects without chronic pancreatitis, patients with chronic pancreatitis have an increased risk of pancreatic cancer.

Cohort studies provide the most reliable evidence to substantiate a link between chronic pancreatitis and pancreatic cancer. Several such studies have been performed, and all show an elevated risk of pancreatic cancer even after excluding patients where there has been a short interval between the onset of pancreatitis and cancer [5-7]. Record linkage studies based on electronically stored data have also confirmed a link between pancreatitis and pancreatic cancer.

Besides alcohol there are other causes of chronic pancreatitis where the risk is also increased. Hereditary pancreatitis is a rare inherited disease with symptoms and findings that mimic other types of chronic pancreatitis. It is inherited as an autosomal disease with an onset in childhood or early adulthood. The cumulative lifetime risk of pancreatic cancer in these patients is about 40% [5,6]. Smoking appears to advance the age of onset of cancer, suggesting a gene–environment interaction [7].

Tropical pancreatitis has many of the characteristics of other forms of pancreatitis, except that the disease is found primarily in southern India and in parts of sub-Saharan Africa. Diabetes and abdominal pain are prominent features; pancreatic cancer is an ominous late development.

Although the link between chronic pancreatitis and pancreatic cancer is established, the molecular pathway for this association has not been fully investigated. In chronic pancreatitis, as in other benign diseases with an increased cancer risk, increased cell turnover and defective DNA repair could lead to pancreatic cancer. Loss of p16 expression, a common precursor of cancer, has been noted in patients with chronic pancreatitis [8]. K-ras mutations, found in nearly all pancreatic cancers, have also been detected in patients with chronic pancreatitis [9].

Other medical causes

Cirrhosis is a chronic degenerative lesion of the liver that is caused by infections (hepatitis B and C) and also by toxic substances, mainly alcohol. Subjects with cirrhosis have a gross excess (over 10-fold) of subsequent primary liver cancer risk (see chapter 5.4). Indeed, cirrhosis is considered a pathogenic step in liver carcinogenesis [10]. History of cirrhosis has also been related to increased risk of oral, pharyngeal and esophageal cancers [11], but incomplete allowance for alcohol drinking remains an open issue for causal inference.

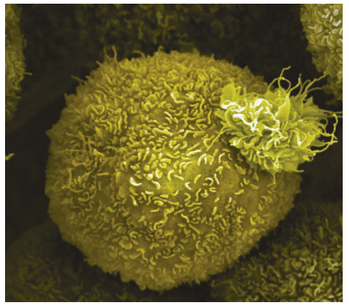


Fig. 2.15.1 *A pancreatic cancer cell*

Diabetes (and particularly type II diabetes) is related to hyperinsulinemia, and to changes in the insulin growth factor (IGF) system, which has been implicated in tumour promotion. Diabetes has been consistently related with excess risk of endometrial cancer, even after allowance for measures of body weight [12], and to colorectal, liver and perhaps pancreatic cancer risk [13].

There is no consistent evidence, in contrast, that stress (defined using several heterogeneous indicators) is related to excess cancer risk or cancer mortality [14].

Drugs and other therapies

The drugs that may cause or prevent cancer fall into several groups. Many cancer chemotherapy drugs interact with DNA, which might also result in damage to normal cells. The main neoplasm associated with chemotherapy treatment is leukaemia, although the risk of selected solid tumours—and specifically those related to viruses, such as liver, cervix or skin cancers—might also be increased. A second group of carcinogenic drugs includes immunosuppressive agents, notably used in transplanted patients. Lymphoma is the main neoplasm caused by these drugs. As discussed in chapter 2.8, hormone replacement therapy in menopause (HRT) increases the risk of breast, endometrial and ovarian cancers, and oral contraceptives increase the risk of breast, cervical and liver cancer, although they also reduce the risk of ovarian and endometrial cancer. Phenacetin-containing analgesics increase the risk of cancer of the renal pelvis.

Radiation for diagnostic purposes is likely to carry a small risk of cancer, which has been demonstrated only for childhood leukaemia following intrauterine exposure. Radiotherapy increases the risk of cancer in and near the irradiated organs. There is no evidence of an increased cancer risk following other medical procedures, including mammography and surgical implants [14].

In any case, the benefits of drugs and other therapies are usually much greater than the potential cancer risk.

REFERENCES

1. Bereston ES and Ney C (1941). Squamous-cell carcinoma arising in a chronic osteomyelitic sinus tract with metastasis. *Arch Surg* 43: 257.

2. Treves N and Pack GT (1930). The development of cancer in burn scars: an analysis and report of thirty-four cases. *Surg Gynecol Obst* 51: 749-782.

3. Balkwill F and Mantovani A (2001). Inflammation and cancer: back to Virchow? *Lancet* 357: 539-545.

4. Lowenfels AB and Maisonneuve P (2006). Epidemiology and risk factors for pancreatic cancer. *Best Pract Res Clin Gastroenterol* 20: 197-209.

5. Howes N, Lerch MM, Greenhalf W, et al. (2004). Clinical and genetic characteristics of hereditary pancreatitis in Europe. *Clin Gastroenterol Hepatol* 2: 252-261.

6. Lowenfels AB, Maisonneuve P, DiMagno EP, et al. (1997). Hereditary pancreatitis and the risk of pancreatic cancer. International Hereditary Pancreatitis Study Group. *J Natl Cancer Inst* 89: 442-446.

7. Lowenfels AB, Maisonneuve P, Whitcomb DC, et al. (2001). Cigarette smoking as a risk factor for pancreatic cancer in patients with hereditary pancreatitis. *JAMA* 286: 169-170.

8. Rosty C, Geradts J, Sato N, et al. (2003). p16 Inactivation in pancreatic intraepithelial neoplasias (PanINs) arising in patients with chronic pancreatitis. *Am J Surg Pathol* 27: 1495-1501.

9. Lohr M, Kloppel G, Maisonneuve P, et al. (2005). Frequency of K-ras mutations in pancreatic intraductal neoplasias associated with pancreatic ductal adenocarcinoma and chronic pancreatitis: a meta-analysis. *Neoplasia* 7: 17-23.

10. La Vecchia C, Negri E, Cavalieri d'Oro L, et al. (1998). Liver cirrhosis and the risk of primary liver cancer. *Eur J Cancer Prev* 7: 315-320.

11. Randi G, Altieri A, Gallus S, et al. (2005). History of cirrhosis and risk of digestive tract neoplasms. *Ann Oncol* 16: 1551-1555.

12. Lucenteforte E, Bosetti C, Talamini R, et al. (2007). Diabetes and endometrial cancer: effect modification by body weight, physical activity and hypertension. *Br J Cancer* 97: 995-998.

13. La Vecchia C, Negri E, Franceschi S, et al. (1994). A case-control study of diabetes mellitus and cancer risk. *Br J Cancer* 70: 950-953.

14. Doll R, Peto R (2005). Epidemiology of cancer. In: Warrell DA, Cox TM, Firth JD, eds., *Oxford textbook of medicine* 193-218.

CANCER EFFORTS IN THE WHO WESTERN PACIFIC REGION

Cancer is now is the second-leading cause of death, after cardiovascular disease, in the Western Pacific Region. It claimed some 2.5 million lives in the Region in 2005, with the number expected to increase by more than 60% to over 4 million deaths in 2030. Cancer also is the leading cause of death in all developed countries in the Region—Australia, Brunei Darussalam, Hong Kong (China), Japan, Macao (China), New Zealand, the Republic of Korea and Singapore. At present, the cancer registry information available for 17 countries in the Region shows that the leading cancers in terms of mortality are lung, liver and stomach cancers. Since 2006, WHO has provided support to Brunei Darussalam, Fiji, Malaysia, Mongolia and Viet Nam for further development of cancer registries and for the development of national cancer control programmes. Support for middle- and low-income countries in the Region has focused on the prevention of lung, liver and cervical cancers, particularly through the development of national cancer control programmes.

Tobacco control initiatives have been developed as the primary focus to reduce lung cancer rates across the Region. By 2006 all Member States in the Region had ratified the WHO Framework Convention on Tobacco Control, making the Western Pacific Region the first in the world to do so. Many countries in the Region have developed effective tobacco control measures and are now implementing specific programmes.

Hepatitis B immunizations have been advocated as the principal measure in liver cancer prevention. In 1991, 29 of the 37 countries and areas in the Region had a hepatitis B virus (HBV) carrier rate greater than 8%. The Regional Office for the Western Pacific has strongly promoted the introduction of HBV vaccine into the national immunization programs of all the Member States. In 2005 a regional goal was set to reduce chronic hepatitis B infection rates to less than 2% among children 5 years of age by 2012. Since then, the Regional Office has been working with countries with high proportions of home births on strategies to deliver timely HBV birth doses. At present, 26 countries and areas in the Region, including China, are estimated to have achieved less than 2% hepatitis B chronic infection rates among children 5 years old, down from an average of 8–14% in the pre-vaccination era. Figure 1 shows the decline in chronic hepatitis B infection rates, especially in children and adolescents, in China.

Figure 2 shows that rates of cervical cancer are highest among the less-developed countries of the Western Pacific Region. Cytology (Pap smear) is carried out in developed countries in the Region and visual inspection (with acetic acid) is promoted as a cost-effective method for developing countries. The Regional Office for the Western Pacific supported Member States in the introduction of two human papillomavirus (HPV) vaccines. Australia was the first country in the world to introduce HPV vaccine, targeting all women age 12–26 years.

website: www.wpro.who.int

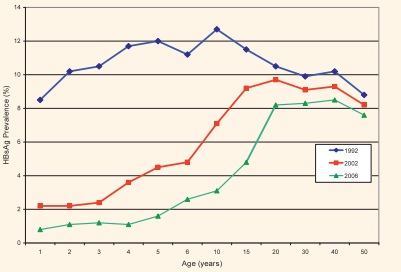


Fig. 1: *HBV population prevalence from National Surveys in China (Preliminary data)*

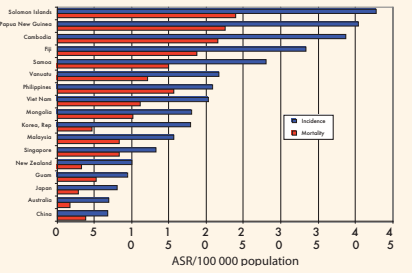


Fig. 2: *CERVICAL CANCER: Age-Standardised Death & Incidence Rates (ASR) for the Western Pacific Region: 2002*

3

Mechanisms of Carcinogenesis

3.1 Molecular Hallmarks of Cancer

Summary

- Cancer is a multi-step process in which cells undergo metabolic and behavioural changes, leading them to proliferate in an excessive and untimely way
- These changes arise through modifications in mechanisms that control cell proliferation and lifespan, relationships with neighbouring cells, and capacity to escape the immune system
- Modifications that lead to cancer include genetic changes that modify the DNA sequence. Another way to change the programme of cells is to modify the conformation of chromatin, the structure that wraps up DNA and regulates its access by DNA reading, copying and repair machineries. Such changes are called "epigenetic"
- Among the 23 000 or so genes that constitute the human genome, a few hundred are commonly targeted by genetic or epigenetic changes. These genes are parts of networks of genes that regulate cell division, differentiation and life span
- The emergence of technologies for genome-wide analysis of genetic and epigenetic changes is advancing our capacity to map patterns of alterations specific for each particular cancer, paving the way to personalised medicine based on molecular diagnosis
- Advances in cancer molecular biology also identify new ways to inhibit the growth of cancer, leading to new, more selective and less toxic forms of cancer chemotherapy

Cancer is a complex disease that is very variable in its presentation, development and outcome from one patient to the other. The same heterogeneity and variability exist at the cellular and molecular level. Cancer is a multi-step process during which cells undergo profound metabolic and behavioural changes, leading them to proliferate in an excessive and untimely way, to escape surveillance by the immune system, and ultimately to invade distant tissues to form metastases [1]. These changes arise through the accumulation of modifications in the genetic programmes that control cell proliferation and lifespan, relationships with neighbouring cells, and capacity to escape the immune system. This process results in the formation of a mass of deregulated cells, which can be qualified as "outlaw" because they do not obey the rules that control normal cell growth and behaviour. Such a mass may be asymptomatic for a long time. However, it will ultimately grow to perturb physiological functions, giving rise to multiple symptoms, depending upon the location and size of the mass, and of the spread of cancer cells within the organism.

Cancer genes

The genetic programmes targeted by cancer are present in scores of genes that are dispersed throughout the human genome. It is believed that human DNA contains about 23 000 genes. Several thousand of these genes (3000–5000) encode proteins involved in genetic programmes that are deregulated in cancer. A dysfunctional gene can result in the production of abnormal levels of a critical protein (either too much or too little), the production of an aberrant protein (with either gain or loss of function), or the complete absence of the protein. For example, mutation in a gene called KRAS turns a small protein located just inside the cell membrane into an amplifier of cell growth signalling. This protein normally works as a signalling intermediate between receptors for growth factors at the cell surface and the molecular wiring systems that send growth signals to the cell nucleus to enact cell division. When the KRAS gene is mutant, the corresponding protein is behaving like a switch locked in the "on" position generating a permanent cell division signal. Mutations of KRAS are common in many cancers, such as colorectal cancers (in 30–40% of the cases) or adenocarcinomas of the lung (in 20–30% of the cases). Such an activated gene is called an "oncogene" because it promotes cell proliferation. In contrast, some genes contribute to cancer development when they are inactivated. This is, for example, the case of the TP53 gene. This gene encodes a protein that naturally acts like an "emergency brake" to avoid inappropriate cell division. Mutation in this gene disrupts the protein, which becomes unable to stop the proliferation of cells when needed. Mutations in TP53 are found in almost every kind of cancer. Such a gene that contributes to cancer development through loss of its function is called a tumour suppressor, because in normal conditions its active products work as a brake to suppress cancer growth [2].

Cellular origin and progression of cancer

Many cancers arise from just one cell (or from a small number of cells) [3]. To become cancerous, this cell must acquire several changes in oncogenes and tumour suppressor genes that will make the cell capable of proliferating well beyond its normal limit. This process will result in the formation of a clone of "outlaw" cells. If such a clone is tolerated by the organism and allowed to remain unperturbed, it may continue to proliferate and, during this process, the cells it contains will accumulate more and more modifications. In such a disrupted context, only the fittest and the most aggressive cells will thrive, taking the place of other, less disorganised cells. This is how tumours develop to become malignant. This is also why cancer is difficult to treat: when patients are given a drug that kills cancer cells with great efficacy, the few cells. This approach is that survive are those that have undergone changes that make them resistant to the drug. This very small group of residual cells may be enough for the cancer to relapse in a form that is worse than its initial form.

For the oncologist and the cancer pathologist, cancer is best described as a progressive disease. It starts as a small, inconspicuous lesion that generally remains confined to its tissue of origin and is considered as clinically benign since, when detected at an early stage, it may be completely resected and may not cause the patient's death. Sometimes, these small lesions appear within a tissue area that is affected by a chronic inflammatory disease, such as cirrhosis in the liver, gastritis in the stomach or intestinal metaplasia (Barrett's oesophagus) in the lower oesophagus. These chronic diseases that represent a favourable terrain for cancer occurrence are called "precursor diseases". When undetected at an early, benign stage, cancer has a chance to develop and progress not only in size but also in its capacity to interfere and perturb neighbouring cells. Such cancers will not be confined any longer: they will spread within the organ affected and then will disseminate to neighbouring organs. They also enter the lymphatic vessels to spread into lymph nodes. Through the lymph or bloodstream, they can travel to distant organs and form colonies, the metastases, in general located in bone, lung, liver or brain. Tumour dissemination is often facilitated by the fact that cancer cells promote angiogenesis, that is, the synthesis of new small blood vessels dedicated to tumour vascularisation, thus improving tumour supply in oxygen and nutrients.

Disseminated cancers are much more difficult to treat. In addition to localised therapy targeting tumour foci (surgery, radiotherapy) they require systemic therapies using cytotoxic drugs (chemotherapy). Chemotherapy is based on the use of toxic substances that interfere with DNA and cell division to preferentially kill cancer cells. This approach is based on the hypothesis that the latter may be more sensitive than normal cells since they replicate their DNA more often in order to divide, thus providing a larger window of opportunity for cell killing through DNA damage. Recently, new methods using molecules that target one particular type of cancer-related molecular changes have been introduced clinically [4]. They include, for example, antibodies directed against cell-surface molecules expressed by cancer cells (such as trastuzumab, an antibody that inhibits a cell-surface receptor called HER-2 which is often over-expressed in breast cancer) or drugs that block the activity of enzymes activated in cancer cells (such as imatinib, which blocks an enzyme activated in many tumours of the gastrointestinal stroma, or erlotinib, which inhibits the enzyme activity associated with the receptor of the epidermal growth factor. Thus, the notion of time and progression is critical in carcinogenesis. This concept has been confirmed in studies using laboratory animals. These have shown that the development of cancer in mice or rats exposed to carcinogens occurred through different steps, with "initiation" (during which the carcinogen creates mutations in the DNA of normal cells), being followed by "promotion" (in which the initiated cells develop a growth advantage over their neighbours allowing them to produce a distinct lesion, and then by progression (in which tumours become more and more aggressive through the accumulation of supplementary genetic and epigenetic modifications). As a result, a number of oncogenes and tumour suppressors are frequently altered in many cancers, irrespective of the organ site or the cause of the disease. The products of these genes are all part of a network of factors that work together to control cell proliferation, differentiation and survival

How do genes become disrupted?

Cancer may start when small changes called mutations occur in the DNA sequence[5]. They can be limited to a single base change, thus changing one of the 3 bases that define a codon and leading to the selection of a different amino-acid to be integrated into a protein. In some cases, this is enough to dramatically change the activity of that protein. Other DNA alterations can affect a large number of bases, sometimes removing from the genome a large stretch of DNA that contains several genes, or translocating it elsewhere into the genome to form new genes made of the fusion of non-contiguous DNA segments, thus leading to the synthesis of new, abnormal proteins. Such changes, whatever their size, are called "genetic alterations" or "mutations". Significantly, these changes can be detected by sequencing the DNA of cancer cells.

The way DNA is read and copied is critically dependent upon the way in which DNA is compacted, packaged and organised. There are "closed" DNA areas (which are locked for editing and copying) and "open" ones (which the cell can copy, read, and use to produce RNA and proteins). Thus, another way to change the programme of cells, aside from DNA mutation, is to modify the overall packaging in order to shut down genes that lie in open areas or to switch on those that lie in closed areas. Such changes cannot be detected just by sequencing DNA. They require the analysis of chemical modifications that regulate the accessibility and readability of DNA. These changes are called "epigenetic".

The role of genetic changes in cancer has been recognised for over 50 years and scientists have now built a long catalogue of genes that are mutated in cancer. In contrast, the role of epigenetic changes has been recognised only relatively recently [6]. In describing the mechanisms of cancer, genetic and epigenetic changes have to be considered together, as two sides of the same coin. They respond to each other and influence each other, generating pathways of sequential changes that determine how a given cell will progressively acquire the characteristics of a cancer cell. Both genetic and epigenetic changes are universally present in human cancer: they induce changes in gene expression that dividing cells can transmit to their daughters over many cell generations. Disrupted epigenetic states may result in functional consequences equivalent to those induced by genetic alterations.

The causes of genetic and epigenetic changes are numerous. The genome contains 3 billion base pairs and, as any molecule in or body, each of them can be modified by reaction with a variety of chemical, physical or toxicological

agents. For example, a number of chemicals classified as carcinogens can attack DNA bases, bind to them and induce modifications in the coding sequence. UV light can form typical changes by bridging together adjacent cytosines to form a dipyrimidine dimer. This results in double mutations, where two Cs are replaced by two Ts. These mutations are "signature" of mutagenesis by UV light in skin cancers. Ionizing radiations induce single or double DNA strand breaks. The main cause of DNA damage, however, is "hiccups" in the physiological processes of DNA replication and repair. Each time a cell divides, it has to produce a perfectly accurate copy of the 3 billion base pairs of its DNA. This process is tightly controlled by very elaborate DNA proofreading and repair systems. However, errors may occur and remain unrepaired. If such error occurs in a gene involved in cancer, this may result in its disruption, conferring on cells a new property that may make them better adapted to life within the deregulated system of a growing cancer mass. The cell will thus thrive in these conditions, and progressively take preeminence to become part of a malignant tumour.

What does it take for a cell to become a cancer cell?

In many respects, a cancer cell is a rogue cell that escapes the laws and rules governing cell community life, thus attaining an independent survival advantage. In doing so, cancer cells strive to adapt and fight off the defence systems of the organism and progressively adopt an aggressive, invasive behaviour. Cancer cells become able to travel within the body and to home preferentially in hospitable organ environments as metastases. Metastatic cancer cells have become so good at adapting themselves to new conditions that they resist many attempts at killing them, including cytotoxic drugs or radiation treatments. This is the reason why most cancers are best treated at an early stage, at a time when cancer cells still have limited adaptive capacity and are thus unable to bypass the effects of treatment.

Recent experimental studies have identified the minimum number of steps needed to develop a fully cancerous cell [7]. Three fundamental rules must be violated. The first is that cells should proceed to divide only when they receive appropriate signals. To break this rule, the cell has to permanently activate cell division by switching on the circuits that become normally activated when the cell is stimulated by a hormone or a growth factor. Rule number two specifies that when confronted by stressful or improper conditions for DNA replication, cells activate self-destruction programmes rather than allow DNA replication to proceed in conditions where genes may become damaged. To bypass these auto-destruction programmes, the cell has to get rid of its safety brakes, which normally prevent aberrant or excessive cell division. These brakes are controlled by two master genes, RB1 (also called the Retinoblastoma gene) and TP53 (which produces the p53 protein, a stress sensor that normally prevents cells from dividing when their environment is disturbed). When these two brakes are removed by mutation, cells can not only divide but also avoid entering programmed cell death, thus allowing the formation of a tumour mass. Rule number 3 determines that normal cells divide only a limited, fixed number of times. In other words, cells have a "division counter" that prevents them from replicating their DNA beyond a certain, predefined number of rounds. Normal cells are only capable of replicating their DNA and dividing for a finite number of times, due to a particular structure at the end of each chromosome called the telomere. The telomere is made of small repeats of DNA sequence which become eroded each time the cell divides. When all repeats are gone, the cell cannot divide any longer and becomes a senescent cell. In the cancer cell, the activation of an enzyme called telomerase allows the addition of new repeats at the end of chromosomes, thus allowing the cell to divide well past the finite number of divisions it has been programmed to make. This process is equivalent to the acquisition of a form of "permanent cell youth".

Achieving these three functional changes is enough for the cell to become cancerous. But at the molecular level, this is not a simple operation. Taken separately, each of these changes may upset normal cell function and lead it to destruction in a process called apoptosis, a type of "cell suicide" that eliminates abnormal cells. Thus, the central problem of a would-be cancer cell is to operate all these changes in a coordinated manner. This is where both genetic susceptibility and environmental changes play a major role. Genetic susceptibility can confer on the normal cells of some people a greater capacity to make rapid changes, thus increasing the chances that they can occur simultaneously in a single cell. Environmental changes may act as natural selection to allow the survival of abnormal cells that appear to be fitter than normal cells in perturbed conditions. This is why cancer is a disease in which both genetic and environmental changes play such important roles. From the molecular point of view, these roles cannot be separated.

The Cancer Box

Despite their intrinsic diversity, cells operate along common schemes in the conduct of the basic processes that control cell proliferation and death. As a result, a number of oncogenes and tumour suppressors are frequently altered in many cancers, irrespective of the organ site or the cause of the disease (Table 3.1.1). The products of these genes are all part of a network of factors that work together to control cell proliferation, differentiation and survival. Figure 3.1.1 represents the outline of what can be defined as "the cancer box", that is, the core network of genes and processes that have to be altered in any cancer cells. This cancer box involves three main signalling processes. Two of them are growth-promoting processes and one is a growth-suppressive mechanism. One of the growth-promoting processes uses as its main effector a protein called beta-catenin. This protein has several intracellular roles. It can locate at the intracellular face of the cell membrane where it plays a role as a component of cell-to-cell junctions and of the intracellular fibre skeleton of the cell. It can also locate in the cytoplasm, where it forms part of a complex that receives growth and proliferation signals captured at the cell surface. When activated by such signals, it can relocate into the nucleus where it stumulates the expression of genes involved in cell proliferation. The gene encoding beta-Catenin, CTNNB1, is disrupted by mutation in 10 to 20% of various epithelial cancers (e.g. lung, breast, liver or colon cancers). Other genes involved in this process are APC (often mutated in colon cancer), MYC and CCND1 (encoding cyclin D1). The other major growth signalling process involved in the cancer box includes cell-surface receptors such as EGFR (the epidermal growth factor receptor), a protein that extends on both sides of the cell membrane. On the external side, it captures growth factors present in the bloodstream or in intercellular spaces. On the internal side, it possesses an enzymatic activity, a tyrosine kinase, which becomes activated when the receptor binds a growth factor. The tyrosine kinase then initiates a cascade of intracellular signals akin to a chain reaction that propagates through amplifying molecules such as the product of the KRAS gene. The ultimate effect of these signals is to activate cell proliferation by stimulation of the progression of the cell cycle. To counteract these signals, the main anti-proliferative process is controlled by the TP53 gene. Its product, p53, can be best described as a sensor of stress, in particular DNA damaging stress. When the cell DNA is damaged and not repaired, p53 senses this abnormality, accumulates in the nucleus and activates a large number of anti-proliferative mechanims, often simultaneously. These anti proliferative mechanisms can block cell cycle progression (thus counteracting the proliferative effects of the two processes described earlier), push the cells to differentiate (thus driving them towards a status were they do not proliferate) or induce a cell suicide programme called apoptosis (leading the cell to self-destruct its DNA and other components to leave only small bodies that are eliminated by the macrophages, the specialised, 'garbage'-collecting cells in the tissues).

The key to the cancer box lies in the way these three processes are interconnected. The main connection is ensured by a very special chromosomal locus, located at the far end of the short arm of chromosome 9. It contains a gene called CDKN2a. This locus is quite unique in the fact that it is made of two overlapping genes that use the same DNA segments as templates for RNA and protein synthesis. In other words, this locus can direct the synthesis of two different proteins that do not have a single common amino-acid. One is called p16 and is a negative regulator of cell cycle (thus exerting anti-proliferative effects). P16 belongs to a family of regulators called CDK inhibitors, that is, factors that inhibit enzymes (cyclin-dependent kinases) that drive cells to a higher rate of proliferation. By blocking these enzymes, CDK inhibitors prevent cell division and induce a mechanism called cell cycle arrest. The other is called p14ARF (for Alternative Reading Frame) and controls the activation of p53. Thus, through its two products, this single gene controls the connection between the various components of the cancer box. Therefore, it is not unexpected that the CDKN2a gene is altered by several mechanisms in almost every cancer.

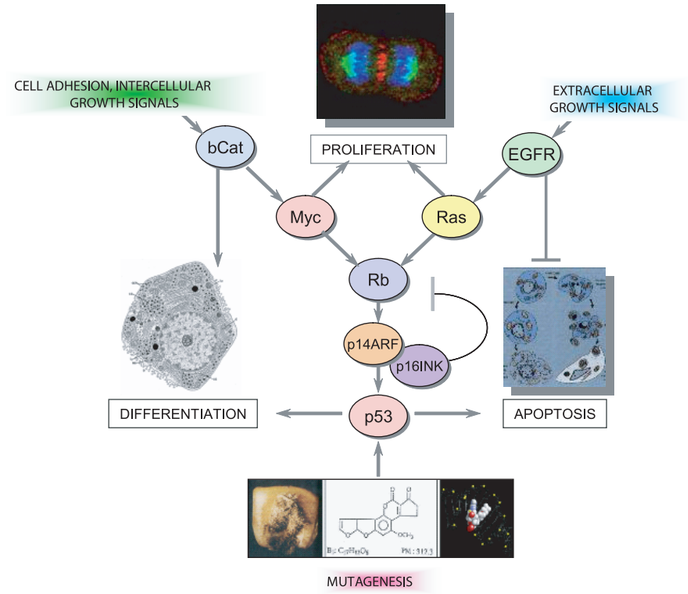


Fig. 3.1.1 *The Cancer Box*
This figure illustrates how several genes may cooperate in cancer development. The three pictures illustrate the 3 phases of a cell's life: division (top), differentiation (left) and programmed cell death (right). Important genes and their cooperation are represented by arrows. Cell adhesion signals are transmitted through betaCatenin towards the components of the cell division machinery, which converge on the RB1 gene (a regulator of cell cycle). Growth signals also converge towards the same control points through genes such as cell surface receptors with tyrosine kinase activity (RTK) and their intracellular transmitters (RAS). At the bottom of the figure is represented the universal "brake" of cell division control: the p53 protein. TP53, the gene encoding p53, is often the target of environmental mutagens, as for example aflatoxin, a contaminant of the diet that generates base changes into DNA. This mutation eliminates the brake effect and allows uncontrolled proliferation.
Source: Pierre Hainaut, unpublished

Genetic changes

Genetic changes are the cornerstone of cancer. The sequencing of the entire human genome has made it possible to identify genetic alterations in cancers in unprecedented detail. About 300 different genes have been shown to be mutated at some frequency in human cancers. Within this catalogue, a shortlist of 20 or 30 genes appear to be frequently mutated in almost any type of cancer (including those of the "cancer box") (Table 3.1.1). These genes may be seen as "master genes" that control very basic functions essential for cell division control.

Detecting mutations in cancer cells has many potential implications for research and therapy. First, mutations can be informative of the evolution of cancer and provide clinically interesting prognostic or predictive information. Second, the first mutations that contribute to cancer occur, by definition, prior to the development of a lesion. Detecting these mutations may thus help in early cancer diagnosis. Finally, in several cases mutations may be good indicators of therapeutic responses, and may help to select therapies that have greater chances of success. This is the case, for example, for mutations in the EGF receptor (EGFR) that are found in 20–40% of lung cancers in never smokers. These mutations constitutively activate the receptor, generating a constant cell proliferation signal. The signal can be blocked by small inhibitory drugs such as gefinitib (Iressa) or erlotinib (Tarceva). These drugs have interesting therapeutic effects in patients with EGFR mutations, but are poorly effective in most other patients.

Cells of many cancers accumulate mutations at a rate significantly higher than in normal cells, a property referred to as "Mutator Phenotype". This property of transformed cells is believed to be critical for the development of cancer as well as for the development of resistance to cancer treatments [8]. The Mutator Phenotype is the consequence of mutations in genes that normally control DNA repair and integrity. Cells with such mutations become unable to correctly repair mutation-inducing DNA damage, and thus accumulate mutations at a much higher rate than normal cells. Molecular mechanisms underlying the Mutator Phenotype may include defects in DNA repair, gene transcription, cell cycle control and cell death.

TP53 tumour suppressor: an example of common genetic change

The most studied of all cancer genes is TP53, which encodes the p53 protein, a tumour suppressor that is mutated in about half of all human cancer cases. A database of all these mutations is maintained at the International Agency for Research on Cancer [9]. It compiles about 24 000 TP53 mutations detected in almost every type of human cancer. We now have a very good understanding of the molecular effects of these mutations. Most of them fall within a part of the protein that binds to DNA, allowing p53 to regulate several dozen of other genes. The mutations are often single base substitution, leading to the replacement of one amino-acid in the protein by another one. This small change is enough to perturb protein folding and to prevent it to bind to DNA, thus inducing a loss of function.

Close examination of the distribution of these mutations show that they occur in a non-random fashion and there are significant differences in mutation patterns among cancers that are strongly associated with exposure to environmental mutagens. These differences are due to the fact that different mutagens can damage DNA in particular ways, thus leading to different types of mutations. Thus, mutations in TP53 can be seen as "molecular signatures" of mutagenic events that contribute to cancer. This makes the TP53 mutation profile a potent biomarker in molecular epidemiology, as a potential reporter of specific mutagenic exposures. This is supported by the evidence showing that mutation patterns in common cancers differ significantly depending on geographic variations in incidence, indicative of differences in exposure to specific environmental carcinogens [10]. For example, in liver cancers, the type and

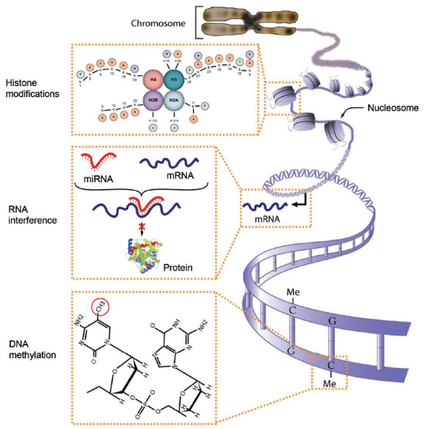


Fig. 3.1.2 *Epigenetic regulation of gene expression, transcription and repair*
The figure shows, from top to bottom, how DNA is packaged into a supra-molecular structure, the chromatin, which controls how cellular or environmental signals can act on DNA. Changes in these structures have a critical impact on how gene works. These changes are called "epigenetic".
Source: Zdenko Herceg and Thomas Vaissiere, unpublished

frequency of mutations is very different between patients in Europe and the USA and those in many countries of Africa or Southeast Asia. The difference is due to the impact of a particular mutagen, aflatoxin, which is produced by a fungus that contaminates many food components in tropical areas. This mutagen is virtually absent from the western diet, but induces a characteristic TP53 mutation that contributes to liver cancer in regions of sub-Saharan Africa and South East Asia.

In many cancers, presence of a mutation in TP53 is correlated with a rather poor prognosis and bad response to treatment. So far, this fact has had only limited impact in the clinics because the same information could be deduced from other markers routinely scored by the pathologist: the size of the tumour, its grade, the extension of the disease into lymph nodes, etc. However, it has recently been recognised that TP53 mutations may help to distinguish between tumours that, to the pathologist, look the same. For example, in breast cancers, presence of a TP53 mutation allows the identification of tumours that are at a high risk of progression among tumours classified by the pathologist as of "good prognosis". It is therefore possible to single out those patients and offer them more aggressive treatment. It would not be justified to give such a treatment to all patients because the risk of secondary effects would outweigh the benefits, since most of them actually do not need such treatment.

TP53 mutations can also be detected outside tumour tissues, in particular in body fluids such as blood. The presence of mutant TP53 in blood is due to the fact that cancer masses release small amounts of dead cells that originate from the tumour and therefore contain the same mutation. Detection of such mutations in the plasma may be exploited for early cancer detection. Indeed, TP53 mutations in plasma DNA have been reported in patients with cancers of the colon, pancreas, lung and liver. For example, the aflatoxin-induced TP53 mutation mentioned above is detectable in the plasma of non-cancer subjects from China who are chronic carriers of Hepatitis B virus,

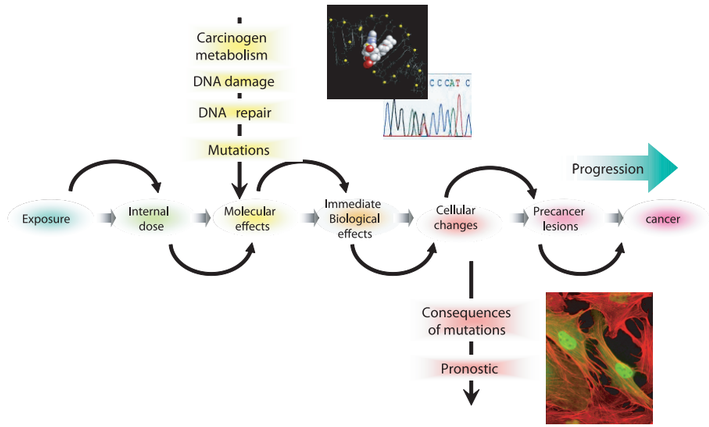


Fig. 3.1.3 *How cancer progresses, from environmental risk factors to overt disease*
Source: Pierre Hainaut, unpublished

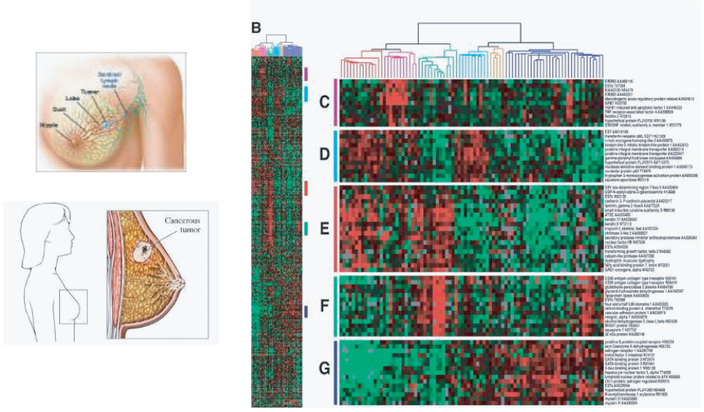


Fig. 3.1.4 *Gene expression patterns in breast cancer. Each individual dot represents the expression of one gene. The colour indicates the level of expression (red: high; green: low)*
From Sorlie [16] assembled from several published figures

up to 5 years ahead of the development of liver cancer [11]. Studies on TP53 also illustrate another characteristic of genetic mutations that cause cancer: some of them can occur in the germline and be transmitted as inherited traits. Thus, the persons who inherit these mutations are born with a cancer-causing gene that is present in all the cells of the body. These persons are at very high risk of developing cancer. Inheritance of a TP53 mutation causes a serious familial cancer syndrome, the Li-Fraumeni Syndrome (LFS). Members of families who inherit the mutation often have tumours in their childhood or teenage years, and require specific medical surveillance and care to detect and cure these cancers at the earliest possible stage.

Epigenetic changes

The field of epigenetics is one of the most rapidly expanding fields of modern biology, with enormous implication on our thinking and understanding of biological phenomena and diseases, notably cancer. Historically, the term epigenetics was used to describe all biological phenomena that do not follow normal genetic principle. The term was coined by Conrad Waddington in 1942 to describe the discipline in biology which studies "the interactions of genes with their environment that bring the phenotype into being". Since then, a number of biological events that are not coded in DNA sequence itself have been considered epigenetic phenomena. These include imprinting (the conditioning of parental genomes during gametogenesis ensuring that a specific locus is exclusively expressed from either maternal or paternal genome in the offspring), paramutations (heritable changes in one allele induced by another allele) in plants, and X-chromosome inactivation in females. One of the most remarkable recent discoveries is that different epigenetic events may share common underlying molecular mechanisms. These advances turned academic and public attention to the potential application of epigenetic mechanisms to biomedical research and important public health issues.

In a broader sense, epigenetics can be considered as an interface between genotype and phenotype. In other words, epigenetics encompasses mechanisms that modify the final outcome of the genetic code without altering the underlying DNA sequence. The importance of epigenetic principle is highlighted by the fact that all cells in any given organism share an identical genome with other cell types, yet they can exhibit strikingly different morphological and functional properties. Therefore, it is obvious that epigenetic events define the identity and proliferation potential of different cells in the body, the features that are typically deregulated in cancer. Nowadays, epigenetics may be defined as the study of all changes that are stably transmitted over many rounds of cell divisions, but that do not alter the nucleotide sequence (genetic code). Epigenetic inheritance includes DNA methylation, histone modifications and RNA-mediated silencing, all of which are essential mechanisms that allow the stable propagation of gene activity states from one generation of cells to the next. Consistent with the importance of epigenetic mechanisms, deregulation of epigenetic states is intimately linked to human diseases, most notably cancer [6,12]

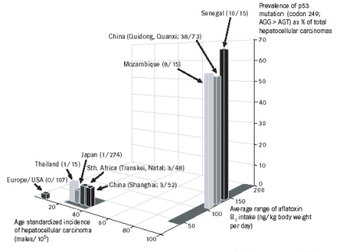


Fig. 3.1.5 *Mutation in TP53 at codon 249 in liver cancers induced by exposure to aflatoxin, a contaminant of the diet in many low- resource countries*
The graph compiles data from various countries on incidence of liver cancer, on levels of aflatoxin contamination in food and on the prevalence of the mutation at codon 249 in liver cancers.

DNA methylation

The best-studied epigenetic mechanism is DNA methylation. The methylation of DNA refers to the covalent addition of a methyl group to the 5-carbon (C^5) position of cytosine bases that are located 5′ to a guanosine base. This is a very small chemical modification of the DNA molecule that while it does not alter the DNA code, may have major regulatory consequences. Aberrant DNA methylation is tightly connected to a wide variety of human cancer. Two forms of aberrant DNA methylation are found in human cancer: the overall loss

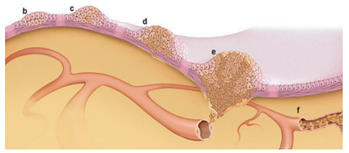


Fig. 3.1.6 *Steps in cancer formation in an epithelial tissue, from first cancer cell to invasion*

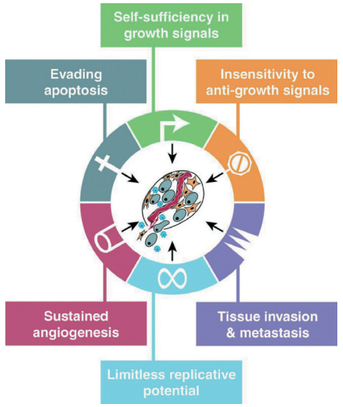


Fig. 3.1.7 *Hallmarks of cancer, after Hanahan [7]*
To become cancerous, a cell has to acquire complementary changes in 6 basic mechanisms

of 5-methyl-cytosine (global hypomethylation) and gene promoter-associated (CpG island-specific) hypermethylation [13,14]. While the precise consequences of genome-wide hypomethylation are still debated (activation of cellular proto-oncogenes, induction of chromosome instability), hypermethylation of gene promoters is in turn associated with gene inactivation. When hypermethylated, gene promoters become unable to bind the factors that are responsible for gene expression. The gene thus becomes inactivated. A large number of studies indicated that the silencing of tumour suppressor genes and other cancer-related genes may occur through hypermethylation of their promoters.

Unscheduled hypermethylation of gene promoters represents an attractive target for early diagnosis, risk assessment and cancer prevention. For example, the genes that are the target of DNA hypermethylation early in tumour development, in a high percentage of cases, and specific to cancer type, are of particular interest. A number of studies showed that the *p16^{INK4a}* (*CDKN2A*) tumour suppressor gene is among the most frequently silenced cancer-associated genes in human cancer, and that this silencing is associated with promoter hypermethylation. Unscheduled addition of methyl markers (*de novo* methylation) at the *p16^{INK4a}* promoter is one of the most frequent epigenetic alterations detected in a wide range of human cancers. In addition, silencing of *p16^{INK4a}* by promoter

Fig. 3.1.8 *Breast cancer cells*

hypermethylation is highly tumour-specific and appears to be the earliest event in some cancer types, making this gene an attractive target for preventive strategies. While cancer epigenetics have focused primarily on DNA methylation changes as biomarker, cancer-specific modifications of chromatin proteins (histones) and the expression profiles of microRNAs (a family of small non-coding transcripts important for stable repression of specific genes) as potential biomarkers remain largely unexplored.

The CIMP phenotype

The studies on DNA methylation involving multiple genes revealed that some cancer types exhibit concurrent methylation of groups of cancer-associated genes, a phenomenon known as the CpG island methylator (CIMP) phenotype [15]. Although the CIMP phenotype has been studied primarily in colorectal cancer, other studies provided evidence that the CIMP phenotype may also be present in different cancer types including hepatocellular carcinoma, gastric cancer, pancreatic cancer, glioblastomas, oral cancer, leukaemias and solid tumours [15]. However, it should be noted that the CIMP-positive tumours represent only a subset of cancers with distinct epigenotype. Analogous to the contribution of the Mutator phenotype to genetic changes, the presence of the CIMP phenotype may explain the simultaneous occurrence of methylation of many genes in some (but not all) cancer types. This may be exploited for prognostic purposes but also in the design of "epigenetic therapy".

Despite a wealth of studies providing evidence for an association between abnormal DNA methylation patterns in a variety of human cancers, the causes and underlying mechanism of this phenomenon remain unclear. Specific agents (epimutagens) or combinations thereof in the environment, diet or lifestyle may promote, and/or relieve resistance against, unscheduled methylation and/or histone modifications, leading to altered gene expression and oncogenic process. Large population-based cohorts and case–control studies may offer excellent opportunities to test the contribution of repeated and chronic exposure to epimutagens in the environment and nutrition to abnormal levels and patterns of DNA methylation in specific cancers.

Perspectives for combating cancer

Until recently, genetic and epigenetic studies on cancer have so far been exploited primarily for improving the knowledge of the mechanisms of cancer development. However, the recent emergence of powerful technologies for genome-wide analysis of genetic and epigenetic changes is dramatically advancing our capacity to identify multiple changes in gene expression as well as genetic or epigenetic

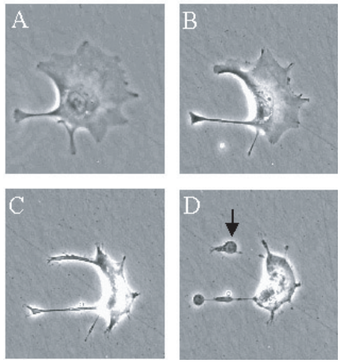


Fig. 3.1.9 *Steps in apoptosis*

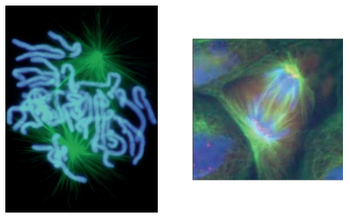


Fig. 3.1.10 *Two microphotographs of dividing cells*

signatures in specific cancers. This affords an opportunity to map the pattern of genetic and epigenetic alterations that is specific for each particular cancer. This information is the first step towards a form of personalised medicine where patients will be treated and followed up according to protocols that will take into account the molecular properties of a given cancer. The road to such personalised medicine is however still very long. It will require that tests for genetic and epigenetic alterations become part of routine and affordable practice in the hospital. It will also necessitate the performance of clinical trials to show which treatment protocol gives the best results according to the pattern of genetic and epigenetic changes. The near future will likely bring insights into which alterations or combinations thereof can be interpreted as reliable biomarkers of exposure to cancer risk factors and tumorigenesis. This in turn will enhance priority setting in selecting new drugs to be developed to combat cancer.

ONCOGENES
PDGF Codes for platelet-derived growth factor. Involved in glioma (a brain cancer)
EGFR Codes for the receptor for epidermal growth factor. Involved in glioblastoma (a brain cancer) and breast cancer
HER-2 or ERBB2. Codes for a growth factor receptor. Involved in breast, salivary gland and ovarian cancers
RET Codes for a growth factor receptor. Involved in thyroid cancer
KRAS Involved in lung, ovarian, colon and pancreatic cancers
NRAS Involved in leukaemias
MYC1 Involved in leukaemias and breast, stomach and lung cancers
NMYC Involved in neuroblastoma (a nerve cell cancer) and glioblastoma
LMYC Involved in lung cancer
BCL2 Codes for a protein that normally blocks cell suicide. Involved in follicular B cell lymphoma
CCND1 or **PRAD1** Codes for cyclin D1, a stimulatory component of the cell cycle clock. Involved in breast, head and neck cancers
CTNB1 Codes for beta-catenin, involved in liver cancers
MDM2 Codes for an antagonist of the p53 tumor suppressor protein. Involved in sarcomas (connective tissue cancers) and other cancers
TUMOUR SUPPRESSOR GENES
APC Involved in colon and stomach cancers
DPC4 Codes for a relay molecule in a signalling pathway that inhibits cell division. Involved in pancreatic cancer
NF-1 Codes for a protein that inhibits a stimulatory (Ras) protein. Involved in neurofibroma and pheochromocytoma (cancers of the peripheral nervous system) and myeloid leukemia
NF-2 Involved in meningioma and ependymoma (brain cancers) and schwannoma (affecting the wrapping around peripheral nerves)
CDKN2A or MTS1 Codes for the p16 protein, a braking component of the cell cycle clock.
Involved in a wide range of cancers
RB1 Codes for the pRB protein, a master brake of the cell cycle. Involved in retinoblastoma and bone, bladder, small cell lung and breast cancer
TP53 Codes for the p53 protein, which can halt cell division and induce abnormal cells to kill themselves. Involved in a wide range of cancers
WT1 Involved in Wilms' tumour of the kidney
BRCA1 Involved in breast and ovarian cancers
BRCA2 Involved in breast cancer
VHL Involved in renal cell cancer

Table 3.1.1 *Common oncogenes and tumour suppressor genes involved in human cancer*
From Weinberg, Scientitic American 1996, with modifications

Suggested further reading and links

Weinberg, R.A. How cancer arises, Scientific American, Sept 1996, pp 62-70; link to pdf: http://www.bme.utexas.edu/research/orly/teaching/BME303/Weinberg.pdf

Inside Cancer: a multimedia guide to cancer biology. http:/www.insidecancer.org/

REFERENCES

1. Merlo LM, Pepper JW, Reid BJ, et al. (2006). Cancer as an evolutionary and ecological process. *Nat Rev Cancer* 6: 924-935.

2. Olivier M, Petitjean A, Marcel V, et al. Recent advances in p53 research: an interdisciplinary perspective. *Cancer Gene Ther* Advance online publication 19 September 2008. DOI: 10.1038/cgt.2008.69.

3. Nowell PC (1976). The clonal evolution of tumor cell populations. *Science* 194: 23-28.

4. Baselga J (2006). Targeting tyrosine kinases in cancer: the second wave. *Science* 312: 1175-1178.

5. Herceg Z and Hainaut P (2007). Genetic and epigenetic alterations as biomarkers for cancer detection, diagnosis and prognosis. *Molecular Oncology* 1: 26-41.

6. Cortez CC and Jones PA (2008). Chromatin, cancer and drug therapies. *Mutat Res*.

7. Hanahan D and Weinberg RA (2000). The hallmarks of cancer. *Cell* 100: 57-70.

8. Loeb LA, Bielas JH, Beckman RA (2008). Cancers exhibit a mutator phenotype: clinical implications. *Cancer Res* 68: 3551-3557.

9. *IARC TP53 Mutation Database, R13, November* 2008. Available from: http://www-p53.iarc.fr/ Date Accessed: November 14, 2008.

10. Hainaut P and Hollstein M (2000). p53 and human cancer: the first ten thousand mutations. *Adv Cancer Res* 77: 81-137.

11. Jackson PE, Kuang SY, Wang JB, et al. (2003). Prospective detection of codon 249 mutations in plasma of hepatocellular carcinoma patients. *Carcinogenesis* 24: 1657-1663.

12. Herranz M and Esteller M (2007). DNA methylation and histone modifications in patients with cancer: potential prognostic and therapeutic targets. *Methods Mol Biol* 361: 25-62.

13. Feinberg AP and Tycko B (2004). The history of cancer epigenetics. *Nat Rev Cancer* 4: 143-153.

14. Jones PA and Baylin SB (2002). The fundamental role of epigenetic events in cancer. *Nat Rev Genet* 3: 415-428.

15. Issa JP (2004). CpG island methylator phenotype in cancer. *Nat Rev Cancer* 4: 988-993.

16. Sorlie T, Perou CM, Tibshirani R, et al. (2001). Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. *Proc Natl Acad Sci U S A* 98: 10869-10874.

3.2 DNA Damage Response and DNA Repair

Summary

- Even under normal cellular conditions, genomic DNA is under constant threat from DNA damage and DNA breaks that are constantly produced by endogenous and exogenous (environmental) genotoxic agents
- DNA repair machineries represent an arsenal of tools devised by cells to repair DNA damage and hence defend themselves against constant challenge to genomic integrity
- One of the major achievements of the last two decades has been the isolation and characterisation of the genes and their protein products involved in different pathways of DNA repair
- Recent studies revealed that all types of DNA repair (including nucleotide excision repair, base excision repair, and double strand break repair) are complex and dynamic processes that require careful orchestration of many enzymes, adapter proteins and chromatin-modifying activities
- Defects in key players and pathways involved in DNA damage response and DNA repair can lead to cancer and other human diseases

Sources of DNA damage

Exogenous sources. There are a number of agents or phenomena capable of inducing DNA lesions (Figure 3.2.1). They result in DNA base modifications, formation of covalent bridges between complementary strands, single strand breaks (SSBs) and double strand breaks (DSBs) [1]; note that SSBs may also be transformed into DSBs. These insults can have several sources, such as food, water, chemical products, radiation and others. For instance, the aflatoxins are group of carcinogenic fungal metabolites that are found in foodstuffs contaminated with *Aspergillus* strains. The detection of both DNA and protein adducts in humans exposed to 1,3-Butadiene provided key pieces of evidence to support the evaluation by an IARC group that concluded that 1,3-Butadeine was probably a human carcinogen (group 2A) [2].

Some electrophyl molecules carrying alkyl functions have a high affinity for nitrogen molecules of purine and pyrimidine bases. The resulting alkylation can lead to the creation of punctual mutations, but also destabilises the binding between two adjacent nucleotides, thus generating both SSBs and DSBs. A number of alkylating agents are present in cigarette smoke, explaining in part the cancerigenic properties of the cigarette. One of these agents is methylmethane sulfonate (MMS), which is frequently used in laboratories in order to study DSBs. Cigarette smoke contains several other genotoxic agents, including benzo[a]pyrene, that have been found to increase the frequency of mutations [3,4].

Different types of radiation can also produce DNA damage. The ultraviolet (UV) radiation from the sun, for example, can produce a covalent linkage between two adjacent pyrimidine bases in DNA to form, among others, thymine dimers. Ionizing radiation can also create DNA damage either directly or indirectly; directly by producing the formation of radicals on sugars that are present in the DNA chain, and indirectly by provoking the radiolysis of water molecules, generating radical ions that act on phosphodiester bonds that link the nucleotides. If the distance between the two sites of damage created by two radicals is short, the DNA chain may break, which is why the DSBs are the most frequent types of breaks caused by gamma irradiation.

Endogenous sources. Even under normal cellular conditions, genomic DNA is subject to spontaneous endogenous changes (Figure 3.2.1). The chemical events that lead to DNA damage include hydrolysis, oxidation and electrophilic attack. These reactions are triggered by exposure of cells to exogenous chemicals (e.g. environmental agents, food constituents), but they can also result from endogenous metabolic processes.

The most frequent spontaneous chemical reactions that create DNA damage in cells are depurination and deamination. Depurination, caused by thermal fluctuations, represents the linkage of the N-glycosyl of purine bases to deoxyribose hydrolyze. About 5000 purine bases (adenine and guanine) are lost every day from the DNA of each human cell because of depurination. Deamination transforms cytosine to uracile or thymine at a rate of 100 bases per cell per day. In addition, it has long been hypothesised that the presence of methylated CpG sequences *per se* are the major cause of mutability in mammalian genomes. Considerable attention has focused on the cause of CpG sites because this can be a common site of mutations or DNA methylation, detected in a range of genetic diseases as well as in many cancers [5,6]. All hypotheses and experimental studies seem to agree on the importance of methylation of cytosine residues. Methylation increases the rate of hydrolytic deamination and also increases the reactivity of neighbouring guanines to electrophiles [5,7].

Other examples of endogenous chemical events leading to DNA damage are apurinic/apyrimidinic (AP) sites that can be produced by spontaneous hydrolysis, alkylation-induced hydrolysis or glycosylase-catalysed base-excision repair. Oxygen radical attack on DNA leads to a plethora of oxidised bases, as well as strand scission. Chromosomal alterations are initiated *inter alia* by double-strand breaks resulting from oxidative cleavage of the DNA backbone or enzymatic cleavage during chromatin remodelling (e.g. by topoisomerase II). DNA replication itself contributes about ten double-strand breaks per cell cycle in the form of stalled or blocked replication forks [8].

DNA repair

Genomic DNA within each human cell is constantly exposed to an array of damaging agents of both environmental origin, exemplified by sunlight and tobacco smoke, and of endogenous origin, including water and oxygen [9]. This scenario necessitates constant surveillance so that damaged nucleotides may be removed and replaced before their presence in a DNA strand at the time of replication leads to the generation of mutations [10]. Restoration of normal DNA structure is achieved in human cells by one of several DNA repair enzymes that cut out the damaged or inappropriate bases and replace them with the normal nucleotide sequence. This type of cellular response is referred to as "excision repair", and there are two major repair pathways which function in this manner: "base excision repair", which works mainly on modifications caused by endogenous agents, and "nucleotide excision repair", which removes lesions caused by environmental mutagens. UV light is probably the most common exogenous mutagen to which human cells are exposed, and the importance of the nucleotide excision repair pathway in protecting against UV-induced carcinogenesis is clearly demonstrated in the inherited disorder xeroderma pigmentosum. Individuals who have this disease lack one of the enzymes involved in nucleotide excision repair and have a thousandfold greater risk of developing skin cancer following exposure to sunlight than do other individuals. Seven genes, ranging from XPA to XPG, are defective in XP syndrome [11].

One of the great achievements of the last two decades has been the isolation and characterisation of the genes, and their protein products, involved in base excision repair and nucleotide excision repair. It has become apparent that certain proteins so identified are not exclusively involved in DNA repair but play an integral part in other cellular processes such as DNA replication and recombination.

Excision repair

The first step in both base excision repair and nucleotide excision repair is the recognition of a modification in DNA by enzymes that detect either specific forms of damage or a distortion in the DNA helix. Recognition of damage is followed by an excision step in which DNA containing the modified nucleotide is removed. Gap-filling DNA synthesis and ligation of the free ends complete the repair process.

Nucleotide excision repair may occur in the non-transcribed (non-protein-coding) regions of DNA (Figure 3.2.2). A distortion in DNA is recognised, probably by the XPC-hHR23B protein (I). An open bubble structure is then formed around the lesion in a reaction that uses the ATP-dependent helicase activities of XPB and XPD (two of the subunits of TFIIH) and also involves XPA and RPA (II-III). The XPG and ERCC1-XPF nucleases excise and release a 24- to 32-residue oligonucleotide (IV), and the gap is filled in by PCNA-dependent polymerases (POL) epsilon and delta and sealed by a DNA ligase, presumed to be LIG1 (V). Nucleotide excision repair in regions that are transcribed (and hence code for proteins) requires the action of TFIIH [12].

DNA base excision repair (Figure 3.2.3) involves the removal of a single base by cleavage of the sugar-base bond by a damage-specific DNA glycosylase (e.g. hNth1 or uracil DNA glycosylase) and incision by an apurinic/apyrimidinic nuclease (human AP1) [13]. Gap-filling may proceed by replacement of a single base or by resynthesis of several bases in the damaged strand (depending on the pathway employed).

More complex and unusual forms of damage to DNA, such as double strand breaks, clustered sites of base damage and non-coding lesions

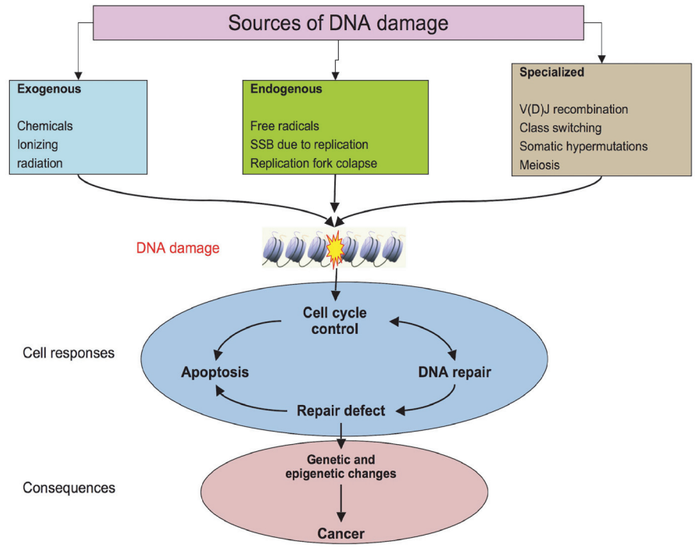


Fig. 3.2.1 *Causes, cellular responses and consequences of DNA damage. Source: Zdenko Herceg, unpublished*

that block the normal replication machinery are dealt with by alternative mechanisms. Inherited human diseases in which the patient shows extreme sensitivity to ionizing radiation and altered processing of strand breaks, such as ataxia telangiectasia and Nijmegen breakage syndrome, constitute useful models to study the repair enzymes involved in these processes. Indeed, if elucidation of base excision repair and nucleotide excision repair was the great achievement of the late 1990s in this field, then understanding strand break repair will probably be the great achievement of the next decade. This will have important consequences. Certain cancers are often treated with radiotherapy, and a small percentage of patients show considerable sensitivity to their treatment, with the result that treatment schedules are reduced to try to avoid adverse reactions. A better understanding of the possible causes of this radiosensitivity, including characterisation of the enzymes involved in the repair of DNA damage produced by ionizing radiation, may lead to better tailoring of radiotherapy doses to individual patients.

DNA double-strand breaks

DSBs are arguably the most dangerous type of DNA lesions that are constantly generated during the life of a cell. DSBs result from both exogenous and endogenous factors and represent an important threat to the integrity of the genome as they can lead to mutation induction, oncogenic transformation or cell death (Table 3.2.1). Mammalian cells may be subject to at least 10 000 different lesions every day, which may well represent a low estimate. In order to efficiently deal with DSBs the cell has evolved multiple cellular processes that are initiated in response to DNA damage including checkpoint activation, DNA repair, and changes in gene transcription. These processes will counteract the omnipresent DNA-damaging effects of endogenous and environmental genotoxic insults.

Detection and signalling of DSBs. The DNA damage checkpoint can be defined as a network of interacting pathways operating in concert to recognise damage in the DNA and elicit the response. It shares characteristics of a signal transduction pathway, and the participating proteins can be formally divided into sensors, transducers and effectors. Sensor proteins recognize DNA damage, directly or indirectly, and function to signal the presence of these abnormalities and initiate the biochemical cascade. Transducers are typically protein kinases that relay and amplify the damage signal from the sensors by phosphorylating other kinases or downstream target proteins; this can also be identified as signalling. Effector proteins include the ultimate downstream targets of the transducer protein kinases, and these can actually be the repair proteins.

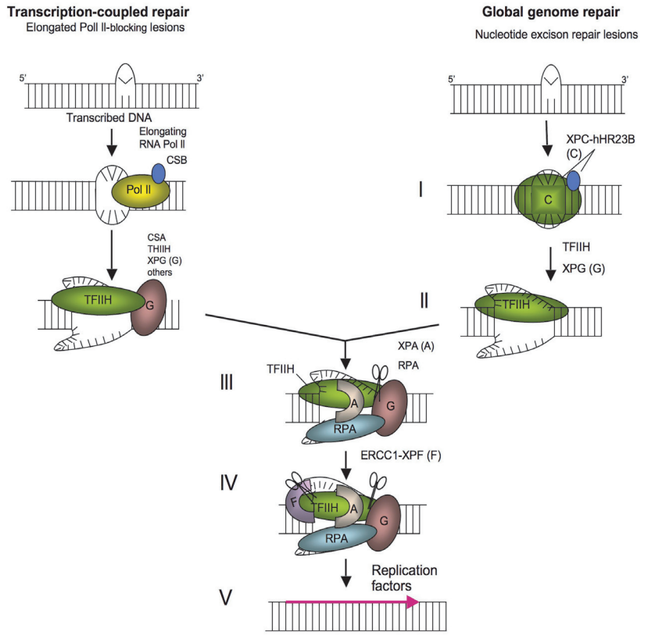


Fig. 3.2.2 *Stages of nucleotide excision repair (NER). There are two NER pathways that are involved in the removal of UV-induced and carcinogen-induced DNA lesions. The NER pathway involves a large number of proteins including damage recognition proteins (XPA, XPC, RPA), helicases (XPB, XPD) and nucleases (XPF, XPG), which interact to form a complex protein machinery. In transcription-coupled NER pathway, DNA lesions are recognized when they stall RNA polymerase II, whereas in global genome NER, the lesions are recognized by the proteins XPC and hHR23B. After the lesions are detected, both pathways are similar. The XPB and XPD helicases of the multi-subunit transcription factor TFIIH unwind DNA around the lesion (II). Single-stranded binding protein RPA stabilizes the intermediate structure (III). XPG and ERCC1-XPF cleave the borders of the damaged strand, generating a 24-32 base oligonucleotide containing the lesion (IV). The DNA replication machinery then fills in the gap (V). Mutations in the genes encoding proteins involved in NER lead to the condition known as xeroderma pigmentosum in humans, which is characterised by extreme UV sensitivity and a wide spectrum of other abnormalities*

In order for DSBs to be repaired efficiently, DNA damage first must be detected and the information transmitted to the effectors and DNA repair proteins through a signalling pathway. Of all these steps, however, the detection of DNA breaks is one of the least known. The major genes that can act as detectors and transducers in DNA damage response are the ATM (*Ataxia Telangiectasia* Mutated) superfamily of kinases and p53, activation of which seems to be important for DNA damage detection and cell cycle arrest. Defects in these important players and pathways can lead to cancer and other human diseases. One of the first DNA damage signalling events and the most easily detectable in DNA damage response is the phosphorylation of at the H2A variant, H2AX at serine 139 by the phosphatidylinositol-3 kinase-like family of kinases (PI3K) at DSB sites. The presence of γH2AX is important for both types of DSBs: repair HR (Homologous Recombination) and NHEJ (Non Homologous End Joining) and is required for the retention/accumulation of repair proteins at the break site. ATM, ATR (ATM and Rad3 related protein), and probably DNA-PKcs, all members of the PIKK family, are responsible for the phosphorylation of H2AX, and thus can represent the detectors of DNA damage. The activation of these detectors could be explained in two ways. First, DNA breaks produce a modification in the chromatin structure or spatial organisation, and this modification appears to be sufficient for the autophosphorylation of ATM and its activation.

In the case of NHEJ repair, the heterodimer Ku70/Ku80 seems to be the first detector, because it instantly binds to the damaged ends and recruits DNA-PK. TRRAP is a member of the PIKK superfamily, indicating that it, like other members of this family, it may have a role in DNA damage response. However, TRRAP lacks the kinase catalytic activity, preventing it from phophorylating downstream targets, but it still has an effect in later stages of DNA damage response through the P53 pathway. P53 plays a critical role in the control of cellular proliferation through the checkpoint activation. Following DNA damage, several kinases including Chk2, CAK, ATM, ATR and DNA-PK can phosphorylate p53 leading to its stimulation and to an enhance binding to DNA. Mutations in the genes involved in DNA damage detection and signalling are frequently found in human cancer.

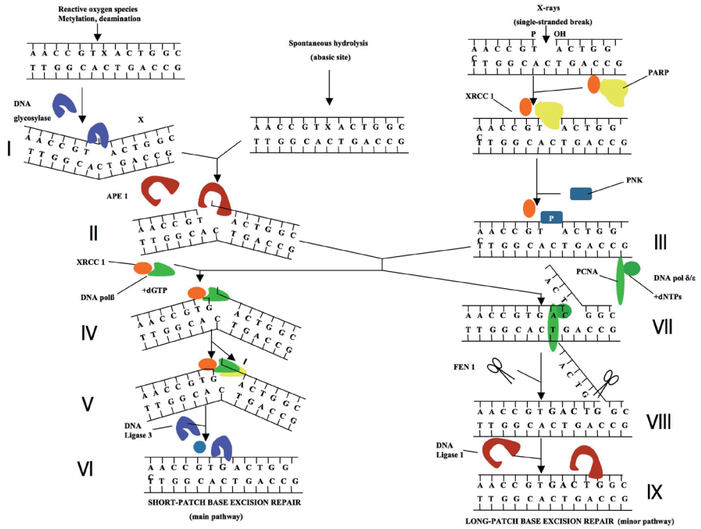


Fig. 3.2.3 *Stages of base excision repair. Many glycosylases, each of which deals with a relatively narrow spectrum of lesions, are involved. The glycosylase compresses the DNA backbone to flip the suspect base out of the DNA helix. Inside the glycosylase, the damaged base is cleaved, producing an "abasic" site (I). APE1 endonuclease cleaves the DNA strand at the abasic site (II). In the repair of single-stranded breaks, poly(ADP-ribose)polymerase (PARP) and polynucleotide kinase (PNK) may be involved. In the "short-patch" pathway, DNA polymerase b fills the single nucleotide gap and the remaining nick is sealed by DNA ligase 3. The "long-patch" pathway requires the proliferating cell nuclear antigen (PCNA) and polymerases b, e and d fill the gap of 2-10 nucleotides. Flap endonuclease (FEN-1) is required to remove the flap of DNA containing the damage and the strand is sealed by DNA ligase 3*

– *Repair of DSBs.* Two major types of DSB repair, homologous HR and NHEJ, have evolved to deal with the DNA damage constantly generated [14]:
– HR reconstitutes the missing DNA using a homologous copy, usually the sister chromatid. Thus this type of DSB repair occurs more often in G2 phase after DNA replication where the two chromatids are present.

NHEJ is less complicated then HR but is error prone. It processes DNA ends and religates them without any modifications, thus often creates errors.

There also exists a third type of DSB repair that is used less often: Single strand annealing (SSA), which shares components with both NHEJ and HRR and utilises a limited cohesion zone of several base pairs in order to religate DNA ends, in the same way as NHEJ.

The mammals predominantly use the HR whereas lower eukaryotes use NHEJ more often. It is believed that that NHEJ plays a more important role than HR in mitotically replicating cells. HR may play a more prominent role

Gene	Cellular phenotype	Mouse-knockout phenotype
Non-Homologous end-joining (NHEJ)		
Ku70	Radiosensitivity, impaired V(D)J recombination	Radiosensitivity, SCID phenotype, T-cell tumours, growth retardation
Ku80	Radiosensitivity, impaired V(D)J recombination	Radiosensitivity, SCID phenotype, T-cell tumours, growth retardation
DNA-PKcs	Radiosensitivity, impaired V(D)J recombination	Radiosensitivity, SCID phenotype, T-cell tumours
XRCC4	Radiosensitivity, impaired V(D)J recombination	Embryonic lethality, apoptosis of post-mitotic neurons
LIG4 (Ligase IV gene)	Radiosensitivity, impaired V(D)J recombination	Embryonic lethality, apoptosis of post-mitotic neurons
Homology-directed repair (HDR)		
ATM	Radiosensitivity, chromosomal instability, radioresistant DNA synthesis	Radiosensitivity, T-cell tumours, neurological dysfunction, growth retardation, infertility
BRCA1	Not viable	Embryonic lethality
BRCA2	Not viable	Embryonic lethality
RAD51	Not viable, chromosomal aberrations	Embryonic lethality
RAD52	Impaired homologous recombination	Moderate impairment of homologous recombination
RAD54	Radiosensitivity, MMC sensitivity, impaired homologous recombination	Radiosensitivity
XRCC2	Radiosensitivity	Embryonic lethality, chromosomal instability
NHEJ and HDR combined		
MRE11	Not viable, chromosomal instability	-
RAD50	Not viable	Embryonic lethality

***Table* 3.2.1** *Cellular and mouse-knockout phenotypes associated with mutations in DNA double strand break repair genes*

during meiosis and when sister chromatids are available during late S and G2 stages of the cell cycle, whereas NHEJ is more important during G1 and early S stages. To simplify, it is generally accepted that the predominance of one mechanism over the other is dependent on the cell cycle stage and the type of DSB [14].

DNA repair by NHEJ is more error prone but less demanding then homologous recombination. This type of repair does not need to match the damaged sequence to its intact copy on the homologous chromosome (which is typically at a distant site in the nucleus) or bring the two into close proximity. NHEJ repair is divided into several stages, starting with the processing of the damaged ends, then the establishment of molecular bridge between the strands that facilitates the ligation and finishing by the filling of missing bases and ligation (Figure 3.2.4). The KU heterodimer, consisting of a tight complex of KU70 (70 kDa) and KU80 (86 kDa), would first recognise the DNA break, and tends to cling to the DNA end. There is considerable evidence that cellular end-joining systems have activities capable of processing all these aberrations. These activities are carried out by specialised endonucleases like Tdp1 and APE1. This cleaning step is very important in eliminating the chemical modifications, thus preventing religation.

The Ku70/Ku80 heterodimer then binds to DNA-PKcs forming the so-called DNA-PK holoenzyme. Formation of the DNA-PK holoenzyme complex on a DNA end results in activation of its kinase activity. This activation involves localised denaturation of the extreme end of DNA and threading of a few bases of the single strands into defined channels bringing the two DNA strands closer to each other.

The next step is the recruitment of ligase IV through the DNA-PK. The effects of Ku and DNA-PK on the activity of XRCC4/ ligase IV are complex, but it is known that all of these proteins, either alone or in a concert, promote end-to-end association of linear DNAs WRN, Artemis and MRE11, all nucleases with putative roles in end-joining. Their catalytic activity could be important to process or "clean" the damaged bases on the break site before the ligation takes place.

The final step of NHEJ consists of first replacing the damaged bases that have been eliminated and then religating the DNA ends. Additional factors involved in NHEJ repair include PNKP and BRCA1. BRCA1 binds to the MRN complex, and this interaction seems to be important for end joining in vitro. However the exact *in vitro* function of BRCA1 during NHEJ is still not clear.

Homologous recombination (HR). Generally, repair of DSBs by HR is considered most active in the late stages of the cell cycle (late S and G2), because homologous sequences in the form of sister chromatids, homologous chromosomes or DNA repeats are required. The homologous sequence of the damaged sequence is used as template and no single base is lost or changed, making this type of repair error-free. However, even though it rarely generates errors, HR may result in crossovers and lost of heterozygosity (LOH), and HR events can be classified according to whether or not they result in crossing-over between the homologous sequences. HRR is performed by the RAD52 epistasis group of proteins, which includes the products of *RAD50–55*, *RAD57*, and *RAD59*, the RAD51 paralogs RAD51b, c, d and *MRE11*. In addition, HR also involves BRCA proteins (BRCA1, BRCA2), XRCC proteins (XRCC2 and XRCC3), and the MRN complex.

The first event believed to occur during HRR is resection of the DNA to yield single strand overhangs. In yeast, the resection is thought to involve the MRN complex (Figure 3.2.4). However, this complex has an endonuclease activity, but no 5'-3' exonuclease activity essential for the resection. NBS1, a member of the MRN complex, is phosphorylated by ATM on serine 343. The NBS1 subunit appears to be important for transmitting signals from DNA damage sensors to MRN. It is thus possible that the phoshorylation of NBS1 activates the exonuclease property of the MRN complex. Other cofactors may also be needed to help the MRN complex resecting the DNA.

The second step in HR is the unwinding of the two complementary strands (Figure 3.2.4). The RAD50 subunit of MRN has ATPase activity that is believed to facilitate DNA unwinding. Then the RPA protein (human single strand binding (SSB) protein) is recruited to single-stranded DNA, and is thought to protect it from the nuclease activity and to help the activity of RAD51, the equivalent of the bacterial RECA protein. RAD51 forms nucleoprotein complexes on SS DNA tails coated by RPA to initiate the intersection and exchange between the damaged DNA strand and the intact one situated on the sister chromatid. The RAD51 paralogs RAD55 and RAD57 act as accessory proteins and are believed to facilitate action of RAD51. Similarly, Rad52 helps RAD51 to form DNA exchange intermediates, and it is believed that Rad54 may help in unwinding the DNA at the DSB to facilitate access of other repair factors. BRCA1 and BRCA2 are believed to be important at early points of HR and perhaps coordinate repair with other cellular processes.

The activities of all these different proteins lead to the formation of a so-called "Holliday junction" (Figure 3.2.4). In this context, each single strand of the damaged strand is coupled with a homologous region of the model DNA strands. High fidelity is provided by this crossing over of different strands. HR can then go in either of two directions. Non-crossing-over, resulting from dis-

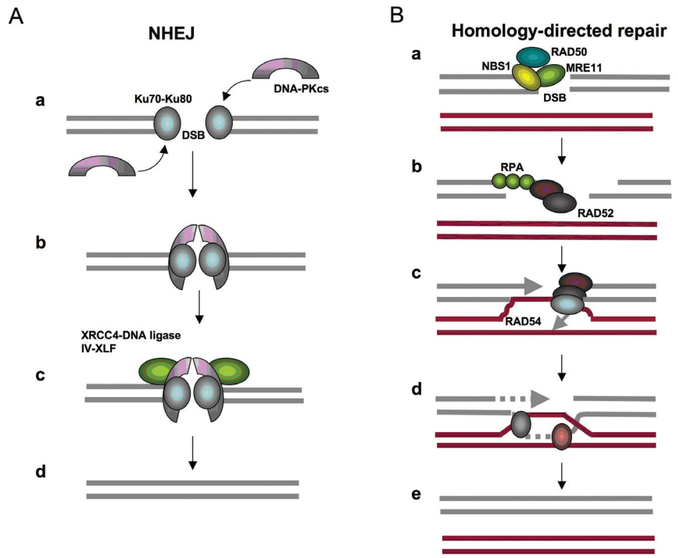


***Fig.* 3.2.4** *Pathways of DNA double strand break (DSB) repair. In Non Homologous End Joining (NHEJ), a single Ku heterodimer binds to each free DNA end of a DSB and recruits DNA-PKcs, resulting in the formation of the DNA-PK complex. Subsequently, Xrcc4/Ligase IV complex binds to each of the DNA ends and interacts to form a tetramer that may serve to bridge the DNA ends. Other repair proteins are likely involved in this pathway, including the MRE11/RAD50/NBS1 (Xrs2) complex. In Homologous Recombination (HR) repair, DSB is recognised by MRN (a complex of MRE11, RAD50 and NBS1), followed by the resection of DNA ends allowing binding of RPA, RAD51 and RAD52 to the single stranded DNA. A homologous region in an intact chromosome is then invaded (mediated by RAD52) followed by pairing (mediated by RAD54). DNA synthesis occurs from the invading end of the damaged DNA, extending the repair region and forming a Holliday junction (a cross-stranded structure that occurs between four strands of DNA during recombination). This junction translocates along the DNA in a process mediated by a branch migration complex and is cleaved by a resolvase. Source: Zdenko Herceg, unpublished*

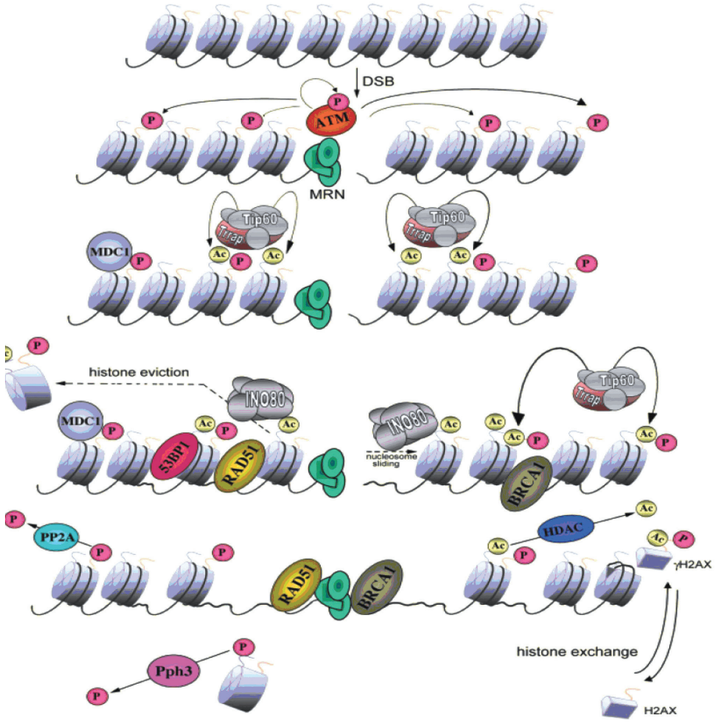


Fig. 3.2.5 *The interplay between chromatin modifying/remodelling activities and DNA repair machinery during the repair of DSBs. In response to a DSB, MRE11-RAD50-NBS1 (MRN) complex and ATM are recruited to the site of DNA break. Activated ATM kinase phosphorylates histone H2AX that allows binding of the early response proteins such as MDC1. This is followed by the recruitment of the TRRAP/TIP60 HAT complex that acetylates histone H4. Histone acetylation unwinds chromatin and/or serves as a binding platform, both of which facilitate the recruitment of remodelling complexes, such as the INO80 and SWR1, and late DNA repair proteins, such as RAD51 and BRCA1. The presence of INO80 may facilitate the eviction or sliding of the nucleosomes in the immediate vicinity of the break site to allow 5′-3′ resecting and generation of a 3′ single-strand DNA (ssDNA) overhang. This allows RAD51 and BRCA1 to stimulate DSB repair through homologous recombination. After the DSB is repaired, dephosphorylation of incorporated or evicted γH2AX may be mediated by Pph3 and PP2A. The third mechanism of attenuation of γH2AX signal involves the exchange of γH2AX (after its prior acetylation by TRRAP/TIP60 complex) with the unphosphorylated form. Finally, deacetylation of histones occurs to allow chromatin reassembly after DNA break is repaired [16]*

engagement of the Holliday junction followed by DNA pairing and gap filling in the damaged homologue, appears to be strongly favoured during HR in mammalian cells. The other possibility is to go through the classical path, in which the Holliday junctions are resolved by endonucleolytic cleavage, with an equal probability of yielding either a crossover or a noncrossover event. The last step would be filling of the gaps by DNA polymerase and the sealing of the breaks by ligase. However, the DNA polymerase and ligase necessary for this step have not yet been identified.

Repair of DSBs in the context of chromatin. Repair of DSBs is the processes that utilises DNA as substrate and subsequently needs to access the naked DNA. However, in a cell, naked DNA is vulnerable to nuclease digestion and other insults, and without some type of organisation, it would occupy more volume than necessary. Consequently, eukaryotic cells compact DNA into chromatin. The structure of chromatin fulfils essential functions not only by condensing and protecting DNA, but also in preserving genetic information and controlling gene expression. However, given its compacted structure, chromatin hinders several important cellular processes including the detection and repair of DNA breaks [15]. Repair of DSBs, either through HR or NHEJ, is a complex and dynamic process that requires careful orchestration of many enzymes and adapter proteins. In addition, a major hurdle is compacted chromatin, which must first be relaxed to allow access of the DNA repair machinery to damaged DNA. To achieve this, cellular mechanisms that alter the structure of chromatin must first function so that the broken DNA is made accessible to repair factors. Recent studies provided evidence on how the repair machinery gains access to broken DNA in highly condensed chromatin and how the repair process is coordinated with other chromatin-based processes, such as transcription [16]. These studies showed that chromatin modifying/remodelling activities have been associated with DNA repair. Biochemical and molecular studies have revealed different histone modifications associated with DNA repair and identified molecular players responsible for these modifications (Figure 3.2.5). Chromatin modifying/remodelling activities may thus be a part of an arsenal of tools devised by cells to facilitate repair of DNA breaks and hence defend themselves against constant challenge to genomic integrity. These activities include post-translational modifications of histones and ATP-dependent nucleosome mobilisation (chromatin remodelling). An additional mechanism that may facilitate DNA repair by altering chromatin structure involves exchange of histone variants into nucleosomes around break sites. Reversal of chromatin modifications also requires specific enzymatic activities to restore the structure of chromatin once DNA repair has been completed.

Consistent with the roles of chromatin modifying factors in critical cellular processes, growing evidence suggests that aberrant chromatin modification/remodelling is associated with cancer. Recent studies underscore the fact that DNA repair and other DNA-based processes, such as gene transcription and DNA replication, require elaborate coordination of chromatin modifying/remodelling activities. These studies reveal histone proteins as key carriers of epigenetic information, constituting a fundamental and critical regulatory system that extends beyond the genetic information. Therefore, these findings are the foundation for further investigation into the role of chromatin-based mechanisms in critical cellular processes and human cancer.

Other repair pathways

Human cells, in common with other eukaryotic and prokaryotic cells, can also perform one very specific form of damage reversal, the conversion of the methylated adduct, O6-methylguanine, in DNA back to the normal base. O6-Methylguanine is a miscoding lesion: both RNA and DNA polymerases "read" it incorrectly when they transcribe or replicate a DNA template containing it. As this modified base can pair with both the base cytosine (its correct partner) and the base thymine (an incorrect partner), its presence in DNA can give rise to transition mutations by mispairing of relevant bases. A specific protein, O6-alkylguanine-DNA-alkyltransferase, catalyses transfer of the methyl group from the guanine base to a cysteine amino acid residue located at the active site of the protein [17]. This error-free process restores the DNA to its original state but results in the inactivation of the repair protein. Consequently, repair can be saturated when cells are exposed to high doses of alkylating agents, and synthesis of the transferase protein is required before repair can continue.

Mismatched bases in DNA arising from errors in DNA replication, for instance guanine paired with thymine rather than cytosine, are repaired by several pathways involving either specific glycosylases, which remove the mismatched bases, or long-patch mismatch repair involving homologues of the bacterial genes MUTS and MUTL. Insertion or deletion loops at microsatellite sequences can be recognised by hMutSa (a heterodimer of hMSH2 and hMSH6) or hMutSb (a heterodimer of hMSH2 and hMSH3). Subsequent recruitment of hMutLa (a heterodimer of hMLH1 and hPMS2) to the altered DNA targets the area for repair, which requires excision, resynthesis and ligation. Single nucleotide mispairing events require hMutSa function for recognition. One important requirement of such repair processes is that they are able to distinguish the correct base from the incorrect one in the mispair. Since both bases are normal constituents of DNA, this cannot be achieved by an enzyme that scans the DNA for a lesion or structure that is not a normal constituent of the DNA. Defects in at least four of the genes whose products are involved in mismatch repair, namely hMSH2, hMLH1, hPMS1 and hPMS2, have been associated with hereditary nonpolyposis colorectal cancer. This is one of the most common genetic diseases, affecting as many as 1 in 200 individuals, and may account for 4–13% of all colorectal cancers. Affected individuals also develop tumours of the endometrium, ovary and other organs. The DNA of hereditary nonpolyposis colorectal cancer tumours is characterised by instabilities in simple mono-, di- and trinucleotide repeats which are common in the human genome. This instability is also seen in certain sporadic colorectal tumour cells and arises directly from alterations in the proteins involved in mismatch repair [18]. Generally speaking, genomic instability is considered as an indicator of, and fundamental to the nature of, malignant cell growth.

REFERENCES

1. van Gent DC, Hoeijmakers JH, Kanaar R (2001). Chromosomal stability and the DNA double-stranded break connection. *Nat Rev Genet* 2: 196-206.

2. IARC (1999). Hexachlorobutadiene. In: *IARC monographs on the evaluation of carcinogenic risks to humans, Volume 73, Some chemicals that cause tumours of the kidney or urinary bladder in rodents and some other substances*. Lyon, France: International Agency for Research on Cancer 277-294.

3. IARC (1986). Preamble. In: *IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans, Volume 39, Some chemicals used in plastics and elastomers*. Lyon, France: International Agency for Research on Cancer 13-32.

4. Hoffmann D, Hoffmann I, El-Bayoumy K (2001). The less harmful cigarette: a controversial issue. a tribute to Ernst L. Wynder. *Chem Res Toxicol* 14: 767-790.

5. Fryxell KJ and Moon WJ (2005). CpG mutation rates in the human genome are highly dependent on local GC content. *Mol Biol Evol* 22: 650-658.

6. Hainaut P and Hollstein M (2000). p53 and human cancer: the first ten thousand mutations. *Adv Cancer Res* 77: 81-137.

7. Pfeifer GP, Tang M, Denissenko MF (2000). Mutation hotspots and DNA methylation. *Curr Top Microbiol Immunol* 249: 1-19.

8. Haber JE (1999). DNA recombination: the replication connection. *Trends Biochem Sci* 24: 271-275.

9. Lindahl T and Wood RD (1999). Quality control by DNA repair. *Science* 286: 1897-1905.

10. Aguilera A and Gomez-Gonzalez B (2008). Genome instability: a mechanistic view of its causes and consequences. *Nat Rev Genet* 9: 204-217.

11. Dworaczek H and Xiao W (2007). Xeroderma pigmentosum: a glimpse into nucleotide excision repair, genetic instability, and cancer. *Crit Rev Oncog* 13: 159-177.

12. Dip R, Camenisch U, Naegeli H (2004). Mechanisms of DNA damage recognition and strand discrimination in human nucleotide excision repair. *DNA Repair (Amst)* 3: 1409-1423.

13. David SS, O'Shea VL, Kundu S (2007). Base-excision repair of oxidative DNA damage. *Nature* 447: 941-950.

14. Valerie K and Povirk LF (2003). Regulation and mechanisms of mammalian double-strand break repair. *Oncogene* 22: 5792-5812.

15. Peterson CL and Cote J (2004). Cellular machineries for chromosomal DNA repair. *Genes Dev* 18: 602-616.

16. Loizou JI, Murr R, Finkbeiner MG, et al. (2006). Epigenetic information in chromatin: the code of entry for DNA repair. *Cell Cycle* 5: 696-701.

17. Margison GP, Butt A, Pearson SJ, et al. (2007). Alkyltransferase-like proteins. *DNA Repair (Amst)* 6: 1222-1228.

18. Imai K and Yamamoto H (2008). Carcinogenesis and microsatellite instability: the interrelationship between genetics and epigenetics. *Carcinogenesis* 29: 673-680.

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3.3 The Cell Cycle

Summary

- The control of cell division is critical to normal tissue structure and function. It is regulated by a complex interplay of many genes that control the cell cycle, with DNA replication (S phase) and mitosis as major checkpoints
- The cell cycle is tightly regulated to minimise transmission of genetic damage to subsequent cell generations
- Progression through the cell cycle is primarily controlled by cyclins, associated kinases and their inhibitors. Retinoblastoma (RB) and p53 are major suppressor genes involved in the G1/S checkpoint control
- Cancer may be perceived as the consequence of loss of cell cycle control and progressive genetic instability

Cell proliferation occurs through a series of stages that are collectively termed the cell cycle. The "cell cycle" refers to the set of ordered molecular and cellular processes during which genetic material is replicated and segregates between two newly generated daughter cells via the process of mitosis. The cell cycle can be divided into two phases of major morphological and biochemical change: M phase ("mitosis"), during which division is evident morphologically, and S phase ("synthesis"), during which DNA is replicated. These two phases are separated by so-called G ("gap") phases. G1 precedes S phase and G2 precedes M phase.

During progression through this division cycle, the cell has to resolve a number of critical challenges. These include ensuring that sufficient ribonucleotides are available to complete DNA synthesis, proof-reading, editing and correcting the newly-synthesised DNA; that genetic material is not replicated more than once; that the spatial organisation of the mitotic spindle apparatus is operational; that the packing and the condensation of chromosomes is optimal; and that there is equal distribution of cellular materials between the daughter cells. Moreover, immediately before or after the cell cycle, various factors interact to determine whether the cell divides again or whether the cell becomes committed to a programme of differentiation or of cell death. Therefore, the term "cell cycle" is often used in a broad sense to refer to, as well as the basic, self-replicating cellular process, a number of connected processes which determine pre- and post-mitotic commitments. These may include the commitment to stop dividing in order to enter a quiescent state, to undergo senescence or differentiation, or to leave the quiescent state to re-enter mitosis.

Molecular architecture of the cell cycle

The molecular ordering of the cell cycle is a complex biological process dependent upon the sequential activation and inactivation of molecular effectors at specific points of the cycle. Most current knowledge of these processes stems from experiments carried out in the oocyte of the frog, *Xenopus laevis*, or in yeast, either *Saccharomyces cerevisiae* (budding yeast) or *Schizosaccharomyces pombe* (fission yeast). The Xenopus oocyte is, by many criteria, one of the easiest cells to manipulate in the laboratory. Its large size (over a millimetre in diameter) means that cell cycle progression can be monitored visually in single cells. Microinjections can be performed for the purpose of interfering with specific functions of the biochemical machinery of the cell cycle. The Xenopus oocyte has proven to be an invaluable tool in the study of the biochemistry of the cell cycle, allowing, among other findings, the elucidation of the composition and regulation of maturation promoting factor (MPF), a complex enzyme comprising a kinase (p34cdc2) and a regulatory subunit (cyclin B), which drives progression from G2 to M phase[1]. In contrast, the exceptional genetic plasticity of yeast has allowed the identification of scores of mutants with defects in cell cycle progression; in mammalian cells, these mutations would have been lethal and it would therefore have been impossible to characterise them. These mutants were called "cdc", for cell division cycle mutants, and many of them have been accorded wider recognition through the application of their names to the mammalian homologues corresponding to the yeast genes.

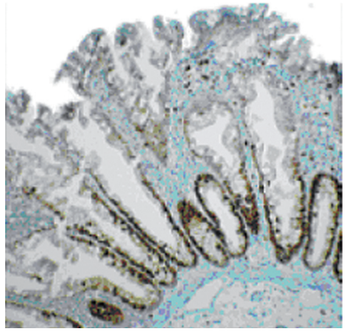


Fig. 3.3.1 *Proliferating cells in the basal parts of the colonic crypts, visualised by immunohistochemistry (stained brown)*

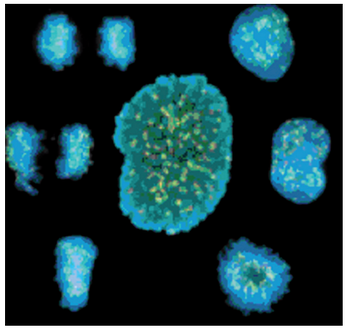


Fig. 3.3.2 *A human osteosarcoma cell nucleus during mitosis. Cell division proceeds clockwise from upper right through interphase, prophase (centre), prometaphase, metaphase, anaphase and telophase. During the cycle, the chromosomes are replicated, segregated and distributed equally between the two daughter cells*

One of the earliest genes to be identified in this way was cdc2. Isolated in *S. pombe*, cdc2 was determined to be able to correct a G2 cell cycle arrest defect. The product of this gene, a serine-threonine kinase of molecular weight 32–34 000 daltons, was subsequently shown to be the yeast homologue of the kinase contained in the Xenopus MPF. This enzyme became the paradigm of a class of enzymes now called cyclin-dependent kinases (CDKs). In their active form, CDKs form heterodimers with cyclins, a class of molecules synthesised in a time-dependent manner during the cell cycle. The progression of the cell cycle depends upon the sequential activation and inactivation of cyclin/CDK complexes [1], a process which requires the synthesis of cyclins, the formation of a complex between a specific cyclin and a CDK and post-translational modification of the CDK to convert the enzyme to an active form (Figure 3.3.3).

Progression through the cell cycle as mediated by cyclins is, in turn, determined by factors categorised as having either regulatory (upstream) or effector (downstream) roles. Upstream of cyclin/CDKs are regulatory factors called cyclin-dependent kinase inhibitors (CDKIs), which regulate the assembly and the activity of cyclin/CDK complexes. Downstream of cyclin/CDKs are effector molecules, essentially transcription factors, which control the synthesis of proteins that mediate the molecular and cellular changes occurring during each phase.

CDKIs are small proteins that form complexes with both CDKs and cyclins [2]. Their role is primarily to inhibit the activities of cyclin/CDK complexes and to negatively regulate cell cycle progression. They constitute the receiving end of many of the molecular cascades signalling growth promotion or suppression of growth. Thus CDKIs may be considered as the interface between the cell cycle machinery and the network of molecular pathways which signal proliferation, death or stress responses. However, by virtue of their complexing properties, some CDKIs also play a positive role in cell cycle progression by facilitating the assembly of cyclin/CDK complexes. For example, p21, the product of the CDKN1A gene (also known as WAF1/CIP1), promotes the assembly of cyclin D/cdk2 complexes in G1 at a stoichiometric 1:1 ratio, but inhibits the activities of these complexes when expressed at higher levels. There are three main families of CDKIs, each with distinct structural and functional properties: the WAF1/CIP1 family (p21), the KIP family (p27, p57) and the INK4 family (p16, p15, p18) (Figure 3.3.3).

Downstream effectors of cyclin/CDKs include proteins mediating three main functional categories: (1) those involved in the control of the enzymes responsible for DNA replication, proof-reading and repair, (2) those involved in chromosome and chromatin remodelling and in the control of genomic integrity, and (3) those involved in the mechanics of cell division (including the formation of the centrosome and the mitotic spindle, and in the resorption of the nuclear membrane). These processes require the coordinated synthesis of hundreds of cellular proteins. Transcription factors of the E2F family play a critical role in the control of gene transcription during cell cycle progression (Figure 3.3.4). In G1, factors of the E2F family are bound to their DNA targets but are maintained in a transcriptionally inactive state by the binding of proteins of the retinoblastoma (pRb) protein family. At the G1/S transition, the sequential phosphorylation of pRb by several cyclin/CDKs dissociates pRb from the complexes, allowing E2Fs to interact with transcription co-activators and to initiate mRNA synthesis [3].

Through this mechanism, E2Fs exert a dual function both as transcriptional repressors in G1, when bound to pRb, and as transcriptional activators in G1/S and in S phase, after dissociation of pRb from the complex. Recent observations suggest that transcriptional repression by E2Fs is essential to prevent the premature activation of cell cycle effectors,

Gene (chromosome)	Product	Type of alteration	Role in cell cycle	Involvement in cancer
p53 (17p13)	p53	Mutations, deletions	Control of p21, 14-3-3σ, etc.	Altered in over 50% of all cancers
CDKN2A (9p22)	p16 and p19arf	Mutations, deletions, hypermethylation	Inhibition of CDK4 and 6	Altered in 30-60% of all cancers
RB1 (13q14)	pRb	Deletions	Inhibition of E2Fs	Lost in retinoblastomas, altered in 5-10% of other cancers.
CCND1	Cyclin D1	Amplification	Progression into G1	10-40% of many carcinomas
CDC25A, CDC25B	cdc25	Overexpression	Progression in G1, G2	10-50% of many carcinomas
KIP1	p27	Down-regulation	Progression in G1/S	Breast, colon and prostate cancers

Table 3.3.1 *Cell cycle regulatory genes commonly altered in human cancers*

which would scramble the temporal sequence of molecular events and preclude cell cycle progression.

Cell cycle checkpoints

The notion of "cell cycle checkpoints" is also derived from early studies in Xenopus oocytes and in yeast mutants. In *S. cerevisiae*, commitment to the mitotic cycle requires the crossing of a "restriction point" called the start transition. Failure to cross this transition results in cells being blocked in the G1 phase of the cycle. Another control point has been clearly identified after S phase, at the transition between G2 and M phases. Cells unable to cross this checkpoint may remain blocked in a pre-mitotic, tetraploid state. Physiologically, this checkpoint is active in germ cells during the second division of meiosis: cells that have undergone the first, asymmetric division of the meiotic cycle arrest in G2 until completing the second division, which is triggered by fertilisation. This concept of "cell cycle checkpoints" was later extended to all mammalian cells[4,5]. It is now common to envisage the mammalian cell cycle as a succession of checkpoints that must be negotiated in order for division to be achieved. There is no clear agreement on how many such checkpoints exist in the mammalian cell cycle, or on their exact position.

Control of cdk1 at G2/M transition

The regulation of the complex between cdk1 (also called p34cdc2) and cyclin B exemplifies how different factors co-operate to control the activation of cyclin/CDK complexes at a cell cycle checkpoint. This activation process requires co-operation between three levels of regulation: association between the two partners of the complex, post-translational modifications of the kinase and of the cyclin, and escape from the negative regulation exerted by the CDKIs.

In early G2, cdk1 is in an inactive form. Its activation requires first association with cyclin B, followed by post-translational modification of

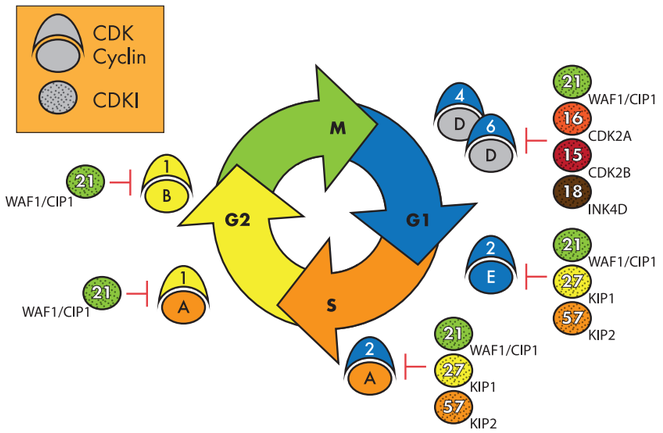


Fig. 3.3.3 *The progression of the cell cycle depends upon the sequential activation and inactivation of cyclin/CDK complexes. This process requires the synthesis of cyclins, the formation of a complex between a specific cyclin and a CDK, and modification of the CDK to convert this enzyme to an active form. The enzyme's activity may be disrupted by a specific inhibitor, a CDKI*

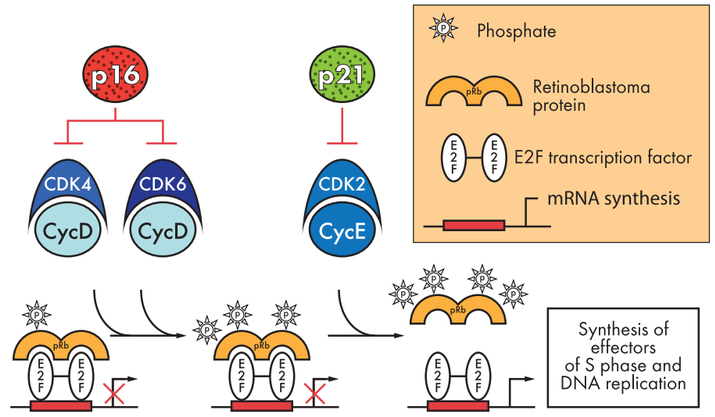


Fig. 3.3.4 *Progression from G1 to S phase is regulated by phosphorylation of the retinoblastoma protein (pRb), in the absence of which DNA replication cannot proceed*

the kinase itself. This modification includes phosphorylation of a conserved threonine residue (Thr161) by a kinase complex called CAK (CDK-activating kinase), as well as dephosphorylation of two residues localised within the active site of the enzyme, a threonine (Thr14) and a tyrosine (Tyr15). The removal of these phosphate groups is carried out by the dual-specificity phosphatases of the cdc25 group, comprising three isoforms in humans (A, B and C). Activation of these phosphatases is therefore crucial for the activation of cyclin B/cdk1 complexes. The phosphatase is directly controlled by a number of regulators, including plk1 (polo-like kinase), an activating kinase, pp2A, (protein phosphatase 2A), an inhibitory phosphatase and 14-3-3s, a signal transduction molecule which complexes with cdc25, sequesters it in the cytoplasm and thus prevents it from dephosphorylating its nuclear targets. Of course, the action of cdc25 phosphatases is counteracted by kinases that restore the phosphorylation of Thr14 and Tyr15, named wee1 and mik1 [2].

Following the activation process outlined above, the cyclin B/cdk1 complex is potentially able to catalyse transfer of phosphates to substrate proteins. However, in order to achieve this, it has to escape the control exerted by CDKIs, such as p21. The function of this CDKI is itself controlled by several activators, including BRCA1, the product of a breast cancer susceptibility gene. The p21 protein is removed from the complex by a still poorly understood phosphorylation process, which also drives rapid degradation of the protein by the proteasome. This leaves the cyclin B/cdk1 complex ready to function, after a final step of autophosphorylation, in which cdk1 phosphorylates cyclin B. The complex is now fully active and ready to phosphorylate many different substrates, such as nuclear lamins, during entry into mitosis.

Regulation of the cell cycle and control of genetic stability

During the cell cycle, a number of potential problems may result in damage to the genome. These problems may arise at three distinct stages: (1) during DNA replication, especially if the cell is under conditions of stress that favour the formation of DNA damage (irradiation, exposure to carcinogens, etc.); (2) following the termination of DNA replication, when the cell effectively "switches off" its DNA synthesis machinery; and (3) during M phase, when the cell must negotiate the delicate task of segregating chromatids equally. A tight coupling between these processes and cell cycle regulation is therefore crucial to allow the cell to pause during the cell cycle in order to afford the time necessary for the successful completion of all the operations of DNA and chromosome maintenance. Failure to do this may result in both genetic and genomic instabilities, which are hallmarks of cancer. Genetic instability is characterised by an increased rate of gene mutation, deletion or recombination (essentially due to defects in DNA repair). Genomic instability results in chromosome translocations, loss or duplication of large chromosome fragments and aberrant chromosome numbers (aneuploidy).

Tens of molecules have been identified as components of the signalling cascades which couple detection of DNA damage and regulation of the cell cycle. One of these is the product of the tumour suppressor gene p53. p53 is specifically activated after various forms of direct DNA damage (such as single or double strand breaks in DNA) and regulates the transcription of several inhibitors of cell cycle progression, particularly at the G1/S and G2/M transitions [6,7]. Other important molecules in this coupling process include the checkpoint kinases chk1 and chk2. Chk1 is activated after replication blockage during S-phase. In turn, chk1 activates wee1 and mik1, two kinases that counteract the action of cdc25 and keep cdk1 in an inactive form. Thus, through activation of chk1, the cell triggers an emergency mechanism that ensures that cells with incompletely replicated DNA cannot enter mitosis.

The cell cycle and cancer

Genes involved in cell cycle control are important among those subject to the genetic alterations that give rise to cancer [8,9]. However, the proliferation of cancer cells requires that the cells retain functional cell cycle processes. The cell cycle alterations seen in cancer are mainly confined to two major sets of regulators: those involved in the negative control of cell cycle progression (inactivation of which leads to accelerated and unchecked cell proliferation) and those involved in coupling the maintenance of genome integrity to the cell cycle (inactivation of which results in cells having gene alterations that progressively accumulate during carcinogenesis) (Table 3.3.1) [8]. Most of the genes corresponding to these two categories fall within the group of tumour suppressors, and many of them are also direct participants in DNA repair processes.

The gene which encodes p16 (CDKN2A/INK4A) has been established as a tumour suppressor gene [10], and mutations and deletions at this site are commonly found in primary human tumours, especially melanoma (although the contribution of another protein encoded by the same locus on chromosome 9p, p14ARF, to suppressor activity remains to be determined). Unlike the CDKN2A/INK4A gene, the CDKN1A gene (encoding p21) is rarely disrupted in cancer. As p21 plays many roles in the negative regulation of almost all phases of the cell cycle, loss of this function might be expected to result in uncontrolled cell division. This is apparently not the case, as

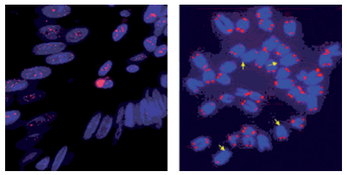


Fig. 3.3.5 *Telomeres contain repetitive DNA sequences that cap the ends of chromosomes. Fluorescence in situ hybridization analysis of human interphase (left) and mouse metaphase chromosome spread (right) is shown, using oligonucleotide probes specific for telomere (red) DNA sequences, and the DNA dye DAPI (blue). Arrows indicate the loss of telomere signal in cells obtained from knockout mice containing mutated telomerase gene*

mice lacking the CDKN1A gene do not show an increased frequency of cancer. This observation illustrates one of the most important characteristics of cell cycle regulatory mechanisms: there is a large degree of redundancy and overlap in the function of any particular effector. Therefore, cancer-causing deregulation of the cell cycle requires a combination of many alterations in genes encoding proteins that, either alone or in concert, are critical for the control of cell division.

Apart from inactivation of negative regulators, a few cell cycle genes may be activated as oncogenes, in that their alteration results in enhanced activity leading to accelerated cell proliferation. The best example of such a cell cycle oncogene is CCND1, the gene encoding cyclin D1, a G1-specific cyclin [11]. This gene is located on chromosome 11p13, within a large region that is amplified in up to 20% of several carcinomas (e.g. breast, head and neck, oesophageal and lung cancers).

There is also limited evidence for transcriptional activation of cyclin A (an S-phase cyclin) and for activating mutations of CDK4 (one of the partners of cyclin D1) in some cancers. Indeed, the high complexity of cell cycle effectors provides an extremely diverse range of possibilities for cancer-associated alterations. In this respect, cancer can be seen as, fundamentally, a disease of the cell cycle.

Telomeres and telomerase

Telomeres are specialised structures at the ends of eukaryotic chromosomes (Figure 3.3.5). These structures contain many copies of G-rich repeats that are highly conserved in most eukaryotic species. Telomeres have arisen as an evolutionary response to the problem posed by the development of linear chromosomes. Chromosome ends may be recognised as DNA breaks; thus cells needed a mechanism to protect natural chromosome ends by "hiding" them from DNA damage recognition machinery. A wealth of studies demonstrated that telomeres function to protect chromosome ends from fusion events and are therefore critical for chromosome stability and genomic integrity.

Studies in the early 1960s suggested that specific human cells can only divide about 50 times, a phenomenon known as the Hayflick limit [12]. This was based on the assumption that the number of divisions is determined by both the initial length of the telomeres and the rate of telomere shortening. Experimental studies demonstrated that the telomeres of normal human somatic cells shorten by 50 to 150 base pairs every time cell division occurs, supporting the theory of the Hayflick limit. Subsequent studies provided evidence that critically short telomeres cease to function as protective structure and cause the cell to trigger cell suicide (apoptosis) or undergo senescence (permanent arrest of cell proliferation) (Figure 3.3.6). Therefore telomerase shortening during cell division appears to act as a cell division counting mechanism. Normal cells thus have a limited proliferative capacity, and this acts as a major barrier against carcinogenesis.

While it is now recognised that telomeres have many more functions than simply protecting chromosome ends, the initial concept of a replication barrier is still valid. Consistent with this notion, recent studies showed that most human cancer activate telomerase at some point during the process of tumour development and progression, a phenomenon typically absent in normal cells. Cells that have accumulated some carcinogenic changes are unable to form clinically significant cancers unless this proliferation barrier imposed by telomere clock is breached. This is supported by the evidence that more than 85% of all cancers achieve this by expressing an enzyme, telomerase, that synthesises new telomeric DNA to replace the sequences lost during cell division [13].

The catalytic subunit of human telomerase, hTERT, was cloned in 1997 [14]. It has subsequently been shown that genetic manipulations of hTERT which result in inhibition of telomerase activity in tumour cells limit their proliferation and often result in cell death. This raises the possibility that telomerase inhibitors may be a very useful form of therapy for many or most types

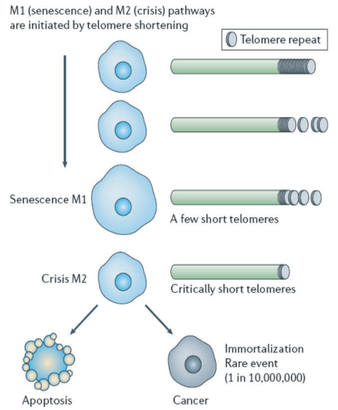


Fig. 3.3.6 *Telomere-mediated senescence and tumorigenesis [13]*

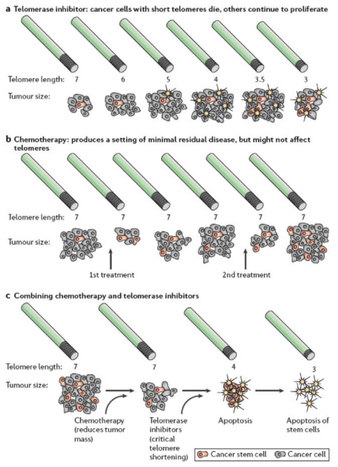


Fig. 3.3.7 *Cancer therapy targeting telomerase [13]*

of cancer. However, in tumours with long telomeres, it may take many cell divisions before telomerase inhibitors exert an anti-tumour effect. When such drugs are developed they will therefore need to be carefully integrated with other anticancer treatments.

It is interesting to note that not all tumours need to activate telomerase. Studies showed that approximately 10% of human tumours rely on a telomerase-independent mechanism to maintain their telomeres. This phenomenon, known as the alternative lengthening of telomeres (ALT) mechanism, relies on recombination between telomeres [15].

Telomerase assays have not yet entered routine clinical practice, but there is considerable interest in their possible use for cancer diagnosis and prognosis. For example, telomerase assays of urine sediments may be useful for diagnosis of urinary tract cancer, and telomerase activity levels may be a predictor of outcome in neuroblastoma [16]. In summary, there have been many important discoveries in the field of telomere research, suggesting that telomeres may be an attractive target for the development of therapeutic intervention in different types of human cancer (Figure 3.3.7). However, more clinical studies are needed to test telomerase-targeted approaches that could lead to effective cancer interventions with minimal side effects. Studies aiming to close many gaps in our understanding of telomere-maintenance mechanism will be instrumental in these endeavours.

REFERENCES

1. Bartek J and Lukas J (2007). DNA damage checkpoints: from initiation to recovery or adaptation. *Curr Opin Cell Biol* 19: 238-245.

2. Boutros R, Lobjois V, Ducommun B (2007). CDC25 phosphatases in cancer cells: key players? Good targets? *Nat Rev Cancer* 7: 495-507.

3. Du W and Pogoriler J (2006). Retinoblastoma family genes. *Oncogene* 25: 5190-5200.

4. Hartwell LH and Weinert TA (1989). Checkpoints: controls that ensure the order of cell cycle events. *Science* 246: 629-634.

5. Orford KW and Scadden DT (2008). Deconstructing stem cell self-renewal: genetic insights into cell cycle regulation. *Nat Rev Genet* 9: 115-128.

6. Hainaut P and Hollstein M (2000). p53 and human cancer: the first ten thousand mutations. *Adv Cancer Res* 77: 81-137.

7. Stark GR and Taylor WR (2006). Control of the G2/M transition. *Mol Biotechnol* 32: 227-248.

8. Lobrich M and Jeggo PA (2007). The impact of a negligent G2/M checkpoint on genomic instability and cancer induction. *Nat Rev Cancer* 7: 861-869.

9. Malumbres M and Barbacid M (2001). To cycle or not to cycle: a critical decision in cancer. *Nat Rev Cancer* 1: 222-231.

10. Strohmaier H, Spruck CH, Kaiser P, et al. (2001). Human F-box protein hCdc4 targets cyclin E for proteolysis and is mutated in a breast cancer cell line. *Nature* 413: 316-322.

11. Santamaria D and Ortega S (2006). Cyclins and CDKS in development and cancer: lessons from genetically modified mice. *Front Biosci* 11: 1164-1188.

12. Hayflick L (1980). Recent advances in the cell biology of aging. *Mech Ageing Dev* 14: 59-79.

13. Shay JW and Wright WE (2006). Telomerase therapeutics for cancer: challenges and new directions. *Nat Rev Drug Discov* 5: 577-584.

14. Lingner J and Cech TR (1998). Telomerase and chromosome end maintenance. *Curr Opin Genet Dev* 8: 226-232.

15. Muntoni A and Reddel RR (2005). The first molecular details of ALT in human tumor cells. *Hum Mol Genet* 14 Spec No. 2: R191-R196.

16. Hiyama E and Hiyama K (2002). Clinical utility of telomerase in cancer. *Oncogene* 21: 643-649.

3.4 Cell Death

Summary

> The term apoptosis refers to a type of cell death that occurs both physiologically and in response to external stimuli, including X-rays and anticancer drugs

> Apoptotic cell death is characterised by distinctive morphological changes different from those occurring during necrosis, which follows ischaemic injury or toxic damage

> Apoptosis is regulated by several distinct signalling pathways. Dysregulation of apoptosis may result in disordered cell growth and thereby contribute to carcinogenesis

> Selective induction of apoptosis in tumour cells is among current strategies for the development of novel cancer therapies

In the adult organism, the number of cells is kept relatively constant through cell death and division, and deregulation of this balance (homeostasis) may trigger pathological conditions such as neurodegenerative diseases and cancer. Apoptosis and necrosis are two forms of cell death, with distinct morphological and biochemical features. While apoptosis accounts for most physiological cell deaths, necrosis is usually induced in pathological situations by accidental, acute damage to cells. Apoptosis, or programmed cell death, is a tightly regulated process under normal conditions that facilitates fundamental processes such as development (for example, by removal of unwanted tissue during embryogenesis) and the immune response (for example, by elimination of self-reactive T cells). This type of cell death is distinguished from necrosis both morphologically (Figures 3.4.1 and 3.4.2) and functionally. Specifically, apoptosis involves single cells rather than areas of tissue and does not provoke inflammation (Figures 3.4.3 and 3.4.4). Tissue homeostasis is dependent on controlled elimination of unwanted cells, often in the context of a continuum in which specialisation and maturation is ultimately succeeded by cell death in what may be regarded as the final phase of differentiation. Apart from elimination in a physiological context, cells that have been lethally exposed to cytotoxic drugs or radiation may be subject to apoptosis.

The process of apoptosis can be described by reference to distinct phases, termed "regulation", "effector" and "engulfing" [1]. The regulatory phase includes all the signalling pathways that culminate in commitment to cell death. Some of these pathways regulate only cell death, but many of them have overlapping roles in the control of cell proliferation, differentiation, responses to stress and homeostasis. Critical to apoptosis signalling are the "initiator" caspases (including caspase-8, caspase-9 and caspase-10) whose role is to activate the more abundant "effector" caspases (including caspase-3 and caspase-7) which, in turn, bring about the morphological change indicative of apoptosis. Finally, the engulfing process involves the recognition of cellular "remains" and their elimination by the engulfing activity of surrounding cells.

Identification of genes mediating apoptosis in human cells has been critically dependent on definition of the ced genes in the nematode Caenorhabditis elegans, members of this gene family being homologous to human BCL2 (which suppresses apoptosis), APAF-1 (which mediates caspase activation) and the caspases themselves (proteases which mediate cell death). The centrality of apoptosis to cancer biology is indicated by excess tumorigenesis in BCL2-transgenic and p53-deficient mice. An appreciation of apoptosis provides a basis for the further development of novel and conventional cancer therapy.

The role of cell death in tumour growth

Apoptosis, or lack of it, may be critical to tumorigenesis [2]. BCL2, a gene mediating resistance to apoptotic stimuli, was discovered at the t(14:18) chromosomal translocation in low-grade B cell non-Hodgkin lymphoma. It thus became apparent that neoplastic cell expansion could be attributable to decreased cell death rather than rapid proliferation. Defects in apoptosis allow neoplastic cells to survive beyond senescence, thereby providing protection from hypoxia and oxidative stress as the tumour mass expands. Growth of tumours, specifically in response to chemical carcinogens, has been correlated with altered rates of apoptosis in affected tissues as cell populations with altered proliferative activity emerge. Paradoxically, growth of some cancers, specifically including breast, has been positively correlated with increasing apoptosis [3].

Interrelationships between mitogenic and apoptotic pathways

A dynamic relationship between regulation of growth/mitosis and apoptosis may be demonstrated using a variety of relevant signalling pathways. Many differing promoters of cell proliferation have been found to possess pro-apoptotic activity. Thus, ectopic expression of the C-MYC oncogene (normally associated with proliferative activity) causes apoptosis in cultured cells subjected to serum deprivation (which otherwise prevents proliferation). Oncogenes that stimulate mitogenesis can also activate apoptosis. These include oncogenic ras, myc and E2F. Mutations in E2F that prevent its interaction with the retinoblastoma protein (pRb) accelerate S phase entry and apoptosis. A function of pRb is to suppress apoptosis: pRb-deficient cells seem to be more susceptible to p53-induced apoptosis.

Agents such as radiation or cytotoxic drugs cause cell cycle arrest and/or cell death [4]. The DNA damage caused by radiation or drugs is detected by various means (Figure 3.4.2). DNA-dependent protein kinase and the ataxia telangiectasia mutated gene (ATM) (as well as the related ATR protein) bind to damaged DNA and initiate phosphorylation cascades to transmit damage signals. DNA-dependent protein kinase is believed to play a key role in the response to double-stranded DNA breaks. ATM plays an important part in the response to DNA damage caused by ionizing radiation, controlling the initial phosphorylation of proteins such as p53, Mdm2, BRCA1, Chk2 and Nbs1. Other sensors of DNA damage include mammalian homologues of the PCNA-like yeast proteins Rad1, Rad9 and Hus1, as well as the yeast homologue of replication factor C, Rad17. Specific molecules detect nucleotide mismatch or inappropriate methylation. Following exposure of mammalian cells to DNA-damaging agents, p53 is activated and among many "targets" consequently upregulated are the cyclin-dependent kinase inhibitor p21 (which causes G1 arrest) and Bax (which induces apoptosis). Thus, the tumour suppressor gene p53 mediates two responses to DNA damage by radiation or cytotoxic drugs: cell cycle arrest at the G1 phase of the cell cycle and apoptosis. The serine/threonine kinase Chk2 is also able to positively interact with p53 and BRCA1. Chk2 and the functionally related Chk1 kinase appear to have a role in the inhibition of entry into mitosis via inhibition of the phosphatase Cdc25.

The regulatory phase

Two major apoptotic signalling pathways have been identified in mammalian cells (Figure 3.4.5). The "extrinsic" pathway depends upon the conformational change in certain cell surface receptors following the binding of respective ligands. The "intrinsic" pathway involves mitochondrial function and is initiated by growth factor deprivation, corticosteroids or DNA damage induced by radiation or cytotoxic drugs.

Cell surface receptors

Apoptosis may be induced by signalling molecules, usually polypeptides such as growth factors or related molecules, which bind to "death" receptors on the cell surface [2]. Such cell death was initially investigated in relation to the immune response, but has much wider ramifications. The best-characterised receptors belong to the tumour necrosis factor (TNF) receptor gene superfamily [5] (Figure 3.4.5). In addition to a ligand-binding domain, death receptors contain homologous cytoplasmic sequence termed the "death domain". Members of the family include Fas/APO-1/CD95 and TNF-1 receptor (which binds TNFa). Activation of the Fas (or CD95) receptor by its specific ligand (FasL or CD95L) results in a conformational change such that the "death domain" interacts with the adaptor molecule FADD which then binds procaspase-8. In some cell types, drug-induced apoptosis is associated with Fas activation. Ultraviolet irradiation directly activates the Fas receptor in the absence of ligand. TRAIL (TNF-related apoptosis-inducing ligand, Apo-2L) has 28% amino acid identity to FasL. TRAIL induces cell death only in tumorigenic or transformed cells and not in normal cells [5].

The regulation of apoptosis by BCL2 family genes

While the members of the "death receptor" family and their ligands have structural elements in common, agents and stimuli initiating the mitochondrial pathway to apoptosis are diverse. Common to these stimuli, however, is a change in mitochondrial function, often mediated by members of the BCL2 family [6]. In humans, at least 16 homologues of BCL2 have been identified. Several family members (including Bcl-2, Bcl-xL, Bcl-W) suppress apoptosis, while others induce apoptosis and may be subdivided on the basis of their ability to dimerize with Bcl-2 protein (Bad, Bik, Bid) or not (Bax, Bak). Phosphorylation of Bad protein by a specific (Akt/PKB) and other kinases prevents dimerization with Bcl-2 and promotes cell survival. At least two distinct mechanisms of action are rec-

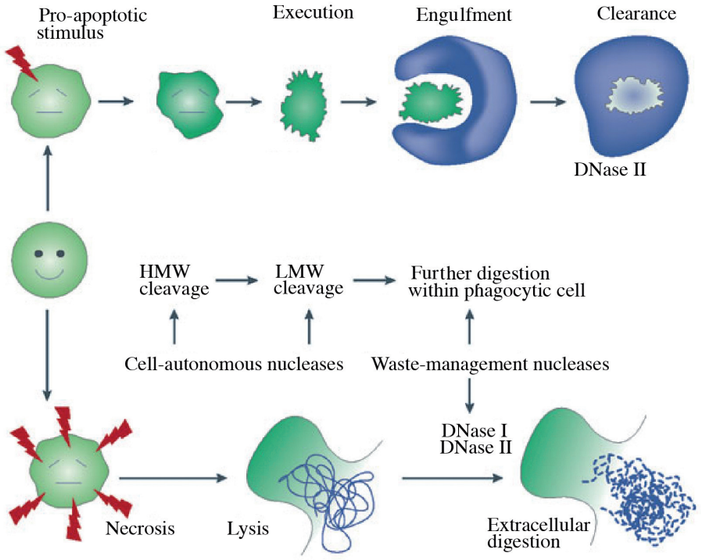


Fig. 3.4.1 *Apoptosis and necrosis are distinguished by characteristic morphological changes and molecular machineries involved in these processes*

ognised: the binding of Bcl-2 (or other members of the family) with either pro- or anti-apoptotic members of the Bcl-2 family or the formation of pores in mitochondrial membranes. Bcl-xL is a potent death suppressor that is upregulated in some tumour types. Bax is a death promoter that is inactivated in certain types of colon cancer, stomach cancer and in haematopoietic malignancies. By dint of relevant binding sites, Bax is under the direct transcriptional control of p53.

Involvement of mitochondria

Apoptosis induced by cytotoxic drugs is accompanied by critical changes in mitochondria [2,7]. Such apoptotic stimuli induce translocation of Bax from cytosol to mitochondria, which induces release of cytochrome c (Figure 3.4.5). Loss of transmembrane potential follows cytochrome c release and is dependent on caspase activation (see below), whereas cytochrome c release is not. Bcl-2 and Bcl-xL reside chiefly in the outer mitochondrial membrane. Bcl-2, Bcl-xL and Bax can form ion channels when they are added to synthetic membranes, and this may be related to their impact on mitochondrial biology [2,8].

In the cytosol after release from mitochondria, cytochrome c activates the caspases through formation of a complex (the "apoptosome") with Apaf-1 (apoptotic-protease activating factor-1), procaspase-9 and ATP. It appears that Bcl-2/Bcl-xL may suppress apoptosis by either preventing release of cytochrome c or interfering with caspase activation by cytochrome c and Apaf-1. Sustained production of nitric oxide (NO) may cause the release of mitochondrial cytochrome c into the cytoplasm and thus contribute to the activation of caspases. However, nitric oxide is involved in several aspects of apoptosis and may act both as a promoter and inhibitor depending on conditions [9].

The effector and engulfing phases

In mammals at least 13 proteases that mediate the breakdown of cell structure during apoptosis have been identified and are designated caspases-1 through -13 [10]. All possess an active site cysteine and cleave substrates after aspartic acid residues. They exist as inactive zymogens, but are activated by different processes which most often involve cleavage of their pro-forms (designated procaspase-8, etc.) at particular sites, thereby generating subunits which form active proteases consisting of two large and two small subunits. Proteolytic cascades may occur with some caspases operating as upstream initiators (which have large N-terminal

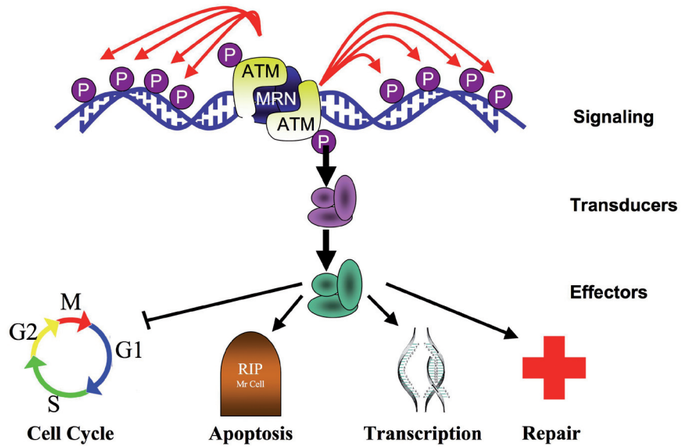


Fig. 3.4.2 *Programmed cell death (apoptosis) is a critical cellular process that may be triggered in response to DNA damage . Source: Zdenko Herceg and Rabih Murr, unpublished*

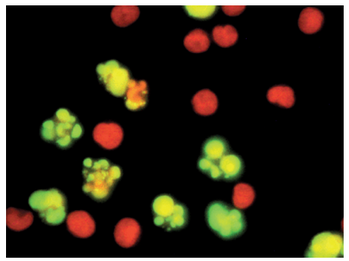


Fig. 3.4.3 *Cancer cells treated with chemotherapy agents often die via apoptosis. The image above shows human lymphoma cells treated with the chemotherapy agent camptothecin. The cells that are undergoing apoptosis appear yellow and show the characteristic membrane blebbing seen in cells dying via apoptosis*

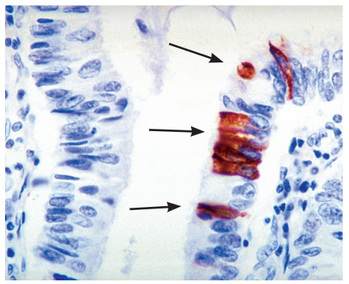


Fig. 3.4.4 *Apoptotic cells in an adenoma, visualised by immunohistochemistry (red). Apoptosis is restricted to single cells, unlike necrosis, which typically involves groups of cells. Apoptosis does not produce an inflammatory response.*

prodomains and are activated by protein-protein interaction) and others being downstream effectors (activated by protease cleavage). As noted earlier, at least two pathways of caspase activation can be discerned: one involving FADD or similar protein-protein complexes and the other mediated by release of cytochrome c. In the former, affinity labelling suggests that caspase-8 activates caspases-3 and -7 and that caspase-3 in turn may activate caspase-6. On the other hand, release of cytochrome c into the cytoplasm results in the activation of caspase-9 which in turn activates caspase-3.

Though the intrinsic pathway to caspase-3 activation may be distinguished from the extrinsic pathway (i.e. that activated by Fas, etc.), some interaction is demonstrable. Thus, caspase-9 is able to activate caspase-8. Nonetheless, the pathways are separate to the extent that caspase-8 null animals are resistant to Fas- or TNF-induced apoptosis while still susceptible to chemotherapeutic drugs; cells deficient in caspase-9 are sensitive to killing by Fas/TNF but show resistance to drugs and dexamethasone. Finally, death of some cells may occur independently of caspase-3. Caspases-3, -7 and -9 are inactivated by proteins of the inhibitor of apoptosis family (IAPs) which are suppressors conserved throughout evolution. The IAP protein "survivin" is overexpressed in a large proportion of human cancers. Little is known about the involvement of caspase mutations in cancer.

Caspase substrates and late stages of apoptosis

Apoptosis was initially defined by reference to specific morphological change. In fact, both mitosis and apoptosis are characterised by a loss of substrate attachment, condensation of chromatin and phosphorylation and disassembly of nuclear lamins. These changes are now attributable to caspase activation and its consequences.

Most of the more than 60 known caspase substrates are specifically cleaved by caspase-3 and caspase-3 can process procaspases-2, -6, -7 and -9 [11]. Despite the multiplicity of substrates, protease activity mediated by caspases is specific and seems likely to account for much of the morphological change associated with apoptosis. Caspases cleave key components of the cytoskeleton, including actin as well as nuclear lamins and other structural proteins. Classes of enzymes cleaved by caspases cover proteins involved in DNA metabolism and repair exemplified by poly(ADP-ribose) polymerase and DNA-dependent protein kinase [12,13]. Other classes of substrates include various kinases, proteins in signal transduction pathways and proteins involved in cell cycle control, exemplified by pRb. Cleavage of some substrates is cell-type specific. Caspase activity accounts for internucleosomal cleavage of DNA, one of the first characterised biochemical indicators of apoptosis. ICAD/DFF-45 is a binding partner and inhibitor of the CAD (caspase-activated DNAase) endonuclease, and cleavage of ICAD by caspase-3 relieves

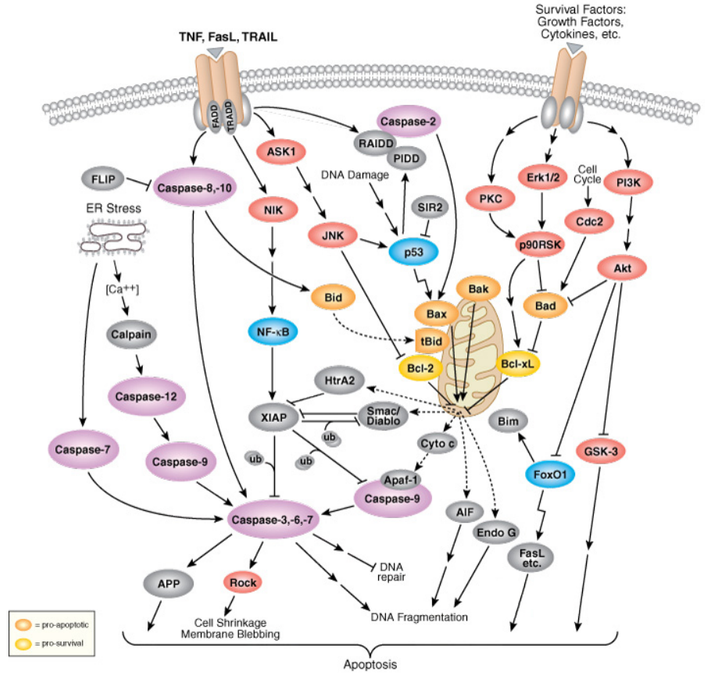


Fig. 3.4.5 *Apoptosis occurs when specific proteases (caspases) digest critical proteins in the cell. The caspases are normally present as inactive procaspases. Two pathways lead to their activation. The death receptor pathway (at the top and left side of the figure) is triggered when ligands bind to death receptors such as CD95/Fas. The mitochondrial pathway is triggered by internal insults such as DNA damage as well as by extracellular signals. In both pathways, procaspases are brought together. They then cleave each other to release active caspase. The binding of ligand (FasL or CD95L) to CD95 brings procaspase 8 molecules together; release of mitochondrial components bring procaspases 9 together. The active caspase 8 and 9 then activate other procaspases such as procaspase 3.*

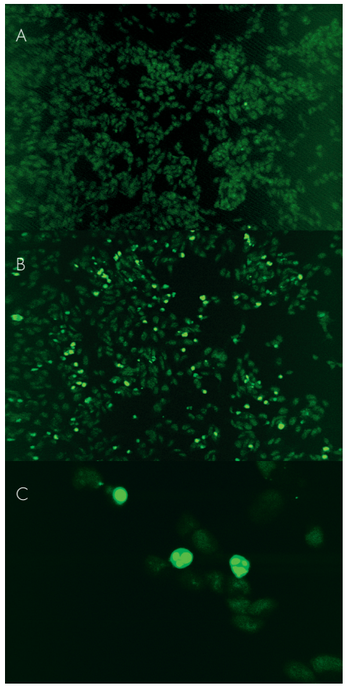


Fig. 3.4.6 *Neuroblastoma cells treated with ionizing radiation undergo apoptosis. The TUNEL assay was used to visualize apoptotic cells (green), before (A) and 24 hours after (B) treatment with X-rays (5 Gray). Close-up shows that the nuclei of the apoptotic cells are fragmented (C).*

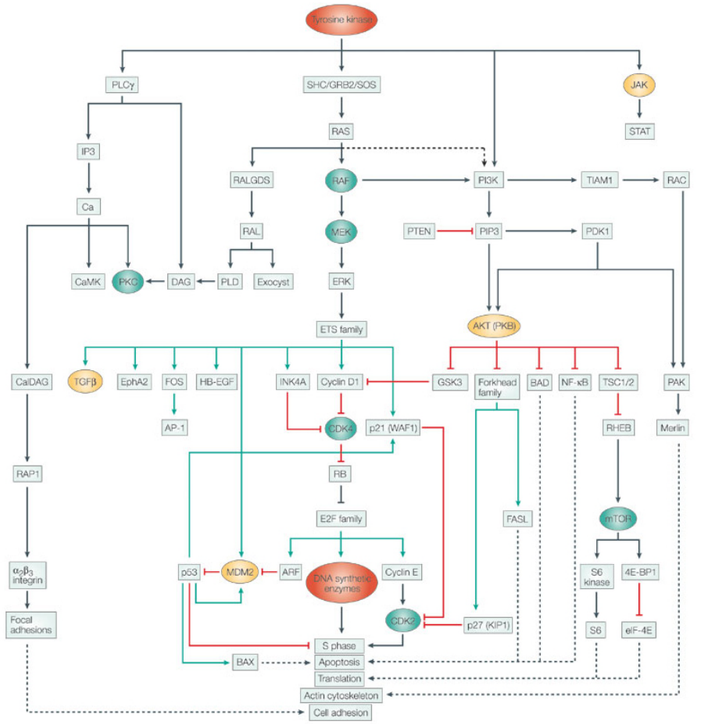


Fig. 3.4.7 *Signaling pathways targeted by anticancer agents. Activation of cell signaling by a selected repertoire of protein tyrosine and serine/threonine kinases is the hallmark of many cancers. Certain tyrosine kinases and serine/threonine kinases have become targets for signal-transduction inhibitors. These are marked by colours according to their current status of development: approved drugs (red); drugs in the clinical trials (green); and drugs in preclinical trials (yellow). Green arrows denote direct transcriptional targets. Red lines show direct inhibitory pathways. Black arrows show direct activation events, and dashed arrows show events that are either indirect or questionable.*

the inhibition and promotes the endonuclease activity of CAD (Figures 3.4.6 and 3.4.7).

Therapeutic implications

In theory, knowledge of critical signalling or effector pathways which bring about apoptosis provides a basis for therapeutic intervention, including the development of novel drugs to activate particular pathways.

Several options are under investigation [14]. More immediately, attempts are being made to exploit knowledge of apoptotic processes to increase the efficacy or specificity of currently available therapy. Simple answers have not emerged. Thus, for example, relatively increased expression of Bcl-2 (which, under many experimental conditions, inhibits apoptosis) is not necessarily indicative of poor prognosis, and the reverse appears true for some tumour types. In experimental systems, cells acquiring apoptosis defects (e.g. p53 mutations) can more readily survive hypoxic stress and the effects of cytotoxic drugs [2,9]. However, clinical studies have not consistently established that mutation of p53 is associated with poor response to chemotherapy [15].

The function of Bcl-2 family members may be subject to interference by small molecules [16]. In preclinical animal models, suppression of Bcl-2 by an antisense oligonucleotide has been shown to retard tumour growth and the approach is currently subject to clinical trial. Likewise, antisense oligonucleotides directed at survivin are being evaluated. The possibility of using recombinant TRAIL to induce apoptosis in malignant cells is under investigation. TRAIL is implicated as the basis of all-trans-retinoic treatment of promyelocytic leukaemia [17]. Also noteworthy is the development of caspase inhibitors for the treatment of certain degenerative (non-cancerous) diseases characterized by excess apoptosis.

Drugs shown to induce apoptosis specifically include chemopreventive agents, exemplified by 4-hydroxyphenylretinamide. Butyrate, a short-chain fatty acid produced by bacterial fermentation of dietary fibre, inhibits cell growth in vitro and promotes differentiation; it also induces apoptosis. Both roles may contribute to its prevention of colorectal cancer. Moreover, cyclo-oxygenase enzyme (COX-2) expression may modulate intestinal apoptosis via changes in Bcl-2 expression. Aspirin and similar drugs which inhibit COX-2 may promote apoptosis and prevent tumour formation.

Drugs targeting signal transduction pathways

In complex multicellular organisms, cell proliferation, differentiation and survival are regulated by a number of extracellular hormones, growth factors and cytokines. These molecules are ligands for cellular receptors and communicate with the nucleus of the cell through a network of intracellular signalling pathways. In cancer cells, key components of these signal transduction pathways may be subverted by proto-oncogenes through overexpression or mutation, leading to unregulated cell signalling and cellular proliferation. Because a number of these components may be preferentially over-expressed or mutated in human cancers, the cell signalling cascade provides a variety of targets for anticancer therapy.

Different approaches have been used to attack these targets and include classical cytotoxic agents as well as small molecule drug inhibitors. In addition, antisense oligonucleotides, vaccines, antibodies, ribozymes and gene therapy approaches have been utilized.

The diagram in Figure 3.4.7 illustrates cell signalling pathways that are targeted by anticancer agents currently undergoing clinical testing. The drug imatinib is already in clinical use. It is hoped that in future, a combination of agents targeting parallel pathways, as well as combinations with classical cytotoxic agents will improve the outcome of cancer patients.

Classes of agents and their potential targets include:

- Inhibitors of ligands, such as recombinant human antibody to VEGF (rHu mAbVEGF)
- Receptors, anti-receptor antibodies and tyrosine kinase receptor inhibitors
- RAS farnesyltransferase inhibitors
- RAF inhibitors
- MEK inhibitors
- Rapamycin analogues
- Protein kinase C (PKC) inhibitors
- Inhibitors of protein degradation
- Inhibitors of protein trafficking

REFERENCES

1. Strasser A, O'Connor L, Dixit VM (2000). Apoptosis signaling. *Annu Rev Biochem* 69: 217-245.

2. Letai AG (2008). Diagnosing and exploiting cancer's addiction to blocks in apoptosis. *Nat Rev Cancer* 8: 121-132.

3. Parton M, Dowsett M, Smith I (2001). Studies of apoptosis in breast cancer. *BMJ* 322: 1528-1532.

4. Rich T, Allen RL, Wyllie AH (2000). Defying death after DNA damage. *Nature* 407: 777-783.

5. Mocellin S and Nitti D (2008). TNF and cancer: the two sides of the coin. *Front Biosci* 13: 2774-2783.

6. Cory S and Adams JM (2002). The Bcl2 family: regulators of the cellular life-or-death switch. *Nat Rev Cancer* 2: 647-656.

7. Youle RJ and Strasser A (2008). The BCL-2 protein family: opposing activities that mediate cell death. *Nat Rev Mol Cell Biol* 9: 47-59.

8. Matsuyama S, Llopis J, Deveraux QL, et al. (2000). Changes in intramitochondrial and cytosolic pH: early events that modulate caspase activation during apoptosis. *Nat Cell Biol* 2: 318-325.

9. Brown GC (2007). Nitric oxide and mitochondria. *Front Biosci* 12: 1024-1033.

10. Krieser RJ and White K (2002). Engulfment mechanism of apoptotic cells. *Curr Opin Cell Biol* 14: 734-738.

11. Riedl SJ and Salvesen GS (2007). The apoptosome: signalling platform of cell death. *Nat Rev Mol Cell Biol* 8: 405-413.

12. Herceg Z and Wang ZQ (2001). Functions of poly(ADP-ribose) polymerase (PARP) in DNA repair, genomic integrity and cell death. *Mutat Res* 477: 97-110.

13. Logue SE and Martin SJ (2008). Caspase activation cascades in apoptosis. *Biochem Soc Trans* 36: 1-9.

14. Nicholson DW (2000). From bench to clinic with apoptosis-based therapeutic agents. *Nature* 407: 810-816.

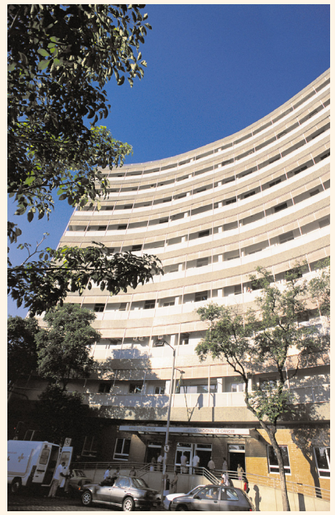
15. Selivanova G and Wiman KG (2007). Reactivation of mutant p53: molecular mechanisms and therapeutic potential. *Oncogene* 26: 2243-2254.

16. Zheng TS (2001). Death by design: the big debut of small molecules. *Nat Cell Biol* 3: E43-E46.

17. Altucci L, Rossin A, Raffelsberger W, et al. (2001). Retinoic acid-induced apoptosis in leukemia cells is mediated by paracrine action of tumor-selective death ligand TRAIL. *Nat Med* 7: 680-686.

CANCER INSTITUTE PROFILE:
National Cancer Institute of Brazil (INCA)

The National Cancer Institute of Brazil (INCA) is the branch of the Ministry of Health responsible for formulating and ensuring the development of cancer control actions across the Brazilian territory. Throughout its 70 years of existence, the INCA has been a landmark in terms of cancer control in Brazil by implementing actions in strategic areas such as prevention, early detection, human resources development, research, surveillance, information and healthcare through SUS, the Brazilian National Unified Health System.



In 2005, INCA launched a new National Cancer Control Policy that considers cancer a public health problem, in compliance with international recommendations. The management of the disease should address early diagnosis and prevention, rather than focussing on the treatment of the advanced stages. The Institute has been developing a Cancer Control Network, where governmental and non-governmental organisations work in association with a purpose: to reduce cancer incidence and mortality, and to ensure the best possible quality of life to patients undergoing treatment.

website: http://www.inca.gov.br/english

3.5 Invasion and Metastasis

Summary

> Metastasis results from the spread of tumour cells from their original location to other organ sites; metastatic disease is the main cause of death from cancer

> The organ distribution of metastases depends upon the type and location of the primary tumour and the route of dissemination of metastatic cells.

> The formation of metastasis involves a series of steps during which cancer cells leave the original tumour, enter lymph or blood circulation, survive and migrate, and colonize distant organs; this complex process is driven by genetic and epigenetic changes.

> Metastasis may develop from a small number of "cancer stem cells" which can change shape and properties to disseminate into the organism and adapt to the conditions of different organs

> Treatment of metastasis often combines local therapy aimed at removing or neutralising the metastases, and systemic therapy aimed at destroying micrometastases as well as preventing the formation of additional ones

The ability of tumour cells to spread from their original location to invade and colonise distant organ sites is the main feature that distinguishes benign from malignant cancers. Metastatic disease is also the major cause of death from cancer. As long as the tumour remains confined to one specific location, it remains curable provided it can be removed surgically and that the tumour does not irreversibly destroy the function of a vital organ. Once tumour cells start to spread into the organism, however, they become more difficult to control. First, they may reach distant organ sites and form secondary tumours, called metastases. Second, the tumour cells that are capable of spreading have acquired special properties that make them more resistant to treatments and to destruction by the immune system. Therefore, detection of distant spread and metastases is often an indicator of poor prognosis for the patient. This is reflected in the TNM classification system, which provides a universal, simple system to describe the anatomic extent of a cancer (Table 3.5.1).

The term "metastasis" comes from the combination of two Greek words, "meta", meaning "next" or "beyond", and "stasis", meaning "location" or "position". A metastasis is therefore a misplaced lesion, a lesion that has changed position. The term "invasion" refers to the process by which a tumour can form metastases: it consists of a series of steps by which growing tumours disturb the architecture of the tissue where they arise, take the space and place of normal cells, infiltrate into healthy areas and cross vessel barriers to enter the lymphatic or blood circulation. Loco-regional invasion is in itself a factor of poor prognosis, but not as poor as distant metastases. A locally invasive (N1) tumour would normally not be counted as metastatic disease. It may remain treatable using the same protocols as non-metastatic, localised lesions, without the need for extended whole-body treatments.

For a long time, metastatic disease has been considered as the ultimate step in cancer progression. It was thought that the most transformed cancer cells acquire the capacity to become independent from their organ of origin, to invade other organs, to travel in the body and to form colonies. This view is challenged by recent discoveries on cancer stem cells, which are capable of self-renewal and also of generating daughter cells that evolve into different cell shapes and phenotypes depending upon interactions with their environment [1]. Thus, in a given cancer, several lines of cancer cell development may exist. Most cells may develop in a certain direction, which preserve traits of the general architecture of the tissue where they arise. These cells contribute to the growing local tumour mass. Other cells may assume different shapes and roles and undergo morphological transitions that allow them to cross barriers and invade other organs. These are the metastatic cells [2]. It follows that metastatic cells can occur even in very small, apparently "early" cancer lesions. This may explain why over 10% of patients presenting to oncology clinics may have metastases without an identified primary tumour. These patients are said to have Cancer of Unknown Primary origin (CUP) or Unknown Primary Tumours (UPT) [3]. In these patients, the primary tumour may be so small that it is not detectable even using sophisticated methods. Yet these occult primary tumours can be the site of formation of cells with a high capacity to spread to other organs and form aggressive colonies.

T = primary tumour	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma in situ
T1	Tumour invades submucosa
T2	Tumour invades muscularis propria
T3	Tumour invades through muscularis propria into subserosa or into non-
	peritonealized pericolic or perirectal tissues
T4	Tumour directly invades other organs or structures and/or
	perforates visceral peritoneum
N = regional lymph nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1 to 3 regional lymph nodes
N2	Metastasis in 4 or more regional lymph nodes
M = distant metastasis	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Table 3.5.1 *TNM classification of cancer of the colon and rectum*

Organ preference of metastases

The organ distribution of metastases depends upon the type and location of the primary tumour (Table 3.5.2) [4]. In many instances, it is determined by the route of dissemination of metastatic cells. For example, sarcomas tend to metastasise to lungs because of the venous drainage of muscles; colon carcinoma cells enter the portal circulation thereby gaining access to the liver. Invasion usually starts in the first array of capillaries encountered within the tumour or in the immediate tumour neighbourhood. Invasion also develops in the first lymph nodes encountered as cancer cells leave their tissue of origin. Metastatic cells can hop from node to node through lymphatic channels and accumulate into draining nodes, from where they can flow into efferent lymph nodes towards many organs. Lymphatic channels may present less of a challenge to tumour cell entry than capillaries because of their scanty basement membrane. The propensity of a tumour cell to invade lymphatic vessels or through capillaries depends upon its ability to adhere to specific structures, such as reticular fibres in the subcapsular sinus of draining nodes or endothelial cells that line blood vessels. Interactions with these structures are dependent upon the types of adhesion molecules expressed by tumour cells, in particular the integrins.

The distribution of metastases is not only a matter of route of dissemination. The most common places for the metastases to develop are the liver, the brain, the bones, the lung and the adrenal glands. There is a propensity for certain tumours to seed in particular organs. This was first recognised by Stephen Paget in 1889, based on his observation from autopsies of 700 women who died from metastatic breast cancer. He formulated the "seed and soil" hypothesis, proposing that specific cancer cells (the seed) have an affinity for certain organs (the soil) [5]. For example, breast cancer cells that have a physiological need for calcium selectively metastasise to bone because they can use it as an abundant source of calcium. In general, cancer cells tend to metastasise to organs where blood and energy supplies are abundant (such as liver or lung) or that are separated from the immune system by a physical barrier (such as the brain).

Primary tumour	Site of metastasis
Bronchial cancer	Adrenal (often bilateral)
Breast ductal carcinoma	Liver
Breast lobular carcinoma	Diffuse peritoneal seeding
Breast	Bone, ovary
Lung	Brain
Ocular melanoma	Liver
Prostate	Bone
Melanoma	Brain

Table 3.5.2 *Site of metastasis of common cancers*

Detecting these metastases is a major challenge, as it is virtually impossible to explore all possible organ locations in sufficient detail. Advances in medical imaging techniques are making it possible to locate lesions of very small size, thus lowering the threshold for detection of metastases [6]. Current research is also focussing on detecting single, disseminating cancer cells in lymphatic or blood vessels, and on identifying patterns of gene expression in primary tumours that may predict their propensity to form metastases.

Molecular biology of metastasis

The metastasic process consists of a series of steps during which cancer cells leave the original tumour site, enter lymph or blood circulation (a process called intravasasion), survive and migrate, and extravasate to colonise distant organs. This complex process implies that candidate metastatic cells acquire many properties through genetic or epigenetic changes [7, 8]. On the basis of their level of participation in the metastatic process, Nguyen and Massagué have distinguished three general classes of metastasis genes: metastasis initiation, metastasis progression, and metastasis virulence (Figure 3.5.1) [9]. Metastasis initiation genes are those that provide an advantage in primary tumours, paving the way for tumour cells to enter the circulation. Metastasis progression genes are those that fulfil certain rate-limiting functions in primary tumour growth, and other specific functions in metastatic colonisation. Metastasis virulence genes are those that provide a selective advantage in secondary sites but not in the primary tumour, thus participating in meta-

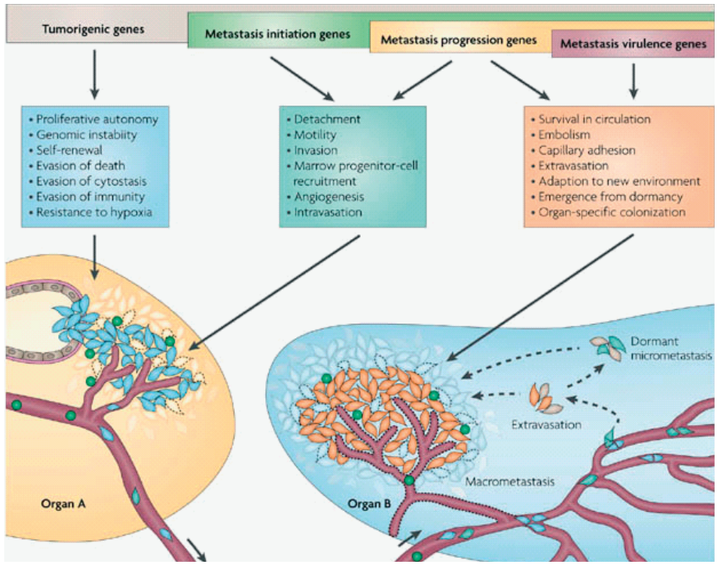


Fig. 3.5.1 *A general view of the sequence of biological events involved in the formation of metastases [9]*

static colonization but not in primary tumour development. However, before becoming candidates to metastasis, malignant cells must fulfil a number of tumorigenic conditions (see *Molecular hallmarks of cancer*, Chapter 3.1): they must be capable of unlimited proliferation, of evasion from the environmental constraints of their tissue of origin, and of attracting a blood supply through the formation of new capillaries and blood vessels, a process called angiogenesis [10]. As tumours grow, they must adapt and respond to environmental pressures such as those exerted by the immune response, the lowering oxygen tension and the increased acidic environment [11]. Such capacities are acquired during tumour initiation and local development, but must remain active throughout the development of metastatic disease, since they are critical for cancer cells to survive during their spread into the organism and during the development distant colonies.

Metastasis initiation. Acquisition of metastatic potential requires that candidate cells break away from the primary tumour and attach to and degrade the protein structures that make up the surrounding extracellular matrix (ECM). Most solid tumours arise from epithelial cells that are normally bounded by basement membranes which separate them from the underlying stroma and mesenchymal compartments. Breaching the basement membrane is the first step in the transition from in situ carcinoma to invasive, potentially metastatic cancer [12]. The basement membrane is composed of a complex of structural proteins including Collagen IV (the major component), laminin, entactin, and heparan sulfate proteoglycans. Interactions of tumour cells with basement membranes and ECM components comprise two critical phase phases: adhesion and matrix dissolution.

Adhesion. Epithelial cells are normally polarised and attached to each other via different types of cell-to-cell junctions, such as tight junctions, adherens junctions and desmosomes, as well as through intercellular adhesion molecules such as E-Cadherin. Initiation of metastasis requires releasing cells from cell-to-cell contacts that keep them into their proper place in the epithelium. Thus, cancer cells usually demonstrate multiple changes in the expression of cell adhesion components [13]. E-Cadherin, in particular, is a frequent target for genetic or epigenetic alterations that down-regulate its function, which may be considered as a tumour suppressor gene. First, its constitutive mutation predisposes to some forms of cancer (such as gastric cancer) and its re-introduction in metastatic cancer cells quench their invasive potential. Secondly, it interacts with beta-Catenin, an important oncogene, and provides a signalling connection between structural cell adhesion and cell proliferation. Loss of E-Cadherin frees beta-Catenin from its anchor at the cell membrane and makes it available for translocation into the nucleus, where it can activate transcription factors involved in stimulating cell proliferation.

Epithelial cells entertain contacts with the basal membranes and with the ECM through many other classes of molecules. Among them, integrins deserve special mention as changes in their expression patterns may have a profound influence on enabling cancer cells to adapt to changes in their micro-environment, a pre-requisite for successful migration. Integrins are cell surface receptors that mediate a dual, signalling and adhesion function [14]. Among the ligands of integrins are fibronectin, vitronectin, collagen, and laminin. Integrins are heterodimeric proteins containing two distinct chains, α (alpha) and β (beta). In mammals, 19 γ and 8 β subunits have been characterised. Through different combinations of alpha and beta subunits, about 24 unique integrins can be generated. The molecular mass of the integrin subunits can vary from 90 to 160 kDa, with the intracellular domain representing only a minor part (40 to 70 amino-acids). Integrins couple the ECM outside the cell to the intracellular cytoskeleton. This bond ensures that the cell can tightly adhere to ECM components without being sheared and ripped away by movements of the ECM. Many differences in integrin expression between benign and malignant cells have been documented. They allow cells to develop different binding and adhesion properties, enabling them to detach from their original support and to seek novel adhesion points on ECM components as well as on cells lining blood or lymphatic vessels.

Other cell adhesion molecules implicated in cancer progression and metastasis include members of the immunoglobulin supergene family such as ICAM-1, ICAM-22, VECAM and PECAM. The latter are upregulated on activated endothelial cells, and can interact with integrins on leucocytes or circulating tumour cells to facilitate their extravasation. CD44 is an adhesion molecule normally present both at the surface of epithelial cells and of lymphocytes. On normal cells, however, CD44 is expressed as different splicing variants in both cell types. A change in splicing patterns from "epithelial-type" to "haematopoietic-type" may assist in carcinoma cell dissemination by providing recognition signals that lymphocytes normally use during their homing to specific tissues [15,16]. Thrombospondin mediates adhesion between circulating tumour cells, platelet and endothelial cells, promoting embolisation (vessel obstruction). This induces endothelial cells to retract, exposing the vessel's basement membrane and providing tumour cells an access for adhering to exposed proteins [17].

Matrix dissolution. Invasive cancer cells show increased expression of many enzymes, as well as decreased expression of their regulators, involved in the degradation of components of the ECM, thus physically opening up breaches that facilitate cancer cell dissemination [8]. One important group of such enzymes is the matrix metalloproteinases (MMP). The MMP family contains a diverse group of enzymes with different substrate preference (collagenase, gelatinase, stromelysin, proenzyme). All family members comprise a leader domain, a propeptide domain and a highly conserved catalytic domain containing a zinc atom involved in substrate binding. They play important roles during normal development and morphogenesis, and their activities are tightly regulated. Activation depends upon cleavage of the leader domain and is regulated by endogenous MMP inhibitors, which include a-2 macroglobulin and tissue inhibitors of metalloproteinases (TIMPs). An imbalance between MMPs and naturally occurring MMP inhibitors may cause an excess of extracellular matrix destruction, allowing cancer cells to invade surrounding tissues and metastasise. Two of the most studies MMPs are MMP-2 and -9 (gelatinase A and B, respectvely). There is clear evidence for increased levels of active forms of MMP-2 and/or 9 in bladder, breast, colon, protaste, lung, oesophageal and gastric cancer tissues. This increased expression can take place in cancer cells and/or in surrounding normal stromal cells, indicating that cancer cells can somehow induce stromal cells to secrete factors that facilitate migration, invasion and, ultimately, metastasis. Urokinase plasminogen activator (uPA) is also frequently upregulated in cancer. It controls the synthesis of plasmin, which degrades laminin and also activates gelatinases. Thus, upregulation of these enzymes in cancer can lead to proteolytic cascades that degrade the basement membranes and components of the stroma [18].

Besides their direct role in degrading ECM components, MMPs are also indirectly involved in promoting metastasis through their roles in angiogenesis. The formation of capillary sprouts is a physiological process that requires localised proteolysis of the stroma (mediated in part by MMP-2 and MMP-9 in addition to uPA). MMP-9 plays a role in the "angiogenic switch" that occurs during cancer progression by releasing VEGF by sequestration in the ECM. Furthermore, these proteases also contribute to sustained tumour growth by the ectodomain cleavage of membrane-bound pro-forms of growth factors, and the release of peptides which are mitogenic and chemotactic for cancer cells.

Metastatic dissemination. Dissemination starts when aggressive tumour cells enter the bloodstream through the newly formed vasculature that they have attracted. This process is facilitated by the particular, incomplete and leaky structure of the blood vessels that is typical of many cancers. Intravasation is also enhanced by an epithelial-to-mesenchymal transition that confers to carcinoma cells plasticity and added motility similar to embryonic cells [19,20]. Although the rate of malignant cell shedding in the bloodstream generally increases with tumour size and grade, dissemination can occur from the early stages of the primary tumour. Only a minute proportion of cells that enter blood vessels or lymphatics will ultimately generate metastases. Indeed, disseminating cells are faced with multiple challenges. Among those, the most significant ones are the capacity to escape cell death due to the detachment of their support (a process called "anoikis", from the Greek word "oikos", meaning "home", preceded by the negative Greek prefix alpha), to escape recognition and destruction by the immune system and to recruit partners that facilitate their circulation and extravasation, including in particular the formation of partner aggregates [21]. Adhesion molecules that mediate attachment to capillary walls play a critical role in the dissemination process.

Numerous innate and adaptive immune effector cells and molecules participate in the recognition and destruction of cancer cells, a process that is known as cancer immunosurveillance. Disseminating cancer cells avoid immunosurveillance through many mechanims that can classified into two broad categories: the outgrowth of poorly immunogenic tumour-cell variants (immunoselection) and the subversion of the immune system (immunosubversion). The former category include a series of mechanisms by which disseminating cancer cells conceal or down-regulate antigens and recognition molecule complexes at their surface. The latter category include the production of sets of cytokines that down-regulate immune responses and the stimulation of regulatory T-cells that induce a form of immune tolerance towards cancer cells. Metastasis appears to correlate with changes in the immunogenic properties of tumour cells.

Metastatic colonisation. The process by which disseminating cancer cells leave the bloodstream to enter the parenchyma of another organ is

termed extravasation. Metastatic cells extravasate by breaching the capillaries in which they are embedded, either by vascular-remodelling events that allow migration across the capillary wall or as a result of mechanical disruption of capillaries by expanding tumour emboli. On entry into another organ, tumour cells are confronted with a different microenvironment in which they must survive, develop, and eventually expand in the same way as they did in their organ of origin. To help them in the process of establishing a new "home" in their adoptive tissue, cancer cells recruit bone-marrow-derived progenitor cells and other local cells that provide a permissive "niche" for metastasis [22]. Once metastatic cells are established, active colonisation proceeds through the recruitment of organ-specific components of the tumour microenvironment, such as the activation of bone-resorbing osteoclasts by breast cancer cells during osteolytic metastasis [23]. Full metastatic colonisation can occur by immediate growth of cancer cells upon their extravasation, or after a prolonged period of micrometastatic dormancy.

Epidermal-mesenchyme transition and the concept of metastatic cancer stem cells

Most solid tumours start with an epithelial phenotype. However, during tumour progression, this phenotype becomes altered and some cells undergo a transition to assume a more mesenchymal phenotype. These mesenchymal-like cancer cells acquire a high migratory capacity and may represent one of the main forms into which cancer cells can disseminate into the organism. Conversely, at the time of extravasation, these cells undergo a reverse mesenchymal-epithelial transition which regenerates high proliferative status and allows formation of a metastasis with a morphology that resembles the primary tumour. It has emerged that this process closely resembles Epithelial-Mesenchyme Transition (EMT), a mechanism that is vital for morphogenesis during embryonic development [20,24]. During gastrulation in mammals, cells migrate from primitive epithelial-like structures to spatially reorganise and form one of the three main embryonic layers, the mesoderm. In this process, epithelial cells acquire fibroblast-like properties, show reduced adhesion to ECM and increased mobility, exactly like metastatic cancer cells.

EMT is essential for many morphogenetic events such as organogenesis, wound healing, tissue remodelling and heart development. A landmark of EMT is the loss of E-Cadherin expression, a phenomenon that is common in many epithelial tumours. However, E-Cadherin expression remains detectable in many invasive tumours, raising questions about the whether EMT is a general phenomenon in advanced cancer, or a property assumed only by a limited number of cells. This paradox has been largely resolved by the observation that, in cancer, EMT could generate cells with properties of stem cells, including in particular self-renewal through asymetric division. In normal tissues, stem cells are present only in proliferative areas such as the basal layer of squamous mucosa or crypts of glandular mucosa. Such stem cells become embedded within small, early cancer masses as static cancer stem cells (SCSC) [2]. These SCS are, to a large extent, responsible for sustained production of daughter cancer cells which assume an epithelial phenotype and constitute the bulk of the tumour mass. In certain conditions, SCSC can undergo EMT and become mobile, migrating cells while retaining their capacity for self renewal. The signals that trigger this EMT may correspond to a form of disturbed wound healing response generated by the breakdown of basal membrane and the increased severity of the tissue lesion caused by the tumour.

Mobile, migrating cancer stem cells (MCSC) may actually represent only a small fraction of the cells that are shed in the bloostream. However, their stem status endows them with the capacity to survive during migration as well as to re-differentiate into epithelial-like cells upon extravasation and colony formation into distant organs. Upon entry into the stroma of a target organ, MCSC may locally recruit normal fibroblasts and other cell types to constitute an appropriate niche for undergoing mesenchyme-epithelial transition and giving rise to rapidly growing metastases. It follows from this model that two critical characteristics of mobile cancer stem cells are the cyclical activation and inhibition of expression of genes involved in EMT, as well as the capacity to recruit normal, non-cancer cells to become essential partners in the metastatic process.

Treatment of metastatic cancer

The presence, number and organ location of metastases are critical parameters in selecting appropriate therapeutic methods. In most instances treatment will consist of a combination of local therapy aimed at removing or neutralising the metastases, and systemic therapy aimed at destroying micrometastases as well as preventing the formation of additional ones [25] [26]. The main local treatments are surgery and radiosurgery (that is, the use of 3-dimensional radiation treatment to deliver high radiation doses in a very delimited area of the body). Systemic treatments include chemotherapy and radiation therapy (which are active against both primary and metastatic cancer cells) as well as biological and, when appropriate, hormone therapy. Biological therapies may use monoclonal antibodies that target cancer cells, or factors that block processes involved in metastasis such as angiogenesis. Current approaches for drug development are focusing on the neutralisation of specific factors involved in invasion and metastasis, such as metalloproteinases or integrins.

The choice of treatment depends upon many factors, principally the type of cancer, the size, number and localisation of metastases, the general condition and age of the patients, and the treatments the patient has already received in the case of secondary metastatic cancer. In many instances, available treatments are not capable to provide a complete cure for metastatic cancer, although they can induce remission, improve quality of life, and significantly increase survival after diagnosis. Finding new, efficient and better tolerated treatments for metastatic cancer is a major challenge in current cancer research and clinical trials.

WEBSITES

How cancer grows and spreads: An interactive, animated presentation that shows how cancer progresses through the 14 stages of a typical cancer. http://www.childrenshospital.org/research/_cancer/index.html

Metacancer: resources and support for metastatic cancer survivors and their caregivers. http://www.metacancer.org/index.php

REFERENCES

1. Li F, Tiede B, Massague J, et al. (2007). Beyond tumorigenesis: cancer stem cells in metastasis. *Cell Res* 17: 3-14.

2. Brabletz T, Jung A, Spaderna S, et al. (2005). Opinion: migrating cancer stem cells - an integrated concept of malignant tumour progression. *Nat Rev Cancer* 5: 744-749.

3. Freudenberg LS, Rosenbaum-Krumme SJ, Bockisch A, et al. (2008). Cancer of unknown primary. *Recent Results Cancer Res* 170: 193-202.

4. Chambers AF, Groom AC, MacDonald IC (2002). Dissemination and growth of cancer cells in metastatic sites. *Nat Rev Cancer* 2: 563-572.

5. Jodele S, Blavier L, Yoon JM, et al. (2006). Modifying the soil to affect the seed: role of stromal-derived matrix metalloproteinases in cancer progression. *Cancer Metastasis Rev* 25: 35-43.

6. Riethdorf S, Wikman H, Pantel K (2008). Review: Biological relevance of disseminated tumor cells in cancer patients. *Int J Cancer* 123: 1991-2006.

7. Yokota J (2000). Tumor progression and metastasis. *Carcinogenesis* 21: 497-503.

8. Bogenrieder T and Herlyn M (2003). Axis of evil: molecular mechanisms of cancer metastasis. *Oncogene* 22: 6524-6536.

9. Nguyen DX and Massague J (2007). Genetic determinants of cancer metastasis. *Nat Rev Genet* 8: 341-352.

10. Hanahan D and Weinberg RA (2000). The hallmarks of cancer. *Cell* 100: 57-70.

11. Fidler IJ, Singh RK, Yoneda J, et al. (2000). Critical determinants of neoplastic angiogenesis. *Cancer J* 6 Suppl 3: S225-S236.

12. Engbring JA and Kleinman HK (2003). The basement membrane matrix in malignancy. *J Pathol* 200: 465-470.

13. Glukhova M, Deugnier MA, Thiery JP (1995). Tumor progression: the role of cadherins and integrins. *Mol Med Today* 1: 84-89.

14. Moschos SJ, Drogowski LM, Reppert SL, et al. (2007). Integrins and cancer. *Oncology (Williston Park)* 21: 13-20.

15. Jothy S (2003). CD44 and its partners in metastasis. *Clin Exp Metastasis* 20: 195-201.

16. Wai PY and Kuo PC (2008). Osteopontin: regulation in tumor metastasis. *Cancer Metastasis Rev* 27: 103-118.

17. Kazerounian S, Yee KO, Lawler J (2008). Thrombospondins in cancer. *Cell Mol Life Sci* 65: 700-712.

18. Duffy MJ, McGowan PM, Gallagher WM (2008). Cancer invasion and metastasis: changing views. *J Pathol* 214: 283-293.

19. Christiansen JJ and Rajasekaran AK (2006). Reassessing epithelial to mesenchymal transition as a prerequisite for carcinoma invasion and metastasis. *Cancer Res* 66: 8319-8326.

20. Guarino M, Rubino B, Ballabio G (2007). The role of epithelial-mesenchymal transition in cancer pathology. *Pathology* 39: 305-318.

21. Simpson CD, Anyiwe K, Schimmer AD (2008). Anoikis resistance and tumor metastasis. *Cancer Lett* 272: 177-185.

22. Psaila B, Kaplan RN, Port ER, et al. (2006). Priming the 'soil' for breast cancer metastasis: the pre-metastatic niche. *Breast Dis* 26: 65-74.

23. Kaplan RN, Psaila B, Lyden D (2006). Bone marrow cells in the 'pre-metastatic niche': within bone and beyond. *Cancer Metastasis Rev* 25: 521-529.

24. Moustakas A and Heldin CH (2007). Signaling networks guiding epithelial-mesenchymal transitions during embryogenesis and cancer progression. *Cancer Sci* 98: 1512-1520.

25. Fidler IJ (2002). Critical determinants of metastasis. *Semin Cancer Biol* 12: 89-96.

26. Fidler IJ, Kim SJ, Langley RR (2007). The role of the organ microenvironment in the biology and therapy of cancer metastasis. *J Cell Biochem* 101: 927-936.

3.6 Emerging Technologies

Summary

> Proteomics is a general term that covers a variety of conceptually related technologies targeting protein expression and function, often in high-throughput formats. Proteomics provides a window to biological function and regulation that is strongly complementary to those provided by genomics and expression profiling

> Micro-RNAs (miRNAs) and small interfering RNAs (siRNAs) are small, double-stranded RNAs that bind to messenger RNAs (mRNAs) and regulate their expression and/or their degradation. si-RNAs have become an extremely powerful research tool for understanding gene function and are thought to have important therapeutic potential

> High density array technologies have been steadily increasing in sophistication and assay density since the mid-1990s. Currently, the three main applications of these technologies are expression profiling (used to measure the expression of many genes simultaneously), array CGH (used to search for DNA duplications or deletions in tumor samples at high resolution), and high-density SNP genotyping (used for genome-wide SNP association studies)

Proteomics

Proteomics is the study of the proteome, the protein complement of the genome in a biological system at a given point in time. The terms proteomics and proteome were first coined in the early 1990s [1], and today this rapidly developing field is employed to study protein localisation, differential expression, post-translational modifications, protein interactions, protein structure and splice variants. Proteins are the main effectors of biological functions, and the knowledge gained from proteomics studies is invaluable for biomarker and drug discovery.

The proteome is dynamic; protein levels depend not only on the corresponding transcript levels but also on a multitude of translational controls and on regulation of protein degradation [2]. Proteomics, in contrast to genomics, also has the potential to explore large-scale measurements of protein modifications and their quantitative changes following cell perturbations, which are often just as important for protein activity as protein expression levels [3].

Completion of the Human Genome Project was critical for the large-scale development of proteomics not only because the genome sequence provides a full list of possible protein coding sequences, but also because the Genome Project changed the paradigm for large-scale biology projects. Just as the human genome project spawned many daughter projects, the Human Proteome Organization (HUPO) has launched initiatives on human organs and cell systems, established standards, and created antibody (Human Protein Atlas) and mouse models to overcome current limitations of proteomics.

The rapid development of proteomics as a field has depended upon substantial technological advances in many specific areas including gel-based or gel-free protein separation and sequencing techniques (shotgun sequencing), protein chips (SELDI-MS, protein-, tissue-, and antibody arrays), mass spectrometry (MS) (sensitivity, resolution, speed and throughput), and bioinformatics [4,5]. Currently there is no technique that can cover the large number of single proteins contained in a complex sample and the wide dynamic range in the abundance of the individual protein species [6], but large-scale studies of protein complexes are emerging that show how the cell organises to deliver function at the molecular level.

Proteomics projects generate enormous quantities of data, and public domain databases have been developed to manage and assemble this information. Examples of existing databases include PRIDE (http://www.ebi.ac.uk/pride/), PeptideAtlas (http://www.peptideatlas.org/), and IMEx (http://imex.sourceforge.net/index.html). A critical consequence of the use of these public databases is that raw data are released after publication of manuscripts so that other investigators can re-analyse original data or incorporate the original data into new studies.

Proteomics provides an attractive approach to study complex diseases including cancer. Clinical proteomics has focused on the discovery of diagnostic, prognostic and predictive disease biomarkers with a particular focus on biomarkers that can be assayed from easily available samples such as blood or urine. However, disease-driven marker discovery (or marker validation) studies are in many respects more difficult than basic science studies. The main difference is that basic science studies can proceed from relatively small numbers of samples gathered under carefully controlled laboratory conditions, while marker validation studies require large numbers of samples gathered from human subjects under clinical conditions. For example, many studies have reported serum peptide signatures revealed by mass spectrometry that appear to distinguish between cancer free controls and individuals with prostate cancer, breast cancer, lung cancer, colon cancer, etc. (for examples, see [7-11]). However, none of these signatures yet enjoy the level of replication that has been achieved by, for example, mRNA expression profiling of breast tumours. The difficulty in extracting replicable disease-associated serum proteomics profiles can in part be attributed to the intrinsic difficulty of the research goal. However, that difficulty also raises challenges, including creation of biological resource centres that contain large numbers of well-documented biosamples of the correct type and in the correct state of physical preservation to support specific proteomics studies, validation of candidate biomarkers in large well-characterised cohorts (dependent on biological resource centres), and reduction of validated proteomics-based bioassays to robust and efficient procedures that will work in the clinic.

micro-RNAs

In 1993, Lee and Ambros discovered that lin-4, a gene known to control the timing of *C. elegans'* larval development does not code for a protein but instead produces a pair of small RNAs [12]. They demonstrated that these small lin-4 RNAs base pair with the 3' untranslated region of the lin-14 mRNA and result in translational repression of this mRNA. The importance of this discovery did not become evident until several years later, when other small RNA molecules with regulatory functions were found [13]. Since then, about 4000 small regulatory RNAs, termed microRNAs (miRNAs), have been identified in a variety of animals, plants, and viruses and have been deposited in publicly available databases, such as miRBase (http://microrna.sanger.ac.uk/).

It is clear now that miRNAs together with small interfering RNAs (siRNAs) are members of a widespread class of small, evolutionarily conserved, non-coding, double-stranded RNAs (dsRNAs) with regulatory functions. miRNA and siRNA differ in terms of their origin and processing. Once in their single-strand form, either can regulate the expression of downstream genes by binding to a target messenger RNA (mRNA) at a specific complementary target sequence and guide the targeted mRNA to the double stranded RNA-induced silencing complex (RISC), responsible for its cleavage or its translational inhibition (Figure 1). Up to 30% of protein-coding genes may be regulated by miRNA [14], including transcription factors, oncogenes and tumour suppressor genes. Therefore miRNAs play an essential role in multiple biological processes. Moreover, miRNA expression has been shown to be deregulated in a number of cancers [15-17].

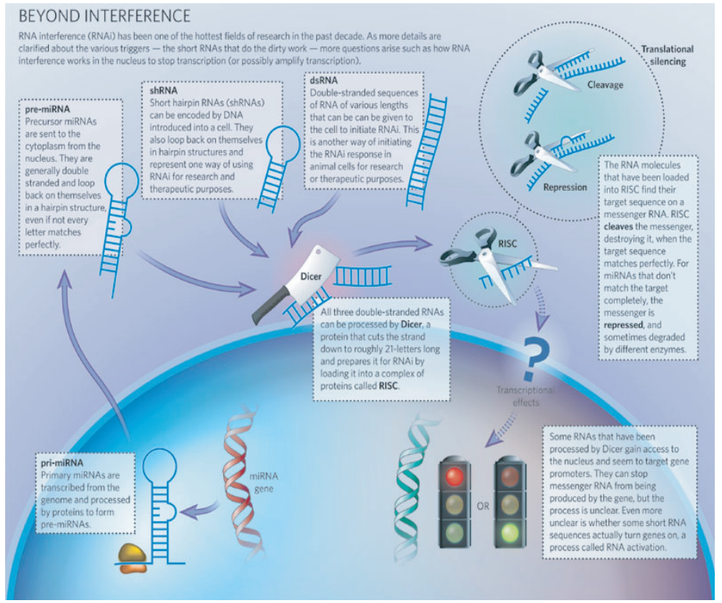


Fig. 3.6.1 *Erika Check (2007) Nature 448, 855-858*

It is clear now that miRNAs together with small interfering RNAs (siRNAs) are members of a widespread class of small, evolutionarily conserved, non-coding, double-stranded RNAs (dsRNAs) with regulatory functions. miRNA and siRNA differ in terms of their origin and processing. Once in their single-strand form, either can regulate the expression of downstream genes by binding to a target messenger RNA (mRNA) at a specific complementary target sequence and guide the targeted mRNA to the double stranded RNA-induced silencing complex (RISC), responsible for its cleavage or its translational inhibition (Figure 1). Up to 30% of protein-coding genes may be regulated by miRNA [14], including transcription factors, oncogenes and tumour suppressor genes. Therefore miRNAs play an essential role in multiple biological processes. Moreover, miRNA expression has been shown to be deregulated in a number of cancers [15-17].

siRNAs are easily designed, synthesised in vitro, and built into expression cassettes that can be used to regulate the expression of experimenter-selected target genes in a laboratory setting. Consequently, siRNA have been used as powerful experimental tool to explore gene function. However, it is becoming more and more evident that the potential applications of RNA interference go much further. Transcriptional profiling using genomic microarrays and beads have enabled the discovery of numerous miRNAs that are differentially expressed in normal tissues compared with tumours and are associated with cancer development, diagnosis, and prognosis [17]. miRNAs have also become targets for development of anticancer gene therapy; antisense molecules that can inhibit miRNA activity are currently being tested for their anti-tumour activity [18].

The discovery of viral encoded microRNAs indicates that viruses also use this mode of gene regulation. Viral miRNAs seem to play an important role in regulating both the viral life cycle and the interaction between viruses and their hosts [19,20]; therefore microRNAs may act as critical modulators of viral mediated oncogenesis. In addition, viral gene-specific siRNAs are theoretically very promising antiviral inhibitors and have been examined in a broad range of medically important viruses.

Without a doubt, the phenomenon of RNA interference has been harnessed to create enormously powerful research tools. RNA interference has clear potential to become an important partner in fighting cancer. Future applications of miRNA-related technologies will become even more powerful as new miRNA targets are identified and miRNA-related regulatory mechanisms better understood.

High density array technologies

Natural deoxyribonucleic acid (DNA) molecules are mixed polymers of the 4 deoxyribonucleotides deoxyadenosine (dA), deoxycytidine (dC), deoxyguanosine (dG) and thymidine (dT). Single-stranded DNA molecules have the very useful characteristic that they hybridise with DNA molecules of complementary sequence to form stable double stranded DNA duplexes. In these duplexes, dA pairs with dT and dC pairs with dG; the hybridisation, or base pairing, is sequence-specific. Therefore, if you know the sequence of one DNA strand, you know the sequence of its complement.

Complementary base pairing is fundamental to the biological processes of DNA replication, transcription of DNA into RNA, and translation of RNA to make protein. In addition, complementary base pairing has been harnessed to create an enormous number of molecular biology protocols. One family of these protocols is high-density array hybridisation, which arose from the earlier protocol of filter hybridisation. The key concept behind filter hybridisation is that a mixed population of DNA molecules can be fractionated, denatured to make single-stranded DNA, and then affixed to a solid support such as a nitrocellulose filter in a way that preserves positional information from the fractionation. If a substantially pure preparation of labelled probe (radioactive or fluorescent or biotinylated, etc.) is then hybridised in solution to the filter, the probe will hybridise to and be positionally concentrated by its complement on the filter. The signal from the label will then reveal the position of its complement on the filter; under suitable conditions, the signal may also reveal the quantity of its complement on the filter. This is the idea behind such venerable procedures as the Southern blot, northern blot, and dot blot.

More recently, the logic behind these protocols has been reversed. That is, a substantially pure population of single-stranded DNA molecules of a specific sequence can be affixed to a specific position or address on a solid support, constituting "a feature", and then allowed to hybridise in solution to a mixed population of many labelled single-stranded DNA molecules. During the hybridisation, the DNA sequence at the feature will find its complement (its target) in the mixed population of labelled DNAs and positionally concentrate the labelled target at its address on the solid support. The signal from the label will then reveal the presence or absence of the target in the mixed population and, under suitable conditions, will also reveal the relative quantity of the target present in the population. Because the sequence of each feature on the solid support is known, the address of the feature encodes the identity (i.e. gene, allele, etc.) of the target to which it hybridises. Packing large numbers of distinct features onto a small solid support is the idea behind high-density array hybridisation.

Over the last 15 years, a number of technical development-oriented labs and biotechnology companies have competed to develop useful high-density array hybridisation applications. Most of the popular applications have fallen into one of four categories: expression profiling, array comparative genome hybridisation (array CGH), genome-wide SNP genotyping and viral serotyping.

For expression profiling, the DNAs affixed at the features on the array are either parts of specific cDNA clones or DNA oligonucleotides that correspond to the sequence of specific RNA transcripts. RNA or cDNA prepared from a particular sample (cell line, tumour, tissue type, etc.) is labelled and then hybridised to the array. After hybridisation, the signal present at each feature of the array provides information about the quantity of the corresponding transcript in the original sample. In principle, multi-gene patterns of gene expression can then be extracted from the expression data and used to group tumours into classes or predict differential treatment responses. One of the early successes of the expression profiling approach was the demonstration that acute myeloid leukemia can be distinguished from acute lymphoblastic leukemia by expression profile alone [21]. A more subtle success has been the stratification of breast cancer into at least four distinct sub-types based on gene expression profiles [22,23].

Comparative genome hybridisation is a procedure for finding DNA copy number changes—amplifications or deletions—in tumour DNA samples. The original CGH strategy was to fluorescently label tumour DNA one colour, label reference genomic DNA a second colour, and then hybridise equal quantities of the two labelled DNAs to a metaphase chromosomal spread. Chromosomal regions that are amplified in the tumour will disproportionately fluoresce in the colour that the tumour DNA was labelled, whereas chromosomal regions that are heterozygously or homozygously deleted in the tumour will disproportionately fluoresce in the colour that the reference DNA was labelled. The drawback of this approach is that the positional resolution provided by hybridisation to metaphase chromosomes is limited to about 20 Mb. To overcome this limitation, various investigators have produced hybridisation arrays where the individual features are fragmented BAC clones, cDNA clones or even long synthetic oligonucleotides. These arrays improve the resolution of array CGH to the level of individual genes or, if oligos are used as probes, even individual exons [24]. Many of the experimental results achieved by expression profiling have been recapitulated by array CGH. For example, Bergamaschi et al recently demonstrated that the breast cancer subtypes identified by expression profiling can also be identified by array CGH [25]. Moreover, array CGH has the advantage over expression profiling that its substrate DNA is much more stable than the RNA required for expression profiling—potentially an important advantage for clinical applications.

Genome-wide SNP association studies (GWA studies) seek associations between common SNPs and risk of one or another disease without having to rely on prior hypotheses of which genes or genetic pathways are involved in the disease. Three trends have merged to make such studies possible: (1) the human SNP haplotype mapping project has mapped and measured disequilibrium between more than 3 000 000 common human SNPs and in so doing showed that genoyping about 500 000 well-selected SNPs captures much of the information present in the full set of 3 000 000 [26]; (2) the total number of features that could be packed on to a high-density DNA hybridisation array increased from the low thousands to several hundred thousand (as of early 2008, more than 1 million), making it possible to genotype a genome-wide representative set of SNPs in a single experiment; and (3) epidemiology research groups have joined into consortia that can assemble series of 5000 or more cases and controls, sufficient to overcome the statistical multiple testing problems inherent in association studies that seek to test hundreds of thousands of independent hypotheses. The combined result has been that in 2007 and 2008, international research consortia announced results from GWA studies in breast cancer, colon cancer, lung cancer and prostate cancer [27-36]. It is also very likely that GWA studies of some of the less common cancers will be completed over the next few years.

Beyond providing irrefutable proof that inheritance of common SNPs does influence the risk of common cancers, what are some of the most interesting results that have emerged from these studies? Perhaps the most intriguing new information has been that SNPs arrayed across a small segment of chromosome 8q, not far from the oncogene MYCC (c-myc), influence the risk of breast cancer, colon cancer, and prostate cancer. A second result has been the finding that that very few SNPs with frequencies of >10% confer odds ratios >1.5. Most of the common risk-SNPs detectable at the scale of GWA study conducted so far confer odds ratios in the range of 1.1–1.2. On one hand, this means that, individually, the risk that they confer is not substantial enough to be medically useful. On the other hand, it may eventually be possible to create polygenic SNP profiles that provide sufficiently informative risk prediction to be clinically useful.

Around the world, scientists and engineers continuously invent new technologies or improve on old technologies. A small fraction of these inventions open whole new avenues of research, leading to important advances in medical science. Another overlapping fraction lead to important improvements in clinical medical practice. Thus today's relatively new technologies become commonplace as we look forward to tomorrow's new technologies.

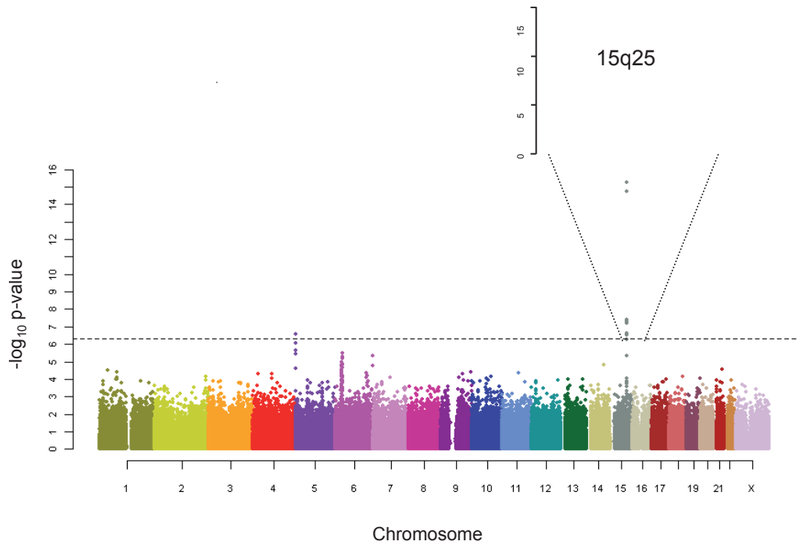


Fig. 3.6.2 *Genomewide SNP scan for lung cancer susceptibility loci. This scatter plot of p-values in −log scale from the trend test for 315 956 variants comparing 2971 lung cancer cases and 3745 controls provides strong evidence for a locus at chromosome 15q25*

REFERENCES

1. Wilkins MR, Sanchez JC, Gooley AA, et al. (1996). Progress with proteome projects: why all proteins expressed by a genome should be identified and how to do it. *Biotechnol Genet Eng Rev* 13: 19-50.

2. Gygi SP, Rochon Y, Franza BR, et al. (1999). Correlation between protein and mRNA abundance in yeast. *Mol Cell Biol* 19: 1720-1730.

3. Cox J and Mann M (2007). Is proteomics the new genomics? *Cell* 130: 395-398.

4. Aebersold R and Mann M (2003). Mass spectrometry-based proteomics. *Nature* 422: 198-207.

5. Washburn MP, Wolters D, Yates JR. (2001). Large-scale analysis of the yeast proteome by multidimensional protein identification technology. *Nat Biotechnol* 19: 242-247.

6. Anderson NL and Anderson NG (2002). The human plasma proteome: history, character, and diagnostic prospects. *Mol Cell Proteomics* 1: 845-867.

7. Ornstein DK, Rayford W, Fusaro VA, et al. (2004). Serum proteomic profiling can discriminate prostate cancer from benign prostates in men with total prostate specific antigen levels between 2.5 and 15.0 ng/ml. *J Urol* 172: 1302-1305.

8. Villanueva J, Shaffer DR, Philip J, et al. (2006). Differential exoprotease activities confer tumor-specific serum peptidome patterns. *J Clin Invest* 116: 271-284.

9. Liu XP, Shen J, Li ZF, et al. (2006). A serum proteomic pattern for the detection of colorectal adenocarcinoma using surface enhanced laser desorption and ionization mass spectrometry. *Cancer Invest* 24: 747-753.

10. Belluco C, Petricoin EF, Mammano E, et al. (2007). Serum proteomic analysis identifies a highly sensitive and specific discriminatory pattern in stage 1 breast cancer. *Ann Surg Oncol* 14: 2470-2476.

11. Patz EF, Jr., Campa MJ, Gottlin EB, et al. (2007). Panel of serum biomarkers for the diagnosis of lung cancer. *J Clin Oncol* 25: 5578-5583.

12. Lee RC, Feinbaum RL, Ambros V (1993). The C. elegans heterochronic gene lin-4 encodes small RNAs with antisense complementarity to lin-14. *Cell* 75: 843-854.

13. Lee RC and Ambros V (2001). An extensive class of small RNAs in Caenorhabditis elegans. *Science* 294: 862-864.

14. Lewis BP, Burge CB, Bartel DP (2005). Conserved seed pairing, often flanked by adenosines, indicates that thousands of human genes are microRNA targets. *Cell* 120: 15-20.

15. Schetter AJ, Leung SY, Sohn JJ, et al. (2008). MicroRNA expression profiles associated with prognosis and therapeutic outcome in colon adenocarcinoma. *JAMA* 299: 425-436.

16. Blenkiron C, Goldstein LD, Thorne NP, et al. (2007). MicroRNA expression profiling of human breast cancer identifies new markers of tumor subtype. *Genome Biol* 8: R214.

17. Lu J, Getz G, Miska EA, et al. (2005). MicroRNA expression profiles classify human cancers. *Nature* 435: 834-838.

18. Melnikova I (2007). Therapies for Alzheimer's disease. *Nat Rev Drug Discov* 6: 341-342.

19. Stern-Ginossar N, Elefant N, Zimmermann A, et al. (2007). Host immune system gene targeting by a viral miRNA. *Science* 317: 376-381.

20. Murphy E, Vanicek J, Robins H, et al. (2008). Suppression of immediate-early viral gene expression by herpesvirus-coded microRNAs: implications for latency. *Proc Natl Acad Sci U S A* 105: 5453-5458.

21. Golub TR, Slonim DK, Tamayo P, et al. (1999). Molecular classification of cancer: class discovery and class prediction by gene expression monitoring. *Science* 286: 531-537.

22. Perou CM, Sorlie T, Eisen MB, et al. (2000). Molecular portraits of human breast tumours. *Nature* 406: 747-752.

23. Sorlie T, Perou CM, Tibshirani R, et al. (2001). Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. *Proc Natl Acad Sci U S A* 98: 10869-10874.

24. Dhami P, Coffey AJ, Abbs S, et al. (2005). Exon array CGH: detection of copy-number changes at the resolution of individual exons in the human genome. *Am J Hum Genet* 76: 750-762.

25. Bergamaschi A, Kim YH, Wang P, et al. (2006). Distinct patterns of DNA copy number alteration are associated with different clinicopathological features and gene-expression subtypes of breast cancer. *Genes Chromosomes Cancer* 45: 1033-1040.

26. Frazer KA, Ballinger DG, Cox DR, et al. (2007). A second generation human haplotype map of over 3.1 million SNPs. *Nature* 449: 851-861.

27. Gudmundsson J, Sulem P, Rafnar T, et al. (2008). Common sequence variants on 2p15 and Xp11.22 confer susceptibility to prostate cancer. *Nat Genet* 40: 281-283.

28. Eeles RA, Kote-Jarai Z, Giles GG, et al. (2008). Multiple newly identified loci associated with prostate cancer susceptibility. *Nat Genet* 40: 316-321.

29. Thomas G, Jacobs KB, Yeager M, et al. (2008). Multiple loci identified in a genome-wide association study of prostate cancer. *Nat Genet* 40: 310-315.

30. Duggan D, Zheng SL, Knowlton M, et al. (2007). Two genome-wide association studies of aggressive prostate cancer implicate putative prostate tumor suppressor gene DAB2IP. *J Natl Cancer Inst* 99: 1836-1844.

31. Hunter DJ, Kraft P, Jacobs KB, et al. (2007). A genome-wide association study identifies alleles in FGFR2 associated with risk of sporadic postmenopausal breast cancer. *Nat Genet* 39: 870-874.

32. Easton DF, Pooley KA, Dunning AM, et al. (2007). Genome-wide association study identifies novel breast cancer susceptibility loci. *Nature* 447: 1087-1093.

33. Broderick P, Carvajal-Carmona L, Pittman AM, et al. (2007). A genome-wide association study shows that common alleles of SMAD7 influence colorectal cancer risk. *Nat Genet* 39: 1315-1317.

34. Tomlinson I, Webb E, Carvajal-Carmona L, et al. (2007). A genome-wide association scan of tag SNPs identifies a susceptibility variant for colorectal cancer at 8q24.21. *Nat Genet* 39: 984-988.

35. Zanke BW, Greenwood CM, Rangrej J, et al. (2007). Genome-wide association scan identifies a colorectal cancer susceptibility locus on chromosome 8q24. *Nat Genet* 39: 989-994.

36. Hung RJ, McKay JD, Gaborieau V, et al. (2008). A susceptibility locus for lung cancer maps to nicotinic acetylcholine receptor subunit genes on 15q25. *Nature* 452: 633-637.

CANCER INSTITUTE PROFILE:
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3.7 Biomarkers at a Crossroads: Implications for Early Cancer Detection and Diagnosis

Summary

> Biomarkers are the signposts during the process of carcinogenesis

> If identified carefully and selected rationally, biomarkers could provide a window of opportunity for risk assessment and cancer diagnosis and hasten the move towards personalised prevention and treatment

> The key to discovery of the right biomarkers lies in the selection of clinically annotated, well characterized specimens, appropriate study designs to address the clinical questions, and associated assays and data analysis

> Validation of biomarkers remains a key bottleneck in bringing biomarkers to clinical fruition. However, the National Cancer Insititute's Early Detection Research Network is addressing this critical step by launching several validation trials, an example of which is presented in this chapter

> The future of biomarker research depends on the successful demonstration of biomarker-based diagnosis, prevention and treatment to earn it acceptance in clinical practice

Carcinogenesis is a complex process requiring the coordinated interactions of numerous genes, proteins, signalling pathways and cell types. As a result of extensive studies on the molecular carcinogenesis of cancer, a number of regulatory pathways and networks have been identified. These pathways have revealed several unique events, marked by structural modifications to cells and the expression of genes and proteins that accompany oncogenic transformation. Thus, both cellular morphology and molecular signatures change during cancer development. By discerning these changes accurately with the help of biomarkers, we can improve the early detection and diagnosis of individual cancers. Biomarkers are the molecular signposts that indicate how far the process of carcinogenesis has travelled across the network or pathway leading to the development of a tumour. Biomarkers are the major measures by which future medicine will be personalised for individuals, and prevention or treatment will be based on unique target-specific molecules, as opposed to standard systemic infusions of toxic chemotherapy agents [1].

Definition of biomarkers

There is no standard definition for "biomarker" that is universally used. In 1999, the US National Institutes of Health/Food and Drug Administration Working Group drafted a definition of a biomarker as a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacological response to a therapeutic intervention [2]. However, this definition is broad and may not be easily understood by the general public. Biomarkers may be defined as quantifiable molecules, including DNA, RNA, proteins and metabolites, that are found in body fluids or tissues at an abnormal level that signal a pathologic condition, such as cancer. A biomarker might be a molecule secreted by a malignancy, or it can be a specific response of the body to the presence of cancer. Alterations in gene sequence or expression and in protein structure and function have been associated with every type of cancer and with their progression through the various stages of development. Changes in gene expression and in protein expression or modification can be used to detect cancer, determine prognosis and monitor disease progression and therapeutic response [3].

Search for biomarkers

Tremendous progress has been made in developing high-throughput technologies that accelerate the discovery of genes and proteins. But the challenge now is to identify the related biomarkers that provide an earlier indication of disease and are more reliable and precise in predictive ability than current clinical methods. This remains a daunting task and continues to challenge researchers with finding the "needle in a haystack." Yet, the technologies that provide the means to inventory components within the "haystack" at an unprecedented rate have exponentially expanded knowledge of the different types of proteins within serum, and opened the way for novel technologies for diagnosing cancers.

The coupling of high-throughput technologies enables samples from hundreds of patients to be rapidly compared. These technologies have greatly advanced the fields of: proteomics (the study of the structure and function of proteins including the way they work and interact with each other inside cells); genomics (the study of the organisation of genomes and the nucleotide sequences of the component genes); and transcriptomics (the study of genes transcribed from DNA within living cells to molecules of messenger RNA as the first step in protein synthesis). As a result, a number of candidate biomarkers have been identified for various cancer types. The next challenge is how to pick the right biomarkers from among the hundreds of promising candidates.

Selecting the right biomarker

The US National Cancer Institute's Early Detection Research Network [4], a consortium of more than 40 laboratories and 300 investigators, has established guiding principles, commonly known as the five-phase approach, for developing, evaluating and validating biomarkers. These guidelines are used to facilitate the transition of biomarkers toward clinical applications. The five phases provide the principles and study design foundations for validating biomarkers headed for clinical use in risk assessment and early detection of cancer. Phase 1, the discovery phase, includes exploratory study to identify potentially useful biomarkers. In Phase 2, the validation phase, biomarkers are thoroughly analysed and verified to determine their capacity for distinguishing between people with cancer and those without. Phase 3 focuses on the capacity of a biomarker to detect preclinical disease by testing the marker against tissues collected longitudinally over time from various research cohorts. Phase 4 comprises prospective screening studies. In Phase 5, large-scale population studies that evaluate both the role of the biomarker for detection of cancer, and the overall impact of screening on the population are conducted [5]. Examples of some biomarkers are provided in Table 3.7.1.

In the context of cancer biomarker testing, the sensitivity of a biomarker refers to the proportion of case subjects (individuals with confirmed disease) who test positive for the biomarker. Specificity refers to the proportion of control subjects (individuals without disease) who test negative for the biomarker. An ideal biomarker test would have 100% sensitivity and specificity; that is, everyone with cancer would have a positive test, and everyone without cancer would have a negative test. The lower the sensitivity, the more often individuals with cancer will not be detected. The lower the specificity, the more often someone without cancer will test positive. None of the currently available biomarkers achieve 100% sensitivity and specificity. For example, prostate specific antigen (PSA), currently the best overall serum biomarker for identifying prostate cancer, has high sensitivity (greater than 90%) but low specificity (about 25%), which results in many men having biopsies when they do not have detectable prostate cancer [6,7]. The serum tumour biomarker for breast cancer, CA15.3, has only 23% sensitivity and 69% specificity, and is only useful in monitoring therapy for advanced breast cancer or recurrence [8]. Other frequently used terms are: positive predictive value, which is the possibility that a person with a positive test has cancer, and negative predictive value, which is the possibility that a person with a negative test does not have cancer. Positive predictive value and, to a lesser degree, negative predictive value are affected by the prevalence of disease in the screened population. For a given sensitivity and specificity, the higher the prevalence, the higher the positive predictive value. The Early Detection Research Network creates the biomarker pipeline for a specific cancer type based on the diagnostic performance criteria discussed above and additional considerations, such as incremental benefits over existing practice of care, cost and acceptance by the patients and caregivers. Once the candidate biomarkers are identified, they are subjected to specimen reference sets collected by the Early Detection Research Network [4] to verify the biomarker achieves the intended clinical goal, such as early detection, diagnosis or prognosis. If the preset criteria for the intended goal are met, the markers move to the next testing stage. An example is provided in Figure 3.7.1.

Use of five-phase guidelines: a case study

In the USA, bladder cancer is the fourth most common malignancy in men and the seventh most common malignancy in women. Bladder cancer occurs in two clinically significant forms: (1) superficial (TNM: Ta, TiS, T1) and (2) invasive (TNM: >T2). Seventy-five percent of individuals with bladder cancer have superficial disease and only a minority of those (approximately 15%) are at risk for disease progression. Most individuals (approximately 70%) with superficial disease will experience relapse during a 10-year period. The majority of recurrences occur within the first 2 years after the diagnosis. Therefore, these individuals require frequent surveillance for recurrence that includes cystoscopy and urine cytology every 3 months for 2 years and then annually, and radiographic evaluation of the upper urinary tract every year. Although urine cytology and cystoscopy are considered standard of care, they are less than optimal in detecting all forms of bladder cancer. The sensitivity and specificity of urinary cytology are 25–50% and 90–100%, respectively. The sensitivity and specificity of cystoscopy is 90–100% and 75%, respectively. Consequently, there is a need to improve the current practice of bladder cancer surveillance [9,10].

Microsatellite analysis is a promising new technique for the surveillance of bladder cancer. The technology, which permits the separation by electrophoresis of polymerase chain reaction-amplified DNA sequences from non-malig-

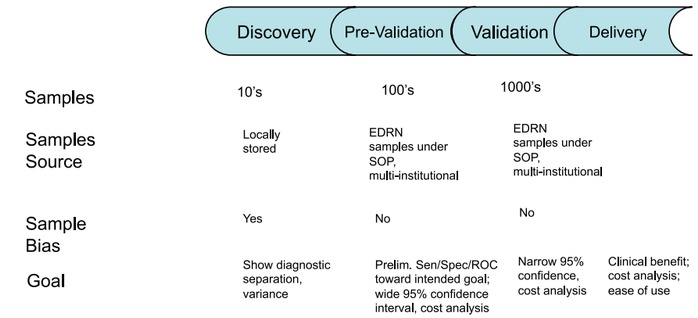


Fig. 3.7.1 *Evolution of the biomarker pipeline from discovery to development to validation to clinical application in the Early Detection Research Network*

nant and malignant sources, has been applied to the diagnosis of solid tumours arising in the colon, lung, oropharynx, kidney and bladder. Microsatellite analysis can detect genetic changes indicative of carcinoma from urothelial cells obtained in voided urine specimens. The genetic profile of DNA purified from urine is compared to that of DNA purified from peripheral lymphocytes that are considered "normal." Once the DNA from uroepithelial cells has been obtained, polymerase chain reaction is performed with specific oligonucleotide primers for each chromosomal locus. The polymerase chain reaction products are then examined for evidence of microsatellite instability (a change that occurs in the DNA of certain cells, such as tumour cells, in which the number of repeats of microsatellites–short, repeated sequences of DNA–is different than the number of repeats in the DNA when it was inherited) and loss of heterozygosity, which are genetic characteristics of epithelial tumours. Preliminary work shows that MSA detects 95% of cancers [9,10]. However, the effectiveness of microsatellite analysis testing must be validated using a prospective collection of samples from geographically diverse populations. The Early Detection Research Network has selected this promising marker for a Phase III clinical trial since this has met all the requirements of Phase I and Phase II clinical research.

The goals of the study are:

– To determine sensitivity and specificity of microsatellite analysis of urine sediment, using a panel of 15 microsatellite markers, in detecting bladder cancer in participants requiring cystoscopy. This technique will be compared to the diagnostic standard of cystoscopy, as well as to urine cytology.
– To determine the temporal performance characteristics of microsatellite analysis of urine sediment.
– To determine which of the 15 individual markers or combination of markers that make up the microsatellite analysis test are most predictive of the presence of bladder cancer.

Three populations will be included in this study. Two of the populations will include 200 participants (100 each) without bladder cancer (controls). The control population will include two cohorts: (1) a cohort of 100 participants without a history of or current urologic diseases or devices and with a normal urinalysis and urine cytology examination, referred to as Control Group 1; and, (2) a cohort of 100 participants with one of four urologic processes requiring cystoscopy, which in the past have had confounding results with urinary tumour detection assays, referred to as Control Group 2. Both control groups will undergo urinalysis and cytology at baseline along with microsatellite analysis, but only the second group (potentially confounding gastrointestinal conditions) will undergo cystoscopy. The rationale is that the first cohort includes truly "healthy" participants with no gastrointestinal complaints; they have no medical reason to undergo a cystoscopy. Requiring cystoscopy would severely limit recruitment, potentially induce selection bias, and expose otherwise healthy participants to the small but known risks associated with cystoscopy. However, the second control cohort is presenting with gastrointestinal complaints that would ordinarily indicate the need for cystoscopy.

The third population to be enrolled will include 300 participants with bladder cancer, both incident and recurrent. This group of participants will undergo urine cytology and cystoscopy at baseline, and quarterly follow-up surveillance cystoscopy and cytology determinations with synchronous microsatellite analysis determinations.

The accrual is now complete and follow-ups are underway. This first-ever study will provide evidence as to whether or not microsatellite analysis should be used alone or in combination with urine cytology and cystoscopy to monitor the progression of bladder cancer.

A number of other validation studies are underway for markers for pancreatic, lung, mesothelioma, prostate and bladder cancers (Table 3.7.1).

Future directions

Because a single biomarker may not have sufficient sensitivity and specificity to be useful for early detection, there is interest in multiplexing biomarkers (that is, developing a panel of them for concurrent use) that would probably perform better than a single diagnostic marker. Flexible technology platforms are being developed by diagnostic companies that allow for the analysis of a number of biomarkers on a single platform. These multiplexed platforms are designed to simultaneously analyse a panel of protein or nucleic acid biomarkers or more than one kind of biomarker. The multiplexing approach can eliminate time-consuming manual processing of samples, making it faster, efficient and more convenient and allowing for real-time data acquisition and efficient sample comparison. Another important innovation in biochip technology is the microfluidic chip-based immunoassay, which can analyse the expression of serum proteins comparable to commercial enzyme-linked immunosorbent assays, a method using antibodies to quantify levels of a biological marker. However, multiplexing can be a confounding task when optimising the assay conditions, and there is still need for the development of efficient tools for analysing such high dimensional and high throughput data.

With continued attention, support and open cross-disciplinary, multi-institutional collaborations, the challenges of finding and developing accurate and useful biomarkers for early cancer detection and cancer risk will fade and new, long-awaited, less-invasive tools brought into clinical use.

Candidate/Panel	Organ	Status	Part of Multiplex	Reference Number
Annexin 1, LAMR 1, 14-3-3theta	Lung Adenocarcinoma	Phase II	yes	[11]
LCN2, TIMP1, REG1A, REG3 and IGFBP4	Pancreatic	Phase II	yes	[12]
SPINK1, PCA3, GOLPH2, TMPRSS2-ERG	Prostate	Phase II	yes	[13]
CA-125, MIF-1, prolactin, osteopontin, IGF-2 and leptin	Ovary	Phase II	yes	[14]

Table 3.7.1 *List of clinical biomarker candidates transitioning through the five-phase approach established by the Early Detection Research Network*

REFERENCES

1. Srivastava S and Wagner P (2007). Risk-based and diagnostics-linked personalized medicine for cancer. *Personal Medicine* 4: 33-43.

2. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework (2001). *Clin Pharmacol Ther* 69: 89-95.

3. Srivastava S (2007). Cancer biomarker discovery and development in gastrointestinal cancers: Early Detection Research Network-a collaborative approach. *Gastrointest Cancer Res* 1: s60-s63.

4. National Cancer Institute (2008). *Early Detection Research Network*. Available from: http://www.cancer.gov/edrn Date Accessed: November 19,2008.

5. Pepe MS, Etzioni R, Feng Z, et al. (2001). Phases of biomarker development for early detection of cancer. *J Natl Cancer Inst* 93: 1054-1061.

6. Ornstein DK and Kang J (2001). How to improve prostate biopsy detection of prostate cancer. *Curr Urol Rep* 2: 218-223.

7. Ito K, Yamamoto T, Ohi M, et al. (2003). Natural history of PSA increase with and without prostate cancer. *Urology* 62: 64-69.

8. Li J, Zhang Z, Rosenzweig J, et al. (2002). Proteomics and bioinformatics approaches for identification of serum biomarkers to detect breast cancer. *Clin Chem* 48: 1296-1304.

9. Mao L, Schoenberg MP, Scicchitano M, et al. (1996). Molecular detection of primary bladder cancer by microsatellite analysis. *Science* 271: 659-662.

10. Steiner G, Schoenberg MP, Linn JF, et al. (1997). Detection of bladder cancer recurrence by microsatellite analysis of urine. *Nat Med* 3: 621-624.

11. Qiu J, Choi G, Li L, et al. (2008). Occurrence of autoantibodies to annexin I, 14-3-3 theta and LAMR1 in prediagnostic lung cancer sera. *J Clin Oncol* 26: 5060-5066.

12. Faca VM, Song KS, Wang H, et al. (2008). A mouse to human search for plasma proteome changes associated with pancreatic tumor development. *PLoS Med* 5: e123 DOI:10.1371/journal.pmed.0050123.

13. Laxman B, Morris DS, Yu J, et al. (2008). A first-generation multiplex biomarker analysis of urine for the early detection of prostate cancer. *Cancer Res* 68: 645-649.

14. Visintin I, Feng Z, Longton G, et al. (2008). Diagnostic markers for early detection of ovarian cancer. *Clin Cancer Res* 14: 1065-1072.

3.8 Stem Cells and Cancer Stem Cells

Summary

> Stem cells constitute a distinct population of cells characterised by the ability to renew themselves indefinitely through mitotic division and to differentiate into a diverse range of specialised cell types

> The two broad types of mammalian stem cells are: the embryonic stem cells that are found in early embryos, and the adult stem cells that are found in many adult tissues

> The main properties of stem cells are self-renewal, essential for maintenance of the stem cells pool, and the ability to differentiate in different lineage required for the integrity and function of tissues

> Cancer stem cell (CSC) is an operational term to functionally define a distinct subpopulation of tumour cells with unlimited renewal potential. Cancer stem cells share many key properties with embryonic stem cells, including the infinitive proliferation potential and the capacity to invade tissues and organs

> Research on stem cells and cancer stem cells holds great promise to advance the design of novel strategies in cancer therapy

The unprecedented pace of discovery in the field of stem cells has turned academic, political and public attention to the potential application of stem cells in medicine and biomedical research. Stem cells are found in all multi-cellular organisms and are likely to be present as a discrete population in most tissues. Stem cells can be grown in culture and differentiated into specialised cells with properties specific to various tissues. Recent landmark discoveries by Takahashi and Yamanaka [1] that induced pluripotent stem cells (iPSCs), which share very similar properties with embryonic stem cells, could be derived from differentiated cells (skin fibroblasts), have already been reproduced for a variety of human cell types [2]. Furthermore, two studies have described the generation of iPSC lines from individuals harbouring both simple and complex genetic diseases [3,4]. Therefore, stem cells have been seen as an essential toolbox in cloning and regenerative medicine. Interestingly, recent advances have revealed that stem cells can be a source of cancer cells, and that better understanding of the behaviour and properties of stem cells could be exploited to devise an arsenal of novel tools to fight against cancer. Although technical advances that allow the isolation and manipulation of embryonic stem cells and possibility of human cloning have provoked intense ethical debates, this should not undermine the tremendous potential of stem cells in the treatment of various human diseases such as neurodegenerative disorders and cancer [5,6].

Embryonic and tissue-specific stem cells

Every cell in the body is a descendent of a single cell (fertilized egg or zygote). The life of an organism starts with fertilisation of an egg, and from this moment until death involves the passage through several developmental stages (Figure 3.8.1). Multiplication of fertilised eggs gives rise to different cell types of the body. This process involves generation of populations of stem cells that can be propagated indefinitely in culture under adequate conditions. These cells are called the embryonic stem (ES) cells that are able to give rise to any cell type and to reconstitute the entire embryo. In addition, many adult tissues contain a discrete population of undifferentiated cells with properties of stem cells. These cells are known as tissue-specific stem cells (somatic stem cells). Hematopoietic stem cells are the best-characterised tissue-specific stem cells that generate all blood lineages and mature blood elements. The adult stem cells are identified in many other tissues such as brain, skin and liver. While only a few tissue-specific stem cells have undergone a rigorous identification and characterisation, it is likely that stem cells are present in any tissue that undergoes renewal.

Tissue-specific stem cells also have the capacity to perpetuate itself through self-renewal and to produce various mature cells of a particular tissue through differentiation [7]. Tissue-specific stem cells constitute a tiny cell population in adult tissues, yet they are essential in the maintenance of tissue homeostasis and their deregulation may trigger diseases, most notably cancer. The two characteristics of stem cells that distinguish them from all other cells are self-renewal and pluripotency. Self-renewal is the capacity of a cell to divide and produce identical daughter cells over long time period. This property is crucial as it allows that stem cells persist for the lifetime of an organism. Pluripotency is the capacity of stem cells to differentiate into many highly-specialised cells such as neurons, muscle fibers, and blood elements. This feature is important for the maintenance of integrity and function of many tissues. Stem cells are essential for the development and integrity and function of an organism and thus can be considered as a precious treasure from the beginning of embryonic life to the death. Given their properties, function and proliferation of stem cells need to be tightly monitored. Deregulation of the surveillance mechanisms for proliferation and differentiation of stem cells may trigger a shift in the balance between self-renewal and differentiation leading to either stem cell loss, associated with degenerative disorders, or abnormal proliferation of stem cells that may be a source of malignant cells.

Cancer stem cells

Stem cells have been discovered a quarter century ago and have been exploited extensively for the generation of genetically-modified animal models (for example, knockout mice), an essential tool in cancer research. However, the identification of the first human stem cells and in particular so-called cancer stem cells triggered unprecedented attention of the cancer research community. It has long been accepted that most tumours are derived from a single cell that has been transformed into a cancer-initiating cell through acquisition of a series of genetic and epigenetic lesions. These initial events allow expansion of transformed cells and formation of a population of altered cells (clone) with capacity to grow and divide in defiance of normal cellular control. Continuing selection of "fitter" and more aggressive cells results in a generation of cancer clones capable of invading and destroying neighbouring tissues and migrating to distant organs to form secondary tumours (metastasis). It is now believed that many human cancers arise from deregulated control of stem cells (Figure 3.8.2). Moreover, recent studies indicated that many genetic and epigenetic changes underlying aggressive and destructive behaviour of cancer are orchestrated by discrete population of cancer cells with stem cell properties. These cells are known as cancer stem cells. The idea that cancer develops from stem cells was suggested as early as 1875 when Cohnheim hypothesised that stem cancer displaced during embryonic development may be the origin of malignant cells later in the life [8]. However, it was not until the identification of the first cancer stem cells that the cancer stem cell concept received considerable attention.

The cancer stem cell hypothesis suggests that cancer clones are maintained exclusively by a rare fraction of cells with stem cell properties. Many cancers are found to contain cells with properties of stem cells. However, in most cases the existence of cancer stem cells has been documented functionally. This means that the presence of cancer stem cells in the bulk of cancer cells is discerned by their capacity to form tumours after transplantation into an immunocompromised animal host (usually mice). These assays revealed that only a small fraction of cancer cells were capable of forming new tumours in the host. Importantly, these cells are shown to be able not only to form tumours upon transplantation but also to recapitulate tumour heterogeneity [10]. However, until very recently it proved extremely difficult to isolate cancer stem cell population using molecular signatures, cell-surface markers or mutation profiles [5,11].

Cancer stem cells share many key properties with embryonic stem cells. These include the infinitive proliferation potential and the capacity to invade tissues and organs, and promote formation of blood vessels for their own supply. While we have seen important progress on the identification of cancer stem cells, the origin of cancer stem cells remains mysterious. It is believed that cancer stem cells may arise in different ways. First, cancer stem cells can be derived from normal tissue-specific stem cells as a result of specific genetic and epigenetic changes that abrogate their proliferation control. Second, differentiated cells that normally have a limited life span can regain stem cell properties (de-differentiate) and become cancer stem cells. Third, it is also possible that normal stem cell fuse with various differentiated cells and resulting hybrid cells may be cancer-initiating cells with stem cell properties [11]. These hypotheses are not mutually exclusive, and the genesis of cancer stem cells may involve more than one mechanism.

Gene wiring that instructs stem cell identity

Although the features that distinguish stem cells from all differentiated cells have been known

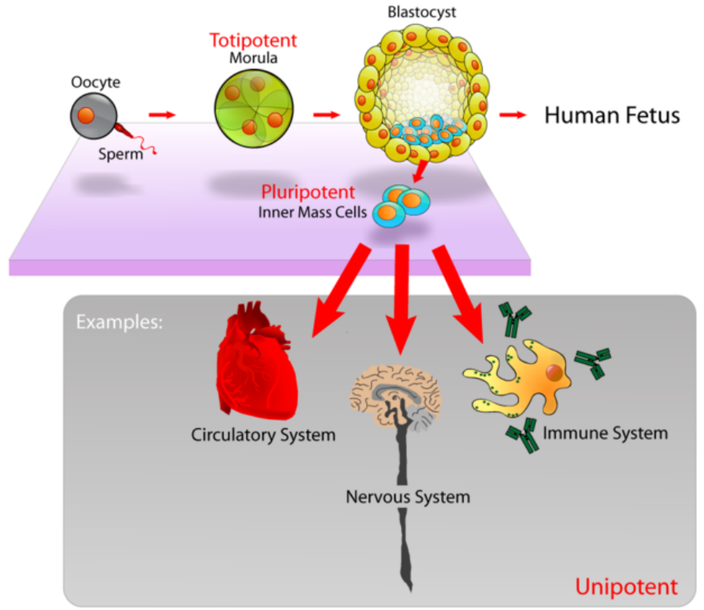


Fig. 3.8.1 *Embryonic stem cells can become all cell types of the body because they are pluripotent. Adult stem cells are generally limited to differentiating into different cell types of their tissue of origin*

for many decades, it was not until recently that we have begun to understand the genetic basis of stem cell identity. The development of powerful tools in genomics for genome-wide screens allowed the identification of genes and gene networks that keep stem cells in a special state. Using these tools, scientists have discovered a handful of genes that are necessary and sufficient to maintain self-renewal and pluripotency, two distinguishing features of stem cells. These genes are known as "masters of stemness". The genes Oct4, Sox2, and Nanog belong to this privileged club [12]. These genes encode for specialised proteins known as transcription factors whose duty is to control the transcription of other genes (Figure 3.8.3). This forms a kind of gene wiring that instructs stem cell behaviour and identity. When these genes are inactivated or mutated, stem cells may differentiate into specialized cells and stem cell pool may be rapidly depleted. This can impede regeneration and integrity of normal tissues leading to degenerative diseases [13].

The discovery of stem cell master genes enabled another even more tantalising adventure: the reversal of specialised (differentiated) cells into immature pluripotent (stem) cells, the process known as de-differentiation—in other words, making specialised cells (such as neurons or muscle fibres) become cells with stem cell properties that would allow the generation of just about any type of cell. This would solve important ethical issues associated with the use of embryos as a source of stem cells. Recent studies demonstrated just that [1,14,15]. Several laboratories showed that the introduction of as few as 4 of master genes into differentiated cells of either humans of mice into stem cells. This remarkable phenomenon argues that differentiated cells can be reprogrammed and that differentiation clock can be reversed. An important implication of these findings is that cancer stem cells may also arise by non-genetic changes that confer certain features to differentiated cells. In support of this hypothesis is the fact that all cells including stem cells in any given organisms share an identical genome (the sum of genetic codes).

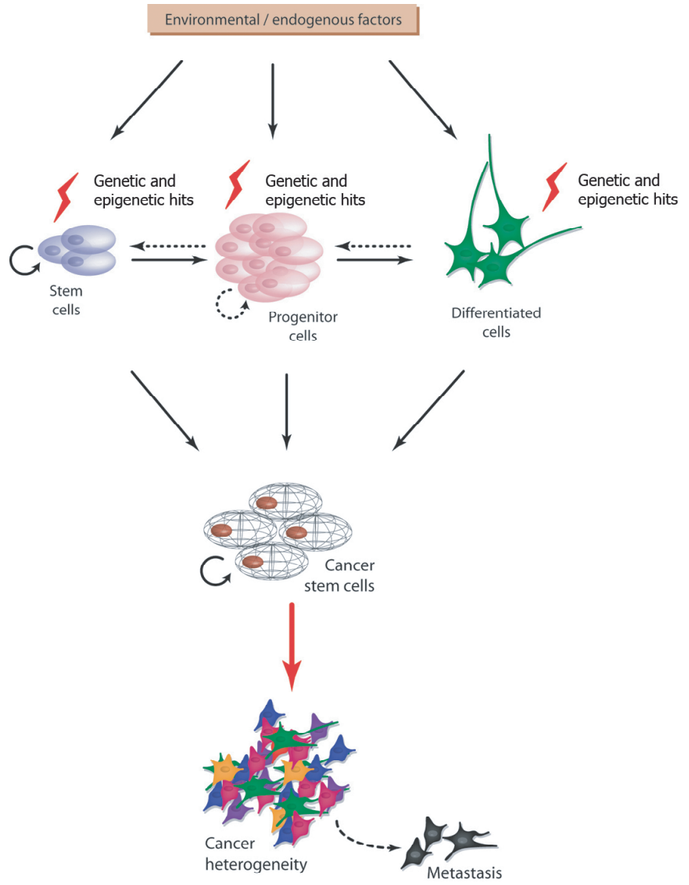


Fig. 3.8.2 *Genetic and epigenetic changes in stem/progenitor cells may be an early event in the development of cancer and give rise to cancer stem cells and contribute to tumour heterogeneity. Abnormal expression and function of a set of genes in more differentiated cells may contribute to reprogramming into a pluripotent state and also cancer stem cells. [9]*

These findings suggest that special features of stem cells are due to non-genetic (epigenetic) events. In other words, gene expression patterns of stem cells but also differentiated cells are controlled by epigenetic mechanisms. Self-renewal and pluripotency represent opposing demands on genome of stem cells. Self-renewal potential requires a long-term memory system for stable maintenance of transcriptional patterns without changes in the genomic code.

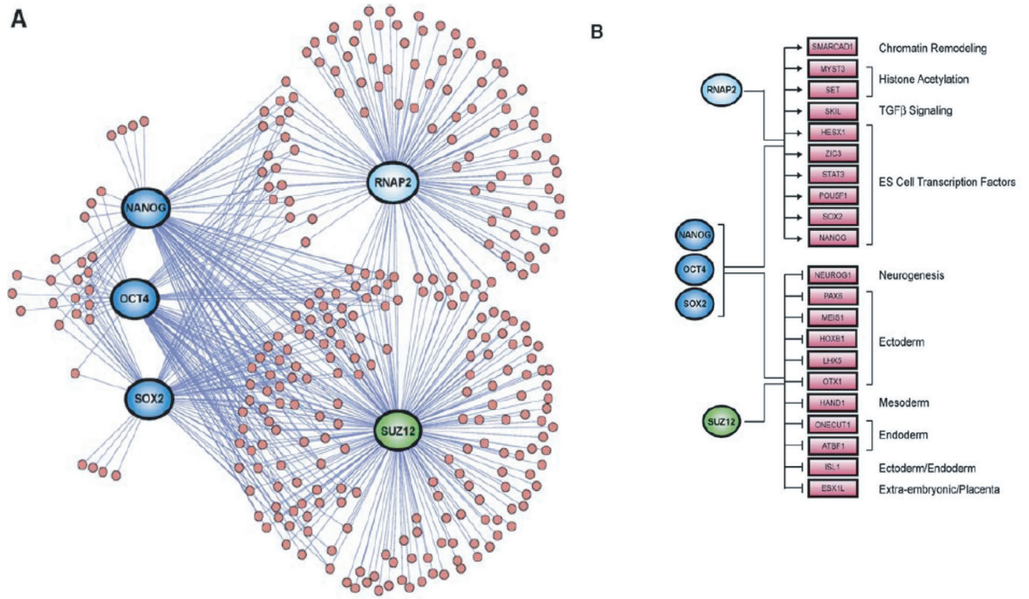


Fig. 3.8.3 *Transcriptional regulatory network governed by several key regulators in human embryonic stem cells.*

In contrast, the potential for multi-lineage differentiation requires plasticity of the genome allowing multiple differentiation decisions. This apparent dichotomy of stem cells is reflected by the presence of specific patterns in DNA methylation (epigenetic modification of DNA molecule which does not involve changes in genetic code) and histone modifications (markings of special proteins which ensure protection and compaction of DNA chain)[9]. Therefore, it is quite plausible that deregulation of epigenetic mechanisms may lead to an altered potential of stem cell self-renewal and expansion of epigenetically modified stem cell pools. Stem cells modified in this manner exhibit no genetic changes, yet they may represent a precursor pool susceptible to acquisition of mutations and further epigenetic alterations. In this scenario, disruption of epigenetic states is the first step of tumorigenesis and is a contributing factor to polyclonal tumour phenotype.

Stem cell and cancer therapy

Much of the current interest in a stem cells and cancer stem cells comes from the realisation that this tiny yet critical population of cancer cells represents an opportunity to devise novel strategies for cancer therapy [5-7]. It is believed that many current protocols for cancer therapy fail and cancer reappears due to the failure to eradicate cancer stem cells. For example, classical chemotherapy regimes have been developed to rapidly shrink tumours; however these effects are transient and are followed by tumour relapse (Figure 3.8.4). This is explained by the fact that current drugs can efficiently kill rapidly growing cancer (non-stem) cells, whereas slower growing cancer stem cells may be spared. Thus, the major challenges will be: (i) to discover efficient ways to identify and isolate tissue-specific stem cells and cancer stem cells; (ii) to gain insights into the mechanisms of self-renewal and pluripotency of normal stem cells and cancer stem cells; and (iii) to pinpoint genetic and epigenetic events that are at the heart of cancer-initiating reprogramming and cancer stem cell development. The ever-increasing research efforts in the field of stem cells carry a promise to provide missing pieces of the puzzle of discovering and targeting the Achilles heel of cancer cells, which would make a major impact on the development of novel strategies to conquer cancer.

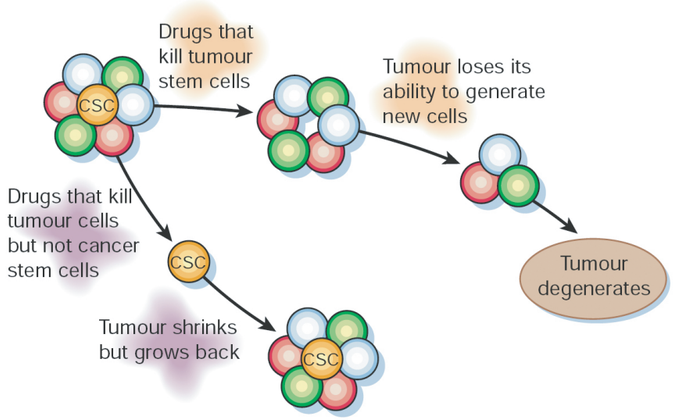


Fig. 3.8.4 *Conventional therapies may reduce tumours by killing mainly differenciated tumour cells. If the putative cancer stem cells are less sensitive to these therapies, then they will remain viable after therapy and re-establish the tumour. By contrast, if therapies can be targeted against cancer stem cells, then they might more effectively kill the cancer stem cells, rendering the tumours unable to maintain themselves or grow. Thus, even if cancer stem cell-directed therapies do not shrink tumours initially, they may eventually lead to cures. [7]*

REFERENCES

1. Takahashi K and Yamanaka S (2006). Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. *Cell* 126: 663-676.

2. Yamanaka S (2007). Strategies and new developments in the generation of patient-specific pluripotent stem cells. *Cell Stem Cell* 1: 39-49.

3. Dimos JT, Rodolfa KT, Niakan KK, et al. (2008). Induced pluripotent stem cells generated from patients with ALS can be differentiated into motor neurons. *Science* 321: 1218-1221.

4. Park IH, Arora N, Huo H, et al. (2008). Disease-specific induced pluripotent stem cells. *Cell* 134: 877-886.

5. Polyak K and Hahn WC (2006). Roots and stems: stem cells in cancer. *Nat Med* 12: 296-300.

6. Baumann M, Krause M, Hill R (2008). Exploring the role of cancer stem cells in radioresistance. *Nat Rev Cancer* 8: 545-554.

7. Reya T, Morrison SJ, Clarke MF, et al. (2001). Stem cells, cancer, and cancer stem cells. *Nature* 414: 105-111.

8. Cohnheim V (1875). Congenitales, quergestreiftes muskelsarkom der nieren. *Virchows Arch Pathol Anat Physiol Klin Med* 65: 64-69.

9. Shukla V, Vaissiere T, Herceg Z (2008). Histone acetylation and chromatin signature in stem cell identity and cancer. *Mutat Res* 637: 1-15.

10. Visvader JE and Lindeman GJ (2008). Cancer stem cells in solid tumours: accumulating evidence and unresolved questions. *Nat Rev Cancer* 8: 755-768.

11. Bjerkvig R, Tysnes BB, Aboody KS, et al. (2005). Opinion: the origin of the cancer stem cell: current controversies and new insights. *Nat Rev Cancer* 5: 899-904.

12. Boiani M and Scholer HR (2005). Regulatory networks in embryo-derived pluripotent stem cells. *Nat Rev Mol Cell Biol* 6: 872-884.

13. Erlandsson A and Morshead CM (2006). Exploiting the properties of adult stem cells for the treatment of disease. *Curr Opin Mol Ther* 8: 331-337.

14. Cowan CA, Atienza J, Melton DA, et al. (2005). Nuclear reprogramming of somatic cells after fusion with human embryonic stem cells. *Science* 309: 1369-1373.

15. Ivanova N, Dobrin R, Lu R, et al. (2006). Dissecting self-renewal in stem cells with RNA interference. *Nature* 442: 533-538.

3.9 Biobanks and Biological Resource Centres

Summary

> Collections of human biological specimens are the cornerstone of research on gene-environment interactions. They are also strategic resources for translational medicine and for the discovery of biomarkers useful in cancer management

> Biobanks are collections of biological samples and associated data that are structured in a way that makes them accessible for research. Such biobanks must abide by extremely strict technical, legal and ethical standards

> Biological Resource Centres regroup biobanks and technical services required to handle all aspects of specimen processing from collection to long-term storage and shipping to laboratories that perform biomarker analyses. BRCs are now at the centre of molecular epidemiology and evidence-based medicine

> Many studies on biomarkers require the analysis of large number of specimens, making it necessary to gather specimens in multiple centres involving several BRCs. Therefore, it is critical to promote the adoption of common minimal standards and protocols that are widely applicable in different field, laboratory or hospital contexts

> IARC, as a research centre with global outreach, is involved in collecting biospecimens in many parts of the world. This chapter summarises the recommendations and guidelines IARC gives to its collaborators worldwide for developing biobanks

Biobanks are at the centre of recent advances in cancer research. A "biobank" is an infrastructure to store biospecimens, e.g. blood samples or tissues, and to make them available for laboratory analyses. The term "Biological Resource Centre" (BRC) is used to identify specialised units that handle the acquisition, quality control, storage, processing and distribution of biospecimens to laboratories where they will be analysed. Thus this is more than just a "bank of samples": it encompasses the whole chain from the study participant (cancer patient or healthy volunteer) to the laboratory that performs biological analyses. Operating a BRC requires compliance with specific regulations and recommendations setting standards for collection, labeling, annotation, processing, storage, retrieval and analysis of the biospecimens, while ensuring biological safety and protection of personal data. The keyword in these tasks is traceability, allowing for the tracking of the biospecimens at all steps from collection to laboratory analyses. These complex operations involve bioethical aspects (How to inform study participants and ask them for consent? Who has the right to decide about how the specimens given in this way should be used? What is the proper action when specimen analysis reveals something unexpected that may be important for the participant? What are the procedures after death of the sample donor?), technical problems (How to make sure that the specimens collected are of consistent high quality? How to best preserve them in the long-term?), development of databases (What information on the participant and on the specimen should be stored? How to protect the confidentiality of this information? How to follow-up patients during and after treatment?), and huge logistical problems (Where to store specimens? How to manipulate them? How to handle, process, transport thousands of specimens?). Finally running a BRC requires highly trained, dedicated staff, defined standard operating procedures, and quality assurance/quality control procedures. This has serious economical implications in particular for the long-term sustainability of large biobanks. This chapter addresses the roles of BRC in cancer research and explains how the development of such BRC will shape not only tomorrow's cancer science but also medical practice.

The need for large biobanks and biobank networks

BRCs play a number of critical roles in all aspects of biological research. The role of BRCs in biological research in general, and their impact on medical, societal and economical issues has been extensively discussed in a recent report of the Organisation for Economic Co-operation and Development [1]. Storing specimens is not a new activity: biologists, natural scientists and doctors, including in particular pathologists, have always preserved samples for diverse scientific and medical uses. In the 19th century, these samples often were tissues or whole organs immersed in glass jars filled with formalin or alcohol. More recently, and indeed as is still the case today, hospital pathologists preserve tissues for diagnosis in paraffin wax. But with the advent of modern genetics and molecular biology, these questions have taken a new, unprecedented twist: it is now possible to analyse hundreds of thousands of markers in the DNA of a single subject, or to measure the whole set of genes expressed by a healthy or diseased tissue. Thus, scientists become capable of performing very detailed and precise molecular characterisation of biological samples.

Research on the molecular mechanisms of cancer has identified many molecules that can be measured and used as indicators of the effects of environmental exposures, of genetic susceptibility, of early steps of cell transformation, of early cancer disease, and of cancer progression towards invasiveness. Such biomarker molecules are critical not only to better classifying and understanding cancer diseases, but also to better detect and diagnose them, prognosticate their evolution, predict their responses to therapy, and provide targets for new drugs aimed at improving cancer treatment. A new area of biomedicine, often referred to as the "-omics", is in full development to combine large-scale biological analysis with bio-computing, generating large amounts of data on the status and level of multiple molecular biomarkers (see chapter on "Biomarkers"). The suffix "-omics", as for example in "genomics", conveys the notion that these approaches are aimed at assessing molecular makers in their wholeness. This distinguishes genomics from genetics, which usually concentrates on the study of a small number of related genes. Similarly, new words have been coined to identify the global study of gene transcription ("transcriptomics"), of proteins ("proteomics") or metabolic activities ("metabolomics"). Studies on human specimens are also becoming critical in the process of discovering new mechanisms involved in causing cancer or in determining its progression, resistance/response to treatment and clinical outcome.

Biobanks and personalised medicine

Collecting and analysing biological specimens is a necessary procedure for pathology-based diagnosis and is also a mechanism for allowing patients to benefit from the applications of molecular cancer research. Today, BRCs are the foundation of three rapidly expanding domains of biomedical sciences: molecular and genetic epidemiology (aimed at assessing the genetic and environmental basis of cancer causation in the general population as well as in families), molecular pathology (aimed at developing molecular-based classification and diagnosis procedures for cancer diseases), and pharmacogenomics/ pharmacoproteomics (understanding the correlation between an individual patient's genotype/phenotype and response to drug treatment). Close involvement of the pathology department at collecting centres is essential to facilitate the use of banked fresh frozen samples in diagnostic procedures. In the future, correct assessment of patient status and therapeutic needs may require the determination of a number of molecular parameters and will require systematic preservation of frozen biospecimens or derived biomaterial. With the continuing improvement of survival after therapy, performing such molecular-based evaluations may become a systematic requirement not only at diagnosis but also at different stages of patient follow-up. While the present chapter specifically deals with biorepositories for research, it is recognised that developing BRCs may rapidly become part of recommended, if not mandatory, medical practice. Thus, gathering know-how and procedures for collecting, storing and analysing human specimens is a major contribution to the development of biomedical practice worldwide. In the chain from laboratory discovery to medical application, biobanks have made a key contribution to life science research and development (R&D). Progress in medicine is dependent upon innovation, development and translation of laboratory findings into clinical practice. Access to human biological specimens is often a prerequisite for such R&D advances. Thus, development of high-quality BRCs has the potential to accelerate and facilitate this translational process.

Importance of networking and exchanges between BRCs

Cancer is a global disease, the understanding and management of which requires comparisons between disease patterns in different parts of the world. In addition, studies on many rare forms of cancer are limited by the difficulty in recruiting a sufficient number of cases within any single collection centre. Furthermore, large numbers of human biospecimens must be available to harness the full potential of novel, large scale technologies in genomics. Due to the molecular diversity of cancer, it is not possible to make accurate distinctions between sets of several thousand of biomarkers by analysing only a few hundred specimens. Statistical power is the key problem. Numbers of specimens analysed must be commensurate with the number of biomarkers simultaneously assessed, as well as with the prevalence of these biomarkers. To achieve this, molecular epidemiological studies often have to include thousands (if not hundreds of thousands) of subjects, recruited in many different locations. Thus, biobanks should be developed not as single autonomous "units" in a given hospital or research institutes, but as parts of a network of biobanks capable of sharing specimens. This leads us to the second basic requirement: the specimens analysed must be of constant, controlled quality, independently of their origin. These large studies must be made strictly comparable. Any lack of due care in specimen collection, processing, transport, storage or distribution to the laboratories may ruin the work of large consortiums of epidemiologists, doctors, nurses and statisticians—not mentioning the ethical responsibility towards subjects who have volunteered to participate in such large studies. Therefore, all laboratories involved in biobanking should adopt common technical standards for specimen collection, storage, annotation and data management. BRCs have an important role in facilitating such exchanges and in providing logistics and infrastructure for multi-centre research projects (epidemiological studies as well as clinical trials). It is recommended that the institution develop tools to enable up-to-date, anonymous information retrieval of clinical annotation on individuals, and set up communications between departments of (e.g.) oncology, surgery, pathology and clinical chemistry.

Legal and ethical implications

Developing and using BRCs requires the active involvement of many actors at different levels (national policy makers, institutional administrators, epidemiologists, pathologists, surgeons, clinicians, bioinformaticians, laboratory scientists) and has complex ethical and legal implications. The perception of these issues and the way they are regulated and managed varies according to legislative, cultural and economical contexts. This paragraph does not intend to provide general answers to these questions, but to put into perspective some important challenges associated to the collection, storage and use in research of human biospecimens. The Helsinki Declaration provides the general framework in which these questions should be addressed [2].

Firstly, the rights of the individuals whose tissues or biological specimens are to be included in the BRC should be strictly considered and protected. Crucial aspects in this process are the development of appropriate methods to obtain informed consent according to the local standards where the definition of protocols are fully

compatible with the three basic ethical requirements of autonomy, beneficence (nonmalevolence) and justice [3]. In this process, it is critical that individuals receive accurate information regarding the potential use of their specimens in large national and international studies as well as in collaborative studies involving third parties such as industrial or commercial partners. Secondly, the institutions that organize and oversee BRCs have the responsibility of protecting individual information and data, to guarantee safe and adequate long-term preservation of banked specimens, to inform, train and protect staff involved in specimen management, to ensure biological and environmental safety, and to make collections accessible and available under defined conditions for research purposes. Thirdly, the scientists who wish to use banked biospecimens for research purposes must submit their research proposals and protocols to appropriate scientific and ethical review. As custodians of the biospecimens, institutions have the duty to take into account the non-renewable nature of the specimens in making priorities for scientific use. In requesting specimens from a biobank, scientists should develop detailed power calculations and provide pilot data to ensure the optimal use of biological resources. Distribution of specimens for research should be done within clear transfer agreements. Such agreements may include return of data and leftover materials to the BRCs. They should also make provisions for users to contribute to the economical sustainability of the BRCs (see below), and should also acknowledge the rights of the BRCs and its scientific contributors to intellectual property derived from research performed using specimens made available by the BRC.

Principles for sustainable Biological Resource Centres

Developing and sustaining a BRC has a high initial cost as well as running financial cost, and can strain economically underprivileged institutions. These constraints are a significant obstacle to developing BRCs in middle or low-resource countries. Lifting these obstacles in these countries requires a significant, international solidarity effort. The public sector (local, national governments, international bodies and organisations) has a responsibility for contributing to the funding of the baseline infrastructure of BRCs. On the other hand, the responsibility for development and maintenance of sustainable and useable specimen collections lies primarily with the clinical and scientific institutions. These institutions should make provisions towards maintenance of infrastructure, equipment, and running costs as well as data management systems. In addition, users of BRCs should contribute to the general financial and structural sustainability of BRCs. Thus, access to biorepositories of human specimens should entail a contribution from researchers, either in the public or private sector, to the costs of collecting, annotating, storing, retrieving and processing of biospecimens. However, human biospecimens should not be sold in any circumstances. Regardless of the role of industry in core funding of BRCs, which is a matter of debate with serious implications, the responsibility for specimen collection and storage must remain within institutions. In defining mechanisms for BRC sustainability, there is a need to develop safeguards against exploitation and improper use of human biospecimens.

Recommendations for BRCs

Protection of persons

The first, basic requirement of a BRC is Safety. This includes protection of persons and of the environment against biological and chemical hazards, as well as protection of the data and information associated to the specimen collected. The management of these risks should be based on a general implementation of a principled, precautionary approach similar to those used in laboratories and clinical settings, and should be embodied in a general safety management plan.

Biological hazards

All biological specimens should be considered as potentially infectious. Their collection and processing represents a source of hazard both for the subject who is the source of the specimens and for the staff involved in these processes. Immunization of BRC staff is recommended when appropriate vaccines are available. In particular, immunization against the Hepatitis B Virus (HBV) is mandatory for staff involved in collecting and processing human blood or tissues. Other significant risks are posed by exposure to the Hepatitis C Virus (HCV), the Human Immunodeficiency Virus (HIV) as well as to the prion that causes Creutzfeld-Jacobs diseases. Further sources of biological risk are identified by Grizzle and Fredenburgh [4] [Picture from http://www.fotosearch.fr/photos-images/symbole-biohazard.html (RF Libres de Droits)]

General laboratory safety

In addition to biosafety, BRCs need to follow strict general safety regulations and procedures in relation to chemical, physical and electrical safety. The use of liquid gases such as liquid nitrogen for cryopreservation is a serious source of hazard. There are also risks associated with the use of chemical fixatives and solvents used in tissue processing. Electrical safety is an important concern. Deep-freezers must be properly wired to adequate sources of electrical supply, and grounded. Work in a BRC also entails a number of occupational hazards typical of the laboratory environment. These risks must be taken into account before setting up a BRC, and their prevention must be integrated in all aspects of the Standard Operating Procedures of the BRC.

Data management and informatics safety

The protection of personal information and individual data associated with specimen collection is a fundamental requirement of a BRC. This should be achieved through the use of safe, structured bioinformatics systems. The mechanisms of access to these systems, as well as the permissions, should be clearly defined. Back-ups should be made on a regular basis to avoid data loss. The communication to third parties or authorities of data files containing personal information and identifiers should be strictly prohibited. Personal data archived in the BRC management system should be protected with the same stringency as patient clinical files.

General considerations for setting up a BRC

A number of factors must be taken into account in setting-up and running a BRC. A detailed description of these requirements can be found in the "best practices for biological repositories" developed by the International Society of Biological and Environmental repositories" [5]. The paragraph below underlines aspects of particular importance in setting up a BRC for cancer research.

Institutional commitment

Many factors contribute to the decision to develop a BRC. In practice, the process often starts from the willingness of medical doctors and scientists to develop a resource useful for diagnosis, prognosis and research purposes. However, initiating a BRC must not only rely on individual action but also requires a clear commitment by the institution to ensure that collections are developed within appropriate legal, ethical, clinical, scientific and technical guidelines, to provide historical continuity in specimen and record keeping, and to ensure that the materials stored by the BRC can be made available for research.

The purpose of the BRC must be clearly formulated and documented. BRCs that contract with third parties for laboratory service should keep detailed records of the nature of the contract, the identity of the contractor, and the inclusive dates of the contract period. In the case of loss of funding or other adverse events that may prevent the institution from maintaining its commitment, it is the responsibility of the institution to take necessary steps to transfer collected specimens and data to another institution that will take over the commitment to the long-term maintenance of the collection.

BRC management and staff

BRCs should be adequately staffed, and the personnel assigned to these tasks must have an appropriate level of training. The BRC should be placed under the overall supervision of a manager with sufficient training, experience and seniority to fulfil the scope of the activities of the BRC. The manager is responsible for operations, including compliance with current regulations. The manager has also a critical role in receiving, processing and answering requests for access to stored specimens.

Running a BRC requires dedicated staff for specimen processing and storage and for data management. The job description, tasks and reporting to authority of each supervisory and technical staff contributing to the BRC must be documented. This is of particular importance in the many instances where the staff contributing to the BRC also performs other tasks within the institution (e.g. pathology service or service activities in molecular biology). Staff must have adequate educational background, experience and training to ensure that assigned tasks are performed in accordance with the BRC's established procedures.

Infrastructure and facilities

The BRC's infrastructure depends upon the types of material being stored, the required storage conditions, the projected retention periods, and the projected use of the materials.

BRCs should have dedicated facilities that are not shared with other activities. Sufficient air conditioning must be provided for air circulation and to maintain ambient temperature equal or less than 22°C at the level of the freezers/refrigerators in order to prevent excess freezer wear and early failure. Rooms that contain liquid nitrogen tanks should be equipped with appropriate air flow systems to avoid the accumulation of N_2 in case of leakage. Storage facilities and instruments should be monitored by appropriate alarm systems (Figure 3.9.1). Response systems must be in place to respond to an alarm in a time frame that prevents or minimises loss or damage to the collection materials.

BRCs should be equipped with a system that adequately limits access to appropriate staff and protects against physical intrusion. In principle, only persons assigned to the BRC operation should have access to the material, and all materials added to or withdrawn are documented (Figure 3.9.2).

BRCs require a constant source of electrical power. Given that all commercial power will fail at some time, a backup power system is required. The most common type of backup power is the motor generator. Such a system should have the capacity to run for sufficient time to allow the restoration of power supply (typically 48 to 72 hrs) and should be regularly tested.

Adequate back-up capacity for low temperature units must be maintained. The total amount of back-up storage required for large repositor-

Fig. 3.9.1 *Monitors of LN2 level*

Fig. 3.9.2 *Controlled access to the BRC*

ies must be determined empirically, but will typically be 1.5–3% of the total freezer capacity.

Every repository should employ basic security systems. The systems must be monitored and alarms responded to 24h per day, 7 days per week. Response systems must be in place such that a responsible individual can take the necessary action to respond to an alarm in a time frame that prevents or minimises loss or damage to the collection materials. Systems should allow for calls to other key staff from a list of staff phone numbers when the first individual fails to acknowledge the alarm.

Storage conditions

Biospecimens should be stored in a stabilised state. In selecting the biospecimen storage temperature, consider the biospecimen type, the anticipated length of storage, the biomolecules of interest, and whether goals include preserving viable cells.

Cryopreservation

Cryopreservation is the recommended standard for preservation of human biological samples for a wide range of research applications. Cryopreservation, is a process where cells or whole tissues are preserved by cooling to low sub-zero temperatures, such as (typically) -80°C or -196°C (the boiling point of liquid nitrogen). At these low temperatures, any biological activity, including the biochemical reactions that would lead to cell death is effectively stopped. However, due to the particular physical properties of water, cryopreservation may damage cells and tissue by thermal stress, dehydration and increase in salt concentration, and formation of water crystals. Table 3.9.1 lists the most commonly accepted cryopreservation standards for human tissue and body fluids. It should be noted that specific applications (e.g. proteomics or development of primary cultures) may require more complex cryopreservation procedures. General information on the principles of cryopreservation may be found at http://www.cryobiosystem-imv.com/CBS/Cryobiology/cons_cbs.asp (Figure 3.9.3)

Specimen freezing is generally performed by placing the specimen in a sealed container, and by immersing the specimen into a rapid freezing medium. The ideal medium for rapid freezing is isopentane that has been cooled to its freezing point (-160°C). To achieve this, the vessel containing the isopentane must be introduced into another container of liquid nitrogen. The freezing point approximately corresponds to the moment when opaque drops begin to appear in the isopentane. Direct contact of the specimen with liquid nitrogen should be avoided, as this damages tissue structures.

Other fixation and preservation methods

Formalin or alcohol fixation and paraffin embedding may be used as an alternative method to preserve tissues at relatively low cost when adequate freezing procedures and storage facilities are not available. Fixed paraffin blocks may be stored in the dark at 22°C in a correctly ventilated cupboard (Figures 3.9.4 and 3.9.5).

Tissues fixed according to strict protocols may be used for DNA extraction. The DNA is usually fragmented but remains suitable for PCR-based analysis of short DNA fragments (up to 1-2 kbp). However, fixed tissues are of limited usefulness for RNA extraction. RNAlater is a commercial aqueous, non-toxic tissue storage reagent that rapidly permeates tissues to stabilize and protect cellular RNA. RNAlater eliminates the need to immediately process tissue samples or to freeze samples in liquid nitrogen for later processing. Tissue pieces can be harvested and submerged in RNAlater for storage without jeopardizing the quality or quantity of RNA obtained after subsequent RNA isolation. However, specimens placed in RNAlater cannot be further used for pathological analysis.

Fig. 3.9.3 *Storage at -196°C in liquid nitrogen*

Temperature	Properties of water/Liquid Nitrogen	Cryopreservation method	Biological relevance
0°C- +4°C	Ice melting	Fridge	
-0.5°C to -27°C	Ice fusion area	Freezer	
-27°C to -40°C	Ice	Freezer	Limit of protein mobility/ DNA stability
-40°C to -80°C	Limit of water molecules mobility	Freezer	RNA stability
-80°C to -130°C	Ice transition	Freezer/Liquid nitrogen	No metabolic activity Recommended storage for blood and urine
-130°C to -150°C	Liquid nitrogen vapour	Liquid nitrogen	Recommended storage for tissue
-150°C to -196°C	Liquid nitrogen liquid	Liquid nitrogen	Possible micro-fractures Recommended storage for living cells

Table 3.9.1 *Basic standards of crypreservation and applications to biological specimens*

Working with Liquid Nitrogen

Where liquid nitrogen (LN_2) refrigeration is employed, an adequate supply of refrigerant must be maintained. The supply maintained on hand should be at least 20% more than the normal re-fill usage to allow for emergency situations.

Handling liquid nitrogen has serious safety implication. Flesh freezes instantly at -196°C, causing severe burns. Because nitrogen displaces oxygen, care must be taken when LN_2 freezers are employed. The risk is inversely correlated with the size of the room. Oxygen level sensors should always be employed when LN_2 freezers are used in a repository.

When bulk storage and piping systems are used, blockage of relief valves and/or overpressure may lead to simultaneous leakage of N_2 from a number of relief valves, causing a "white-out" condition in a matter of a few seconds. Visibility drops to near zero and the oxygen level in the area is below that necessary to sustain life. Personnel must evacuate immediately.

Liquid nitrogen expands to 800 times its original volume at room temperature, causing a form of explosion hazard. Plastic and glass containers can easily explode if liquid is trapped when the container is removed from the freezer. Heavy gloves, a face shield, and a protective garment should always be used under these conditions.

Liquid Nitrogen (LN_2) tanks

The critical temperature for sensitive tissues, organisms and cells is generally considered to be -132°C, the glass transition temperature (Tg). Vapour phase storage is preferred over liquid phase storage. Design of the tank/freezer is critical to allow maintaining a sufficient amount of LN2 in the vapour phase. Use of vapour phase avoids the safety hazards inherent in liquid phase storage, including the risk of transmission of infectious agents (Figure 3.9.6).

Mechanical Freezers

Mechanical freezers are employed in a variety of storage temperature ranges, including -20°C, -40°C, -70 to -80°C, and occasionally -140°C. Freezers should be equipped with alarms set at about 10°C warmer than the nominal operating temperature of the unit (Figure 3.9.7).

Dry Ice

Dry ice or solid-phase carbon dioxide is frequently used as a refrigerant for shipping and emergency backup for mechanical freezers. Handling precautions should be employed when handling this material, which exists at a nominal -70°C. As dry ice sublimates, the CO_2 level in the surroundings can increase. In confined areas the carbon dioxide can displace oxygen, presenting an asphyxiation hazard.

Standard Operating Procedures

BRCs should develop, document and regularly update policies and procedures in a standardized written format incorporated into a Standard Operating Procedures (SOP) manual that is

Fig. 3.9.4 *Fixed formalin paraffin embedded tissues*

Fig. 3.9.5 *Histological slides*

Fig. 3.9.6 *Liquid nitrogen room*

Fig. 3.9.7 *Deep freezers room*

readily available to all laboratory personnel. The SOP manual should specifically include:

- Specimen handling policies and procedures including supplies, methods and equipment
- Laboratory procedures for tests and any aliquoting or other specimen processing
- Policies and procedures for shipping and receiving specimens
- Records management policies
- Quality assurance and quality control policies and procedures for supplies, equipment, instruments, reagents, labels, and processes employed in sample retrieval and processing
- Emergency and safety policies and procedures, including reporting of staff injuries and exposure to potential pathogens
- Policies and procedures for the investigation, documentation and reporting of accidents, errors, complaints and adverse outcomes
- Policies and procedures and schedules for equipment inspection, maintenance, repair and calibration
- Procedures for disposal of medical and other hazardous waste
- Policies and procedures describing requirements of training programs for BRC staff.

BRCs should have an appropriate QA and QC programs regarding equipment maintenance and repair, staff training, data management and recordkeeping, and adherence to Good Laboratory Practice. All BRC operations must be subjected to regular audits. The timing, scope and outcome of these audits should be documented. QA is an integrated system of management activities involving planning, implementation, documentation, assessment, and improvement to ensure that a process or item is of the type and quality needed for the project. QC is the system of technical activities that measures the attributes and performances of a process, or item, against defined standards, to verify that the stated requirements are fully met.

Records Management

BRCs must develop a record management system that permits detailed records to be made concurrently with the performance of each step in the collection, processing and distribution of specimens. This may include but is not limited to: informed consent, procurement, processing, preservation, quarantining, testing, record review, releasing, labelling, storage, distribution and quality control of specimens. Records shall be created and maintained in a manner that allows steps to be clearly traced. Record security systems shall be adequate to ensure confidentiality and safety. Record management should be regularly audited. Records should be kept for at least 10 years after expiration of specimen storage or specimen distribution. Electronic records should be adequately protected (regular back-ups on appropriate media, intrusion-proof management systems).

The BRC should be inventoried at regular intervals (e.g. every two years) to assess the concordance between stored specimens and records. The specific position of every stored aliquot should be tracked. Each freezer, refrigerator or room temperature storage cabinet should have a unique identifier. A convention should be established for numbering shelves, racks, boxes, as well as, each location within the container. The biorepository database should be updated each time a biospecimen is moved within or out of the biorepository.

Specimen labelling

Each specimen should be labelled in such a manner that the labelling will survive all potential storage conditions, in particular dry ice and liquid nitrogen.

- Ink used on the label should be resistant to all common laboratory solvents.
- Labels should be printed with a linear barcode if possible, thus providing a direct link to database software. However, it is also important to include human-readable indications of contents.
- Suggested information for the label is the tissue bank's unique identifier number, sample type and date of collection/banking, plus a barcode if available (Figures 3.9.8 and 3.9.9).

Specimen collection, processing, storage

The methods used to collect biospecimens will vary depending on how the specimens will be processed and what is intended to be the end use. This paragraph provides general recommendations for collection of blood, solid tissues, urine and wide blood cells. These recommendations are derived from those described in the Biorepository Protocols developed by the Australasian Biospecimen Network. [6]

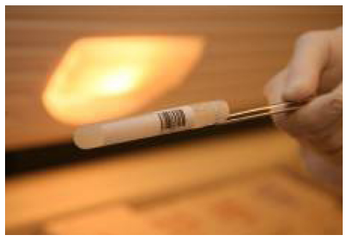


Fig. 3.9.8 *Linear bar-code*

Fig. 3.9.9 *2D Bar-code*

Collection of Blood

Detailed instructions and protocols for collection of blood specimens are given in the Protocols section. The following general guidelines should be considered.

- All blood should be treated as potentially infectious. It is recommended to take tissue bank blood samples concurrently with routine clinical blood samples, so as to limit discomfort to patients.
- Blood may be collected into EDTA, ACD (Acid Citrate Dextrose), lithium heparin, or into a clotted tube containing separating gel. Either EDTA and ACD tubes can be used if DNA is to be extracted or lymphocyte cell lines to be made; however, ACD is more appropriate if there is to be an extended time lapse between blood collection and processing. Lithium heparin is generally only used if cytology studies are being performed. If DNA is to be extracted from the blood or lymphocyte cells lines made, collecting into lithium heparin is not recommended [7].
- Tubes should be clearly labelled (Figure 3.9.10).
- The amount of blood usually collected varies for different diseases. In most cases, 2 tubes (18-20 ml) blood is an ideal collection amount. The volume collected is guided by ethics clearance. Reduced volume of blood in a tube containing additives should be noted so as to avoid confounding of results by variation in additive concentration
- Time of bleed and time of freezing should be recorded, as well as any variations to the processing protocol.
- Blood should be transported at room temperature, unless otherwise specified for particular applications (for some proteomic applications require transport on dry ice).
- All blood should be processed within 24 hours of collection. Cell viability decreases rapidly after 24 hours, resulting in poor cell structure in slide preparations, or degradation of proteins and nucleic acids.
- Serum and plasma should be stored within 2 hours.
- Blood spot collection should be considered as alternative to whole blood when protocols call for easier collection and cheap room-temperature storage [8]. Guthrie cards are made from pure cotton and can be used for the extraction of DNA (Figure 3.9.11).

Collection of Solid Tissues

Solid tissues are collected by biopsy or during surgical procedures. Collection should be carefully planned with surgeons and clinical staff, and all materials and instruments should be prepared in advance.

- The collection of samples for research should never compromise the diagnostic integrity of a specimen. Only tissue exceeding diagnostic needs should be banked.
- All tissue should be treated as potentially infectious; the collection process should be carried out in the most aseptic conditions possible.
- The intact operative specimen should be sent as soon as possible to pathology.
- It is recommended to process specimens within 30min of excision [9]. Transfer of specimens must be carried out as quickly as possible in order to minimise the effect of hypoxia upon genetic expression, and degradation of RNA and other tissue constituents. A record of the timing of events from excision to fixation or freezing should be kept.
- Each specimen receptacle must be clearly labelled (Figure 3.9.12).
- For transport from surgery to pathology, or to the repository, specimens should remain fresh (not fixed) and be placed in a closed, sterile container on wet ice.
- A pathologist should supervise the procurement of the tissue. The pathologists will examine the sample and, allowing adequate tissue for histological diagnosis and assessment of margins, will remove a portion of the tumour and adjacent normal tissue for specimen banking. When selecting specimens, areas with massive ischemia and/or necrosis should be avoided.
- The anatomical site from which the tissue is taken must be recorded and documented by a picture.
- Tissue bank staff must be present in pathology to freeze or fix the tissue as quickly as possible. Tissues should be placed in appropriate containers before freezing. Direct contact of the tissue with the liquid nitrogen should be avoided. Samples requiring snap freezing

Fig. 3.9.10 *Blood sample identification*

Fig. 3.9.11 *Blood spots storage*

Fig. 3.9.12 *Collection of solid tissues*

can be frozen in a Dewar of liquid nitrogen or on dry ice at the time of collection.
- When dry ice / liquid nitrogen is not readily available, tissue collections into RNA*later* may be a good alternative provided that this tissue is not required for diagnosis and clearance is given by the pathologist.

Collection of other specimens

Urine. Urine is easy to collect and is suitable source of protein, hormones, metabolites and DNA from exfoliated bladder cells. However, storage of urine specimens is space-consuming. Urine should be stored at -80°C or in liquid nitrogen vapour.

Buccal cells. The collection of buccal cells is not difficult and does not require highly trained staff. Buccal cell collection should therefore be considered when non-invasive, self-administered or mailed collection protocols are required [8]. Donors who do not give blood may also be asked to donate a buccal cell specimen; however, buccal cell collection will yield only limited amounts of DNA in comparison to blood. A collection kit (containing mouthwash, 50 ml plastic tube, plastic biohazard bottle, and courier packaging) may mailed or given to the participant, along with an instruction sheet.

Specimen annotations, data collection

It is recommended that BRC adopt standardised systems for annotating the characteristics of collected specimens as well as data on the patients or subjects who are the source of these specimens. The nature and extent of data collection may vary depending upon the project in which the specimens are collected as well as depending upon on the type of cancer and nature of specimen collected. The paragraphs below provide a brief outline of the structure of minimal annotation datasets.

Annotations on patients/subjects

- Local Patient Case Code
- Tumour topography and morphology according to the International Classification of Disease–Oncology (ICD-O 10) Histopathological (Figure 3.9.13)
- TNM staging
- Tumour grade
- Age at time of specimen collection (in years)
- Gender
- Place of residence (city/region/country)
- Ethnicity
- History of previous cancer disease
- Evidence for familial history of cancer
- Involvement into clinical trial/cohort study
- If appropriate, information on medical history, treatment and response to therapy, concomitant disease, secondary tumours/laboratory data

Annotations on stored specimen

- Local BRC inventory code
- Tissue condition (tumour/non-tumour/interface)
- Preservation protocol
- Time (in min) elapsed between tissue removal and fixation/freezing
- Duration of storage and record of storage incidents
- History of freezing/thawing
- Amount of tissue collected and amount left over in storage

Specimen shipping and sending

Human biospecimens are considered as "dangerous goods", that is, "articles or substances which are capable of posing a risk to health, safety, property of the environment". According to UN regulations, dangerous goods meet the criteria of one or more of nine UN hazard classes (see links to references below). The relevant class for biological specimens is Class 6, division 6.2: Infectious substances.

The shipping and sending of biospecimens is subject to international regulations. These regulations, applicable to any mode of transport are based upon the Recommendations by the Committee of Experts on the Transport of Dangerous Goods (UNCETDG), a committee of the United Nations Economic and Social Council.

Technical Instructions for the Safe Transport of Dangerous Goods by Air published by the International Civil Aviation Organization (ICAO) are the legally binding international regulations. The International Air Transport Association (IATA) publishes Dangerous Goods Regulations (DGR) that incorporates the ICAO provisions and may add further restrictions. The ICAO rules apply on all international flights. For national flights, i.e. flights within one country, national civil aviation authorities apply national legislation. This is normally based on the ICAO provisions, but may incorporate variations. State and operator variations are published in the ICAO Technical Instructions and in the IATA Dangerous Goods Regulations.

The following links refer to these regulations:

- UNECE (United Nations Economic Commission for Europe)
UN Recommendations on the Transport of Dangerous Goods. Model Regulations.
http://www.unece.org/trans/danger/publi/unrec/rev13/13files_e.html

- IATA (International Air Transport Association)
Dangerous Goods Regulations 2005.
http://www.iata.org/ps/publications/9065.htm

- ICAO (International Civil Aviation Organization)
http://www.icao.int/icao/en/m_publications.html

Fig. 3.9.13 *ICD-O 10 Book*

- WHO (World Health Organization)
Transport of infectious substances 2005
http://www.who.int/csr/resources/publications/biosafety/WHO_CDS_CSR_LYO_2005_22r%20.pdf

When preparing to transport biospecimens, it is important to consider shipping time, distance, climate, season, method of transport, and regulations as well as the type and number of biospecimens to be sent and their intended use. Below are some general guidelines:

Regulations

Infectious substances fall into two categories.

Category A comprises substances which are transported in a form that, when exposure to them occur, are capable of posing permanent disability or life-threatening or fatal disease to humans or animals. Category A specimens include, but are not restricted to, specimens contaminated by highly pathogenic viruses (Ebola, Hantaan, Marburg, Lassa, etc.) or cultures of viruses such as Dengue, Human Immunodeficiency Virus (HIV), Hepatitis B Virus (HBV). The proper shipping name for such substances is UN2814: "Infectious substances affecting humans" or UN2900: "Infectious substances affecting animal only".

Category B comprises substances that do not meet the above criteria. Most human specimens such as blood samples, tissues, exfoliated cells or urine, not contaminated by highly pathogenic viruses, will fall into Category B. The proper shipping name for such substances is UN3373: "Biological Substance, Category B".

Biospecimens or derived products that have been specifically treated to neutralize infectious agents, or for which there is a minimal likelihood that pathogens are present, are not subject to these regulations. The proper shipping name for such substances is "Exempt Human (or Animal) Specimens".

Packaging

The basic triple packaging system applies to all substances. It consists of three layers, as follows:

- *Primary receptacle*: a primary watertight, leak-proof receptacle containing the specimen, packaged with enough absorbent material to absorb all fluids in case of breakage;
- *Secondary packaging*: a second, durable watertight, leak-proof packaging to enclose and protect the primary receptacle. Several primary receptacles may be placed in one secondary packaging but additional absorbent material sufficient to absorb all fluid should be used in case of breakage;
- *Outer packaging*: an outer shipping packaging of suitable cushioning material, protecting the contents from outside influences while in transit (Figures 3.9.14 and 3.9.15).

Use appropriate insulation, e.g. for +8°C to -20°C use gel packs, for -80°C use dry ice, and if samples need to be kept at -150°C, transport them in a dry shipper containing liquid nitrogen. Ensure enough refrigerant is included to allow for a 24-hour delay in shipping.

The triple packaging system also applies to Exempt Human Specimens such as paraffin-embedded samples (that should be shipped at room temperature in insulated packaging to protect from extreme fluctuations in temperature), Guthrie cards (that should be transported in watertight plastic bags) or histopathological slides (that need to be cushioned to prevent breakage). In all cases, desiccants should be used for samples sensitive to humidity.

Labelling

All outer packages must bear United Nations packaging specification marking according to the category in which the specimens fall. For category A, the packaging instruction PI602 applies. For category B, the relevant packaging instruction is PI650. Detailed instructions are described in the IATA "Infectious Substances and Diagnostic Specimens Shipping Guidelines 2005" (www.iata.org).

When shipping biospecimens overseas, be aware of the receiver country's requirements prior to the initiation of the shipment, and ensure that the consignment adheres to these regulations.

Access to stored materials and data for research purposes

Access to human biological specimens for research purposes is crucial for most fields of

Fig. 3.9.14 *Preparation of the basic triple packaging system*

Fig. 3.9.15 *Preparation of the basic triple packaging system*

cancer research and in particular to genomics, proteomics, metabolomics or molecular imaging. Each BRC should establish clear guidelines for distribution and sharing of biospecimens and data, compatible with local, national and international prevailing laws, ethical principles, and protection of Intellectual Property. However, BRCs should not serve exclusively to satisfy individual needs or research projects and all efforts should be made to make specimens and data available to the wider scientific community. So far little has been done internationally to standardize access to biospecimens. The following paragraph, based on the recommendations developed by the NCI [10], develops general principles to guide the procedure for access to specimens for research purposes.

- Although BRCs have the right to establish priorities for access to specimens, in principle, BRCs should commit themselves to providing equal right of access to researchers.
- A mechanism of rapid peer and/or stakeholder review should be in place to set up priorities as to how collected specimens should be allocated to qualified recipient investigators.
- The proposed research project and use of specimen should be consistent with participants' consent, research purpose, and allowable use of specimens.
- Within the above principles, the main criteria for approving request for access should be the scientific validity of the research proposal, the investigator and institutional research qualifications, the investigator written agreement covering confidentiality, use, disposition, and security of specimens and associated data, the investigator's written agreement in a Material Transfer Agreement covering publication, sharing of research results, and ownership of future intellectual property, the Ethical approval of the proposed research, and the funding level for the project.

Constructing and running a large BRC: The example of the EPIC biobank

There are many types of BRC. Tumour banks, for examples, often are hospital-based collections of cancer tissues which are "leftovers" from diagnostic or surgical procedures. Many collections are also developed in the context of clinical trials: the patients recruited in these trials donate blood or tissue specimens, the analysis of which often enrich the results of the trial by allowing a better understanding of the parameters that determine good or bad response to a treatment. But the largest and the more systematic collections are those associated with large cohort studies developed in molecular epidemiological contexts. Typically, in such cohorts, healthy subjects are recruited, donate specimens at the time of recruitment (for example, blood, urine, saliva, or exfoliated cells from the buccal cavity) and are then followed up for a period of time that can extend over several decades. With time, a proportion of these subjects develop chronic diseases, including cancer (and also diabetes, heart diseases and other common conditions). It then becomes possible to compare subjects who developed a particular disease with those who did not, and to carry molecular studies using the specimens collected at recruitment, to identify biomarkers that predict or explain why these individuals have developed the disease under study.

EPIC (European Prospective Investigation into Cancer) is a typical example of such a large cohort study. It was developed by the IARC as a long-term, multi-centric prospective study in Western Europe to investigate the relationships between nutrition and cancer, taking advantage both of the contrast in cancer rates and dietary habits between centres and countries. As a rule, healthy subjects were invited to participate either by mail or in person. Individuals who agreed to participate signed an informed consent agreement and were mailed a questionnaire on diet and a questionnaire on lifestyle. Most participants completed these questionnaires at home and were then invited to a study centre for an examination that included collection of the completed questionnaires, blood donation, anthropometry and measurement of blood pressure. The enrolment of subjects took place between 1992 and 2000. The cohort participants are now followed over time for the occurrence of cancer and other diseases, as well as for overall mortality. The study has recruited 519 978 participants in 23 centres located in 10 European countries.

Blood was obtained by venipuncture and separated into plasma, serum, white blood cells and erythrocytes. They were collected from 385 747 of the 519 978 EPIC study participants. To make storage easier, blood samples were aliquoted into 28 plastic straws containing 0.5 ml each. The samples were then split into two mirror halves of 14 aliquots each. One set was stored locally, and the other one was transported to IARC to be stored in liquid nitrogen in a central biorepository located at IARC, where the specimens are kept under N2 liquid phase at -196°C. The biobank contains about 3.8 million straws, labelled with the participant's ID and colour-coded to indicate its contents.

The EPIC provides a framework for addressing a wide range of questions relevant to cancer. When biological samples are involved, studies mostly use the nested case–control approach. Typically, cases are subjects who developed a particular pathology after they were recruited in the cohort (incident cases) and had not been diagnosed with cancer before or at the time of recruitment. Controls are usually chosen at random among all cohort members who were alive without cancer at the time of recruitment of the case. The logistical tasks related to specimen management, retrieval from the biobank and distribution are handled by the team of Laboratory Infrastructure and Resources (LIR) at IARC. Based on lists of specimens and on their known position in the biorepository, the LIR technicians develop an ordered retrieval plan that minimizes the time of opening of each LN2 tank. Specimen retrieval is performed manually. It takes about 5 minutes to access one specific storage position and to retrieve either one or several straws of materials from the same subject. Standard operating procedures include double checking of 10% of all retrieved specimens to minimise the risk of individual error. On average, a trained technician can retrieve specimens for about 150 subjects over one normal working day. Specimen retrieval is a limiting factor in the pre-analytical processing of EPIC biospecimens and its demand in terms of manpower entails important costs, in particular for studies in which several thousand specimens are included. The LIR team offers a range of biobanking services including automated DNA extraction, quantification, aliquoting in various tube or microplate format, and specimen shipping. Currently, the EPIC biobank is providing support for research by over 250 scientists in Europe and beyond, and has provided the basis to several hundred international scientific publications. Constructing and maintaining such a biobank is a major effort that can be estimated, overall, to over 10 million US dollars.

The future of biobanking

The EPIC example shows the importance of developing large biobanks by networking the efforts of scientists in different countries. There is indeed a huge benefit in networking. Cancer diseases are very diverse and have complex relationships with both the genetic makeup of individuals and their lifestyles, so comparisons across different countries, ethnic groups and cultural backgrounds are extremely informative. Thus, tomorrow's BRC will be made of networks and hubs, interconnecting many collection centres and making it possible to access large series of specimens for research. By networking, it is possible to share the burden of investing into large biobanks as well as the benefits of research. Today's cancer research is a vast, collective endeavour, in which scientists and doctors have to team up in powerful networks, capable of delivering the best of human's mind creativity to the bedside of cancer patients.

IARC at the forefront in BRC "harmonisation" and developing large networks of biobanks

Cancer is a global disease, the understanding and management of which requires comparisons between disease patterns in different parts of the world. In addition, studies on many rare forms of cancer are limited by the fact that it is difficult to recruit a sufficient number of cases within any single collection centre.

It would be extremely damaging if different institutions and countries were to adopt different standards and rules to govern the many aspects of BRC workflow. Large international efforts are being set up to work towards convergence, developing "best practices" and facilitating networking among biobanks. IARC is playing a central role in these initiatives. The Agency is member of the various international forums and working groups where these issues are debated. To promote the adoption and the adhesion to common standards applicable in high-resource as well as low-resource countries, IARC recently coordinated a group of international experts to prepare a Technical Report on "Common Minimum Technical Standards and Protocols for Biological Resource Centres Dedicated to Cancer Research". This document provides all background information necessary to set up and develop a BRC, gives recommendations regarding critical points in BRC workflow, and proposes troubleshooting protocols for every key step in acquiring, handling, preserving and storing biospecimens. By acting at the forefront of the biobanking community, IARC is fulfilling its role as a coordinating centre for international cancer research, in particular towards lower-resource countries.

REFERENCES

1. OECD Directorate for Science, Technology and Industry (2007). *OECD Best Practice Guidelines for Biological Resource Centres*. Available from: http://www.oecd.org/dataoecd/7/13/38777417.pdf Date Accessed: November 15, 2008.

2. 18th World Medical Assembly (1964). Declaration of Helsinki. Recommendations guiding physicians in biomedical research involving human subjects. Helsinki: Finland.

3. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (1979). *The Belmont Report. Ethical principles and guidelines for the protection of human subjects of research*. Bethesda, MD: US Department of Health, Education, and Welfare.

4. Grizzle WE and Fredenburgh J (2001). Avoiding biohazards in medical, veterinary and research laboratories. *Biotech Histochem 76:* 183-206.

5. International Society for Biological and Environmental Repositories (2008). *ISBER Best Practices For Repositories. Collection, storage, retrieval and distribution of biological materials for research*. Available from: http://www.isber.org/Pubs/BestPractices2008.pdf Date Accessed: November 15,2008.

6. Australian Biospecimen Network (2007). *Biorepository Protocols. Revision 4*. East Melbourne, Australia: ABN.

7. Yokota M, Tatsumi N, Nathalang O, et al. (1999). Effects of heparin on polymerase chain reaction for blood white cells. *J Clin Lab Anal* 13: 133-140.

8. Steinberg K, Beck J, Nickerson D, et al. (2002). DNA banking for epidemiologic studies: a review of current practices. *Epidemiology* 13: 246-254.

9. Eiseman E, Bloom G, Brower J, et al. (2003). *Case studies of existing human tissue repositories : "Best practices" for a biospecimen resource for the genomic and proteomic era*. Santa Monica, CA: Rand Corporation.

10. National Cancer Institute. Office of Biorepositories and Biospecimen Research (2007). *NCI Best Practices for Biospecimen Resources*. Available from: http://biospecimens.cancer.gov/practices/ Date Accessed: November 15, 2008.

CANCER IN THE EASTERN MEDITERRANEAN AND NORTH AFRICAN REGION (EMRO)

According to WHO 2002 mortality estimates, cancer is the fourth-ranked cause of death in the Eastern Mediterranean and North African Region (EM Region), after cardiovascular diseases, infectious/parasitic diseases and injuries. It is estimated that cancer kills 272 000 people each year in the EM Region, more than HIV/AIDS, tuberculosis and malaria combined (241 000 deaths per year). Although cancer incidence in the EM region is still much lower than in other parts of the world, the largest increase in cancer incidence among the WHO regions in the next 15 years is likely to be in the EM region, in which projection modelling predicts an increase of between 100% and 180% [Rastogi *et al.* 2004]. At present, resources for cancer control in the EM region as a whole are not only inadequate but directed almost exclusively to treatment. However, the impact of preventive measures on incidence is not fully exploited, while the lack of approaches to earlier diagnosis reduce the value of therapy; the curability of cancer is directly related to its stage at the time of diagnosis, and in the majority of EM countries, cancer is generally diagnosed when at a relatively advanced stage (Table 1).

In response to the above situation, WHO/EMRO has developed a regional strategy for the prevention and control of cancer in its Member States, a draft of which was presented and discussed in a consultative meeting in Marrakesh, Morocco, November 2007 and will be finalised and formally launched in a meeting planned in April 2008. A Regional Alliance Against Cancer, bringing together various NGOs and interested parties working in EM Member States, was formally created during the Marrakesh meeting under the leadership of WHO and in collaboration with the Lalla Salma Association Against Cancer and H.R.H. Princess Lalla Salma, Patroness of Prevention and Care for cancer in the Eastern Mediterranean Region.

The strategy lays a foundation for the development of a coordinated approach that seeks to take advantage of the strengths of some of the regional resources to overcome some of the weaknesses that exist in the Region. An important function of the strategy resides in its twin goals of sensitising authorities in Member States to the pressing need to control cancer more effectively, while at the same time providing technical guidance and a foundational formula for regional cooperation in this endeavour. The strategy encourages countries to develop their National Cancer Control Programmes (NCCP), an essential first step towards more effective cancer control.

The EM regional strategy is in keeping with the WHO Global Action Plan against Cancer (GAPAC) and pursues the same goals, which are to:

- Prevent Preventable Cancers (through avoiding or reducing exposure to risk factors, i.e. prevention strategies);
- Cure Curable Cancers (early detection, diagnostic and treatment strategies);
- Relieve Pain and Improve Quality of Life (Palliative care strategies); and
- Manage for Success (strengthening health care systems; management, monitoring and evaluation of interventions).

WHO/EMRO continues to assist countries to develop their NCCPs, and in 2007 participated in two missions to Yemen and Syria in collaboration with IAEA's PACT Programme.

The pattern of cancer in EM Region is shown in Table 2. Data are obtained from the GLOBOCAN database and updated, for many countries, directly by national focal points based on latest information from their cancer registries. Breast cancer has the highest incidence rate in most countries, while cervical cancer is the leading type of cancer in Djibouti and Somalia.

website: www.emro.who.int

	Breast Cancer			Cervical Cancer		
Stage	USA	Saudi Arabia	Egypt	USA	Saudi Arabia	Egypt
Localised	65%	29%	25.5%	58%	35%	35.9%
Regional	30%	55%	58%	33%	51%	53.2%
Distant	5%	16%	16.5%	9%	14%	10.9%

Table 1. *Stage at diagnosis in breast and cervical cancer as reported by a population based registry in Saudi Arabia [National cancer registry report, 2002], Tanta Cancer registry (Gharbiah 2000-2002, Egypt), and US [SEER, 9 Registries 1988-2003].*

Country	1st cancer	2nd cancer	3rd cancer	4th cancer	5th cancer
Afghanistan	Breast	Stomach	Esophagus	Lung	Oral Cavity
Bahrain	Breast	Lung	Colon	Bladder	Leukaemia
Djibouti	Cervix	Liver	Breast	Esophagus	Kaposi
Egypt	Breast	bladder	NHL	Liver	Lung
Iran	Breast	Stomach	Colon	Bladder	Esophagus
Iraq	Breast	Leukaemia	Lung	Brain and CNS; Larynx	Bladder
Jordan	Breast	Colon	Lung	Bladder	NHL
Kuwait	Breast	Lung	Colon	NHL	Leukaemia
Lebanon	Breast	Lung	Bladder	Cervix	Larynx
Libya	Breast	Lung	Colon	Head & neck; Cervix	Bladder
Morocco	Breast	Lung	Cervix	Prostate	lymphoma
Oman	Stomach	Breast	Lung	NHL	Liver
Pakistan	Breast	Oral Cavity	Lung	Esophagus	Bladder
Qatar	Lung	Breast	Colon	Bladder	Liver
Saudi Arabia	Breast	NHL	Liver	Colon	Thyroid
Somalia	Cervix	Liver	Esophagus	Breast	NHL
Sudan	Breast	Cervix	Oral Cavity	Esophagus	Colon
Syria	Breast	lung	NHL	CNS	Bladder
Tunisia	Lung	Breast	Bladder	Colon	NHL
UAE	Breast	Colon	Blood Leukaemia	Lymphomas	Thyroid
Yemen	Breast	NHL	Colon	NHL	Esophagus

Table 2. *Commonest 5 cancers in EM countries*

4

Acting for Prevention

4.1 Tobacco Control

Summary

> The main benefit from quitting smoking arises from avoiding the more pronounced increase in risk that would result from continuing to smoke

> Quitting smoking before middle age avoids much of the lifetime risk incurred by continuing to smoke, conferring substantially lower lung cancer risk compared with continuing smokers

> The WHO Framework Convention on Tobacco Control (WHO FCTC), the first-ever public health treaty with widespread support worldwide, encompasses a series of stipulations designed to control tobacco use and supply

> Comprehensive smoke-free and tobacco pricing policies, two of the WHO FCTC-endorsed policies, have been effective in reducing exposure to secondhand smoke, diminishing cigarette consumption and increasing quitting smoking

> There are pharmacologic and non-pharmacologic tobacco dependence treatments options, varying in effectiveness, available to aid those who want to quit smoking

Risk reduction

For smoking-induced morbidity and mortality to disappear, smoking initiation in the young must cease. Ironically, it would take many decades for morbidity and mortality trends to reflect the effects of such intervention, mainly due to the lag time of expected health consequences in prevalent smokers who will continue to do so. However, if current smokers quit, the risks of developing or dying from cancer as compared to continuing counterparts would diminish even if stopping after decades of smoking. An assessment of changes in cancer risk and of other diseases caused by smoking with smoking cessation was conducted by an international Working Group of experts convened at IARC in Lyon on March 13-19, 2006 [1,2]. The assessment addressed three questions:

- is the risk of developing cancer, for each of the 13 tobacco-associated cancers considered, lower in former smokers than in otherwise similar current smokers?
- Among otherwise similar former smokers, is the risk of disease lower with more prolonged abstinence?
- Does the risk return to that of never smokers after a long period of abstinence?

Conclusions by the Working Group on the effects of smoking cessation on the risk of developing and dying from lung, laryngeal, oral and oesophageal cancers are shown in Tables 4.1.1 and 4.1.2, indicating a lower risk of cancer at these sites in those who quit as compared to those who continue to smoke [2].

Tobacco control interventions

To arrest the global tobacco epidemic, initiation must be prevented and cessation pursued and maintained actively in the population. Interventions addressing these primary and secondary prevention strategies, for the purposes of this chapter, will be described in two major groups: policy and non-policy approaches—the former directed at the population level (e.g. smoking restriction in public places) and the latter often adopted by individual choice within the framework of recommended guidelines by healthcare professionals and/or regional or national health systems (e.g. pharmacologic and non-pharmacologic alternatives). Given the potential reach of interventions designed to affect an entire population or at a minimum the group of smokers in a geographic unit, policy interventions, in particular those that are WHO-backed, will be covered here in greater depth.

Policy-based interventions

Achieving prevention of initiation and increased cessation of tobacco use are two cardinal public health goals of the World Health Organization (WHO). Accordingly, the WHO and member states were proponents and overwhelmingly supported the first public health treaty conceived to reduce tobacco use worldwide.

The WHO Framework Convention on Tobacco Control (WHO FCTC) encompasses a series of measures, in their totality representing a comprehensive approach, designed to control tobacco use and supply. The body of policies stipulated in the treaty became binding international law on 27 February 2005. Of the 38 articles, articles 6 to 14 cover policy interventions directed at preventing tobacco use, decreasing consumption, reducing toxicity, protecting non-smokers and diminishing tobacco use initiation. Articles 15 to 17 relate to measures controlling the availability of tobacco (Table 4.1.3) [3]. The concerted adherence of countries to the treaty around the world will make it a global response to the tobacco epidemic. However, the reach of the policy interventions included in the WHO FCTC will depend on how effectively countries formulate and implement these policies. As of November 2008, 160 countries have subscribed to the treaty (Figure 4.1.1)[3]. IARC convened a group of international tobacco control policy experts in March 2007 to propose a framework for guiding the evaluation of tobacco control policies expected to be formulated worldwide in response to WHO-FCTC. This framework and its scientific and policy bases will aid tobacco control policy authorities to assess if intended targets are fulfilled [4].

Comprehensive tobacco control programs are more likely to be successful in reducing tobacco use than programs relying in few interventions. Joossens and Raw [5] have proposed a scale to quantify the implementation of tobacco control interventions at country level. Their work is based on a baseline survey conducted in 2005 in 30 European countries. Tobacco control policies taken into account in the scale included price of cigarettes and other tobacco products, smoke-free work and other public places on July 1, 2005, spending on public information campaigns in 2004, comprehensive bans on advertisement and promotion on July 2005, large health warning labels, on 1 July 2005, and cessation services in place. Tobacco control performance varied greatly within Europe, from countries accruing ≥70 points (Great Britain, Ireland, Norway and Iceland) to countries accumulating <30, with results by type of intervention indicating areas where future efforts could be concentrated.

Protection from exposure to SHS. Countries enacting laws banning smoking in public places have shown high compliance and significant decrease in SHS exposure. The banning of smoking in pubs and restaurants in Scotland started in 26 March 2006, with pre-ban concentration levels of particulate matter ($PM_{2.5}$) aver-

Benefits of quitting smoking on risk of developing and/or dying from lung cancer

These conclusions are based on epidemiologic studies comparing lung cancer risk in persons who stop smoking with the risk of those who continue, showing lower lung cancer risk in former than in current smokers.

The main benefit from quitting arises from avoiding the more pronounced increase in risk that would result from continuing to smoke.

Within five to nine years after quitting, the lower lung cancer risk in former compared with otherwise similar current smokers becomes apparent and widens increasingly with longer time since cessation.

Quitting smoking before middle age avoids much of the lifetime risk incurred by continuing to smoke, conferring substantially lower lung cancer risk compared with continuing smokers

The absolute annual risk of developing or dying from lung cancer does not decrease after quitting smoking. An individual who has smoked will always have a greater risk of developing lung cancer in comparison with an otherwise similar individual who has never used tobacco.

There is a lasting increased risk of lung cancer in former smokers compared to never smokers of the same age, even after a long duration of abstinence.

Table 4.1.1 *Benefits of quitting smoking on risk of developing and/or dying from lung cancer*
Adapted from Reversal of Risk After Quitting Smoking [2]

Cancer site	Is the risk lower in former smokers than in otherwise similar current smokers?	Does the difference in risk between former smokers and otherwise similar current smokers become larger with time since cessation?	Does the risk return to that of never smokers after long period of abstinence?
Laryngeal	Yes. The risk is lower in former smokers than in those who continue to smoke	Yes. The benefits of cessation relative to continued smoking increase with longer time since cessation	No. The risk does not return to that of never smokers after a long duration of abstinence. It remains higher for at least two decades
Oral	Yes. The risk of oral and pharyngeal cancer is lower in former smokers than in current smokers	Yes. The reduction in risk for former smokers compared with current smokers increases with longer time since cessation	Yes. The relative risk for former smokers who have stopped for at least twenty years is not increased over that of never smokers
Oesophageal (squamous-cell)	Yes. The risk is lower in former smokers than in those who continue to smoke	Yes. The reduction in risk for former smokers compared with current smokers increases with longer time since cessation	No. The relative risk does not return to that of never smokers; it remains elevated for at least two decades after cessation

Table 4.1.2 *Benefits of quitting smoking on risk of developing and/or dying from laryngeal, oral or oesophageal cancers*
Adapted from Reversal of Risk After Quitting Smoking [2]

aging 246 µg/m^3 (range 8-902 µg/m^3) and post-ban levels 20 µg/m^3 (range 6-140 µg/m^3) equivalent to an average reduction of 86% [6].

A meta-analysis of 26 studies conducted in Australia, Canada, Germany and the USA on the effects of total smoke-free work places documented smoking cessation in adults and younger smokers as well as protection from SHS [7]. This systematic review found an overall reduction in smoking prevalence (3.8%; 95% CI=2.8–4.7%) and number of cigarettes smoked daily in continuing smokers (3.1 cigarettes; 95% CI= 2.4–3.8) with total smoking bans.

One year after the Scottish ban a significant 39% decrease (95% CI=29–47%) in exposure to SHS using biomarkers of exposure (salivary cotinine concentrations) in non-smoking adults has been reported [8]. The drop in exposure was higher for individuals living in households with no smokers (a 49% decline; 95% CI=40–56%). Nonetheless, non-smokers living with smokers experienced a 16% drop in cotinine concentration that was, however, not statistically significant. Findings from the evaluation assessing exposure in primary school students found significant reductions in exposure, as revealed by salivary cotinine concentrations, only in children living in households with no smokers (a 51% drop) or in those where only the father smoked (44%) [9]. These results from the Scotland evaluation pinpoint the importance of the household (and cars) as a source of exposure to SHS.

Price and tax measures to reduce demand. Policies prohibiting smoking in public places are intended to protect the health of all but in particular that of non-smokers. Tax policies on tobacco products also affect a substantial portion of the population and are intended to discourage tobacco use in established and in potential users, in addition to generating revenues. The WHO FCTC contemplates the use of taxes on tobacco products as an effective intervention to control tobacco use by increasing prices and impacting product demand. Chaloupka and colleagues have extensively documented the role of fiscal policies in reducing tobacco consumption and increasing cessation in users and sustaining abstinence in non-smokers [10,11]. Studies from high-resource countries show that a 10% increase in the price of cigarettes, following elevation of taxes, produce a decline in use that varies between 2.5% and 5%, affecting both the prevalence of smoking and the amount consumed [10]. Gallus and colleagues have also studied the effect of price on cigarette consumption in Europe reporting for each 10% increase in the price of cigarettes a drop in consumption of 5–7% [12].

The impact of similar price increments (10%) on tobacco use in low/medium-resource countries appears to be greater, depending on the population studied and the income level referred to (5.4–6.6% in China; 13.3% and 5.2% in lower and higher income groups respectively in Bulgaria) [11]. Long-term reduction in tobacco use as a result of increases in price tend to be higher than short-term effects, reflecting the progressive overcoming of addiction among those who are successful in quitting or in reducing consumption (up to 2% and 8% reduction in consumption in the short and long-term respectively in Brazil) [11]. Income is also a significant variable explaining tobacco demand (i.e. increments in income leading to greater consumption). Changes in smoking behaviour in response to increments in cigarette prices tend to be more pronounced in the young and in less affluent groups in the population.

Cigarette price affects smoking initiation, too, based on studies conducted in both more and less developed countries. Ross and Chaloupka cite results from a study conducted in Vietnam using survey data from different periods and concluding that a 10% increase in cigarette price would decrease smoking initiation by 11.8% [11]. Slater and colleagues [13] have conducted a more sophisticated analysis of US data taking into account cigarette price, point-of-sale advertising and promotion. Their results indicate that for each dollar increase in price the odds that an adolescent moves upward in the smoking uptake ladder will decrease by 24% (never smoker, puffer, non recent experimenter, former established smoker, recent experimenter and current established smoker) [13].

Article 6	Price and tax measures to reduce demand
Article 8	Protection from exposure to tobacco smoke
Article 9	Regulation of the contents of tobacco products
Article 10	Regulation of tobacco product disclosures
Article 11	Packaging and labelling of tobacco products
Article 12	Education, communication, training and public awareness
Article 13	Tobacco advertising, promotion and sponsorship
Article 14	Demand reduction measures concerning tobacco dependence and cessation
Article 15	Illicit trade in tobacco products
Article 16	Sales to and by minors
Article 17	Provision of support for economically viable alternative activities

Table 4.1.3 *WHO FCTC Articles addressing key interventions to reduce tobacco demand and supply (Adapted from WHO, 2003[3])*

Non-policy interventions

The majority of smokers desire to quit smoking, but the path from intention to actual cessation is long in the greater part of smokers. There are pharmacologic (i.e. nicotine replacement therapy, NRT, Table 4.1.4) and non-pharmacologic approaches (i.e. counselling, Table 4.1.5) available to aid smokers quit their dependence on nicotine, the addictive component of tobacco, and both types are often prescribed jointly. There are three pharmacologic therapies that have proven efficacious: nicotine replacement therapy (odds ratio of quitting of 1.5 to 2-fold over placebo), bupropion, an antidepression medication (odds ratio of quitting of 2 over placebo), and varenicline, a nicotine receptor partial agonist that reduces nicotine withdrawal symptoms (odds ratio of quitting of 3-fold over placebo)[14,15]. The characteristics of these therapies are compared in Table 4.1.4. These products have been tested in clinical trials where psychological, behavioural and emotional supports have been available to trial participants. Since approximately 70% of smokers want to stop smoking, it is imperative that smokers become aware of the existence of these pharmacologic approaches and that healthcare providers use every opportunity possible to assess patient's desire to quit, provide information on quitting aids, advise additional support of non-pharmacologic interventions for the treatment of tobacco dependence and if possible follow smokers in their quitting attempts (Table 4.1.5).

More recently, vaccine technology has been used to produce antibodies against nicotine as an approach to prevent relapse in former smokers and to allow quitting smoking. Several vaccines have been formulated and tested in animals and humans with cessation success been observed in those mounting strong antibody responses [16]. At present, 3 vaccines have been tested in Phase II clinical trials, each using a different antigen (nicotine) presentation approach: Ta-NCI (Celtic Pharma, Hamilton, Bermuda) binds nicotine to recombinant

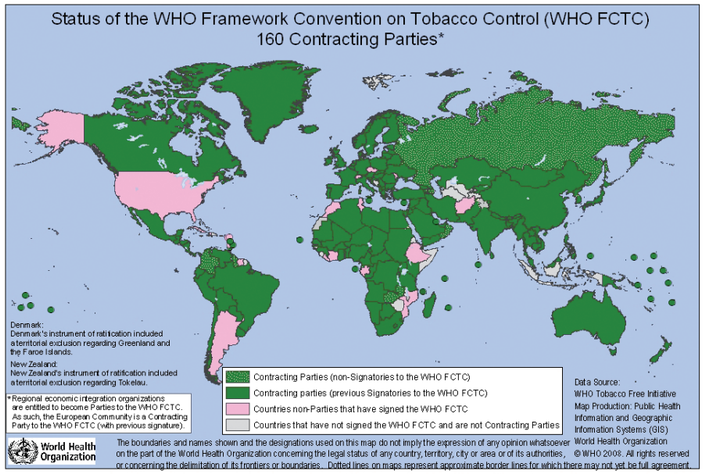


Fig. 4.1.1 *Status of the WHO FCTC 160 Contracting Parties*

cholera toxin B; NicQb (Cytos Biotechnology, Zurich, Switzerland) employs virus-like particles from the bacteriophag Qb; and NicVax® (Nabi Pharmaceuticals, Boca Raton, Florida, USA) uses recombinant exoprotein A [15]. The nicotine vaccine can also bring about a reduction in the amount smoked by making the metabolism of nicotine slower and inducing its effect to last longer, hence reducing craving.

The duration of the vaccine immunity is, however, unknown at present. Dosing and administration schemes are being formulated in order to carry on Phase III clinical trials that will reveal vaccine efficacy. The potential use of this secondary prevention approach is very promising given the number of smokers who wish to quit and the number of former smokers who desire to remain abstinent.

Discussion

Two WHO FCTC-endorsed policies with impact at the population level and several approaches to treat tobacco dependence have been presented in this chapter. The success of these policies in achieving reductions in tobacco use and protection in non-smokers will depend on a more complex array of factors than those included in this chapter, such as total or partial ban of smoking restrictions in work and public places, enforcement of restrictions, tax avoidance, smuggling of tobacco produces and/or proliferation of grey markets to name few. Still, these are policies that have been shown to decrease the use of tobacco products and that are receiving global attention in response to the activation of the WHO FCTC legislative clock. These are not the only policy interventions effective in curbing tobacco use. Suppression of tobacco advertising, promotion and sponsorship, education and communication campaigns to raise awareness and product labelling, for example, have been shown to modulate tobacco use in adolescents and adults.

Lung cancer rates are influenced by smoking initiation and smoking cessation in the population. At present, there are many countries showing increasing trends in lung cancer mortality in younger age groups where there are no evident trends in decreasing smoking initiation and/or

increasing smoking cessation. If these smoking trends remain unaltered, projected lung cancer incidence and mortality will grow rather than decrease. Policies leading to smoking cessation and preventing smoking initiation must be fostered and maintained. Also important, smokers and former smokers can and should be assisted in their attempts to quit and remain abstinent by receiving pharmacologic and nonpharmacologic intervention treatments within the healthcare system or as advised by the principal healthcare provider. However, smokers tend to avoid clinic-based smoking cessation programmes but on the other hand respond to environmental prescriptions such as smoking bans. Hence the importance of policy-based interventions designed to deter tobacco use and eventually leading to the denormalisation of this behaviour.

Drug	Dose	Duration of treatment	Contraindications	Adverse effects*
Nicotine replacement therapy	Dose is adjusted to level of nicotine dependence and is decreased progressively over treatment period Patch: 21–42 mg/d initially Gum: 8–10 pieces (2 or 4 mg each) per day Inhaler: 4–6 puffs per day Lozenge: 9–20 lozenges per day	8–12 weeks; can be longer (up to 1 year) for the prevention of relapse	Patch: allergy to constituent of nicotine patch	Patch: skin irritation, sleep disturbance Gum or lozenge: mouth irritation, sore jaw, dyspepsia, hiccups Inhaler: mouth and throat irritation, cough
Bupropion, sustained release (Zyban)	150 mg/d for first 3 days, then 300 mg/d	8 weeks; can be longer (up to 1 year) for the prevention of relapse	Seizure, central nervous system tumour, bipolar disorder, alcohol withdrawal, benzodiazepine withdrawal, use of monoamine oxidase inhibitor, anorexia, bulimia, liver disease	Insomnia, seizure, gastrointestinal disturbance, jitteriness
Varenicline (Champix)	0.5 mg/d for first 3 days, then 0.5 mg twice daily for the next 4 days and 1 mg twice daily thereafter	12 weeks; can be longer (up to 24 weeks) for the prevention of relapse	None	Nausea, vomiting, constipation, flatulence, bad taste in the mouth, abnormal dreams, sleep disturbance

Table 4.1.4 *Pharmacologic treatment of tobacco dependence. Adapted from Le Foll and George, 2007[14]*
**Most frequent adverse events*

Intervention	Description	Estimated efficacy odds ratio (95% CI)
Advice from physician to quit smoking	Even a short intervention (3 minutes or less) can increase a person's motivation to quit and can significantly increase abstinence rates. Since an estimated 70% of smokers visit a physician each year, physicians have a substantial opportunity to influence smoking behaviour	1.3 (1.1–1.6)
Self-help materials	Self-help materials come in the form of pamphlets, videotapes, audiotapes, hotlines/helplines and information on websites. Such materials may be more effective than no intervention in motivating people to quit, but they are not as effective as materials tailored for individual smokers	1.1 (0.9–1.3)
Proactive telephone counselling	Telephone counselling is efficacious in assisting people interested in quitting smoking. However, the effects are not additive when it is combined with nicotine replacement therapy	1.3 (1.1–1.4)
Group counselling	Group therapy offers individuals the opportunity to learn behavioural techniques for smoking cessation and to provide each other with mutual support. There is limited evidence that the combination of group therapy with other forms of treatment (e.g., advice from a health professional or nicotine replacement therapy) produces extra benefit	1.3 (1.1–1.6)
Individual counselling	Face-to-face individual counselling with a health care worker not involved in the patient's routine clinical care is efficacious. However, there is no significant additive effect when it is combined with nicotine replacement therapy. Brief counselling may be as effective as intensive counselling	1.6 (1.3–1.8)
Intra-treatment social support	Support is provided during a smoker's direct contact with a clinician	1.3 (1.1–1.6)
Extra-treatment social support	Interventions that increase social support in the smokers' environment are efficacious. The clinician should help the patient in requesting social support from family, friends and coworkers and in establishing a smoke-free home	1.5 (1.1–2.1)

Table 4.1.5 *Nonpharmacologic interventions for the treatment of tobacco dependence and their estimated efficacy. Adapted from Le Foll and George, 2007[14]*
Note: CI = confidence interval

REFERENCES

1. Dresler CM, Leon ME, Straif K, et al. (2006). Reversal of risk upon quitting smoking. *Lancet* 368: 348-349.

2. IARC (2007). *IARC Handbooks of Cancer Prevention, Tobacco Control. Volume 11, Reversal of Risk After Quitting Smoking*. Lyon, France: International Agency for Research on Cancer.

3. World Health Organization (2003). *WHO Framework Convention on Tobacco Control*. Available from: http://www.who.int/fctc/en/ Date Accessed: October 12, 2008.

4. IARC (In Press). *IARC Handbooks of Cancer Prevention, Tobacco Control. Volume 12, Methods for evaluating tobacco control policies*. Lyon, France: International Agency for Research on Cancer.

5. Joossens L and Raw M (2006). The Tobacco Control Scale: a new scale to measure country activity. *Tob Control* 15: 247-253.

6. Semple S, Creely KS, Naji A, et al. (2007). Secondhand smoke levels in Scottish pubs: the effect of smoke-free legislation. *Tob Control* 16: 127-132.

7. Fichtenberg CM and Glantz SA (2002). Effect of smoke-free workplaces on smoking behaviour: systematic review. *Br Med J* 325: 188.

8. Haw SJ and Gruer L (2007). Changes in exposure of adult non-smokers to secondhand smoke after implementation of smoke-free legislation in Scotland: national cross sectional survey. *Br Med J* 335: 549.

9. Akhtar PC, Currie DB, Currie CE, et al. (2007). Changes in child exposure to environmental tobacco smoke (CHETS) study after implementation of smoke-free legislation in Scotland: national cross sectional survey. *Br Med J* 335: 545.

10. Chaloupka FK, Hu TW, Warner KE, et al. (2000). The taxation of tobacco products. In: Jha P, Chaloupka FK, eds., *Tobacco control in developing countries*. Oxford: Oxford University Press.

11. Ross H and Chaloupka FJ (2006). Economic policies for tobacco control in developing countries. *Salud Publica Mex* 48: S113-S120.

12. Gallus S, Schiaffino A, La Vecchia C, et al. (2006). Price and cigarette consumption in Europe. *Tob Control* 15: 114-119.

13. Slater SJ, Chaloupka FJ, Wakefield M, et al. (2007). The impact of retail cigarette marketing practices on youth smoking uptake. *Arch Pediatr Adolesc Med* 161: 440-445.

14. Le Foll B and George TP (2007). Treatment of tobacco dependence: integrating recent progress into practice. *CMAJ* 177: 1373-1380.

15. Murtagh J and Foerster V (2007). Nicotine vaccines for smoking cessation. *Issues Emerg Health Technol* 1-4.

16. Maurer P and Bachmann MF (2006). Therapeutic vaccines for nicotine dependence. *Curr Opin Mol Ther* 8: 11-16.

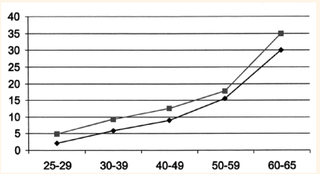
CANCER INSTITUTE PROFILE: Centre Regional Francophone de Formation a la Prevention des Cancers Gynecologiques (CERFFO pcg)

The French-speaking Regional Centre for Training in Gynaecologic Cancer Prevention (known by its French acronym CERFFO), located in Conakry, Guinea, provides information, training and technical assistance based on practical solutions that insure the implementation and continuation of gynaecologic cancer prevention strategies fitted to social, cultural and environmental settings of our region.

The centre has three missions: Training, Research and Services Management.

At the centre, reproductive health providers may further new assessment approaches for screening and treating major gynaecological cancers, improve healthcare systems in diagnosis and health management, and contribute to the implementation of gynaecologic cancer prevention programs with respect to national policies and programs for fighting against cancer.

Through their wide range of multidisciplinary skills, the staff of CERFFO also collaborates with specialised agencies in the implementation of regional research projects, assisting in innovative studies of the impact and evolution of national programmes aimed at reducing gynaecologic cancer incidence and mortality. The Centre also contributes to the education and training of healthcare professionals and researchers via its short-term training schedule for enhancing the managerial and pedagogical skills of project leaders and programme officers.



4.2 Prevention of Occupational Cancer

Summary

> In high-resource countries, prevention of occupational cancer is likely to have occurred during the last decades thanks to regulation and improvement of working conditions. However, quantifying the effect of this change is difficult

> Regulation (e.g. setting of standards) often has to rely on experimental data, as evidence from epidemiological studies is often lacking

> Measures aimed to prevent occupational cancer should be implemented in low-resource countries as well

Over the past 50 years, the number of occupationally-induced cancers has likely decreased in high-resource countries [1]. This is the result of several different trends. The decline in blue-collar heavy industry and the corresponding growth of white-collar knowledge industries has served to decrease the number of workers in particularly "dirty" occupations. At the same time, many industries have instituted procedures and processes that provide much cleaner work sites than in the past [2]. The motivations for this are complex and multi-dimensional. In part, this is a by-product of epidemiologic research carried out in the past [3,4]. In many countries the identification and characterisation of occupational carcinogens triggers regulatory actions intended to reduce the permissible exposure levels. Such actions may range from substitution of one substance in an industrial process for another, modification of industrial procedures or ventilation/emission control procedures, or the use of protective equipment by workers. But the real benefits of such regulations may be quite non-specific. That is, while regulations concerning a particular carcinogen may serve to reduce the risk of cancer in relation to that carcinogen, cleaning up an industrial process induces reduction in exposure to many substances, some of which may be in the hidden part of the iceberg of occupational carcinogens.

It is impossible to estimate how many occupational cancer cases have been prevented, but it is certainly a partial success story. In addition, there has been a growing realisation on the part of many industries that good industrial hygiene makes good business sense. The cautionary tales of companies that have suffered from regulatory or legal opprobrium, as well as compensation costs, as a result of being identified as a "cancer-causing company" might have served as an incentive for other companies to clean up.

Setting standards for regulatory purposes is a difficult task that relies on epidemiologic, toxicologic and other data [5,6]. Historically, these standards have usually been based on considerations of acute toxicity; increasingly, however, cancer has become a key endpoint. The main problem with setting standards aimed at reducing carcinogen exposure is the lack of reliable epidemiologic data on dose-response relationships. For the most part, the regulators must rely on animal data, with complex mathematical models used to translate the animal experience into terms that are relevant for human risk assessment.

One approach, which can only be implemented if a known carcinogen has not yet been introduced into industrial practice, is to ban its introduction. On occasions when an agent has been used and shown to be carcinogenic in one country, that information can then be used by other countries. For example, following reports from the United States on the increased bladder cancer risk among workers exposed to 4-aminobiphenyl, its introduction was banned in the United Kingdom [7]. Substitution of products known to be carcinogenic has been used successfully, as in the example of asbestos and man-made mineral fibres. More common have been attempts to reduce exposure levels to known or suspect carcinogens. Successful examples include: the virtual elimination of radiation-related cancer risk among nuclear

Fig. 4.2.1 *Clothing to prevent contamination*

Pollutant	Decrease
Carbon monoxide (CO)	37%
Lead	78%
Nitrogen dioxide (NO_2)	14%
Ozone	6%
Particles of ≤10 µm diameter (PM-10) PM-10 measurements began in 1988	22%
Sulfur dioxide (SO_2)	37%

Table 4.2.1 *Percent decrease in air concentrations of six key air pollutants, USA (1986-1995)*

Country	Year	Butadiene concentration (mg/m3)	Interpretation
Australia	1991	22 (Probable human carcinogen)	Time-weighted average
Belgium	1991	22 (Probable human carcinogen)	Time-weighted average
Czechoslovakia	1991	20	Time-weighted average
		40	Ceiling
Denmark	1993	22 (Potential occupational carcinogen)	Time-weighted average
Finland	1998	2.2	Time-weighted average
France	1993	36	Time-weighted average
Germany	1998	34 (Human carcinogen)	Technical exposure limit
		11	
Hungary	1993	10 (Potential occupational carcinogen)	Short-term exposure limit
The Netherlands	1996	46	Time-weighted average
The Philippines	1993	2200	Time-weighted average
Poland	1991	100	Time-weighted average
Russia	1991	100	Short-term exposure limit
Sweden	1991	20 (Suspected of having a carcinogenic potential)	Time-weighted average
		40 (Suspected of having a carcinogenic potential)	Ceiling
Switzerland	1991	11 (Suspected of being a carcinogen)	Time-weighted average
Turkey	1993	2200	Time-weighted average
United Kingdom	1991	22	Time-weighted average
United States:			
ACGIH (Threshold Limit Value)°	1997	4.4 (Suspected human carcinogen)	Time-weighted average
NIOSH (Recommended Exposure Limit)	1997	(Potential occupational carcinogen: lowest feasible concentration)	Time-weighted average
OSHA (Permissible Exposure Limit)	1996	2.2	Time-weighted average

Limits and guidelines from International Labour Office (1991); United States Occupational Safety and Health Administration (OSHA, 1996); American Conference of Governmental Industrial Hygienists (ACGIH, 1997); United States National Library of Medicine (1997); Deutsche Forschungsgemeinschaft (1998); Ministry of Social Affairs and Health (1998). ° Countries that follow the ACGIH recommendations for threshold limit values include Bulgaria, Colombia, Jordan, Republic of Korea, New Zealand, Singapore and Viet Nam.

Table 4.2.2 *International occupational exposure limits and guidelines for butadiene (which is classed by IARC as an established human carcinogen, Group 1)*

industry workers [8], the significant decrease in liver cancer risk among workers in the vinyl chloride industry following recognition of its carcinogenicity in the 1970s [9], the significant decrease in lung cancer risk among American workers exposed to chloromethyl ethers following recognition of its carcinogenicity in the 1950s [10], and the significant decrease in lung cancer risk among Norwegian nickel refinery workers following recognition of cancer risks in the 1930s [11].

The decrease in exposure to occupational carcinogens may be due to reduced emissions, improved ventilation or use of personal protection by the workers. As a general rule, the first two approaches are more efficient in achieving a durable reduction in exposure than is the use of protective equipment. Reduction of emissions can be easily achieved for chemicals produced under controlled conditions, such as intermediates formed during chemical manufacturing processes. However, reduction of exposure at the sources might be difficult to achieve for substances that are use under less controlled conditions, such as motor exhausts.

Screening of occupationally exposed workers has been proposed as an additional measure to prevent cancer deaths. However, for none of the cancers for which it has been proposed is there evidence of efficacy. This is the case in particular of lung cancer and mesothelioma among asbestos-exposed workers, and bladder cancer among workers exposed to aromatic amines [12,13].

Operative measure	Examples
Preventing exposure	
Use of gloves and face mask	Pharmacists handling cytotoxic drugs
Full respirator	Specified emergency procedure for spillage of hazardous material
Controlling exposure	
Environmental monitoring	Measurement of asbestos fibre level in breathing zone
	Film badge to assess radiation exposure
Assessing uptake and excretion	Urinary measurement of metabolite, e.g. dimethylphosphate in workers exposed to dichlorvos
	Urine analysis for haematuria
	Determination of protein adducts and screening for preneoplastic lesions in MOCA {4,4'- methylenebis(2-chloroaniline)}-exposed workers
	Determination of DNA adducts in coke oven workers exposed to polycyclic aromatic hydrocarbons

Table 4.2.3 *Means to either prevent or determine the level of exposure to occupational carcinogens*

There has been significant improvement in occupational hygiene conditions in large industries in high-resource countries [2]. The challenge is to extend this improvement to smaller enterprises and to medium- and low-resource countries, where there remain significant problems of exposure to such agents as asbestos, crystalline silica and pesticides [14].

Compound	Average ambient air concentration [mg/m^3]	Cancer associated	IARC classification
Acetaldehyde	5	Nasal tumours in rats	2B
Acrylonitrile	0.01 – 10	Lung cancer in workers	2A
Arsenic	(1 – 30) x 10^{-3}	Lung cancer in humans	1
Benzo[a]pyrene	No data	Lung cancer in humans	1
Bis(chloromethyl)ether	No data	Epitheliomas in rats	1
Chloroform	0.3–10	Kidney tumours in rats	2B
Chromium VI	(5 – 200) x 10^{-3}	Lung cancer in workers	1
1,2–Dichloroethane	0.07 – 4	Tumour formation in rodents	2B
Diesel exhaust	1.0 – 10.0	Lung cancer	2A
Nickel	1 – 180	Lung cancer in humans	1
Polycyclic aromatic hydrocarbons (benzo[a]pyrene)	(1 – 10) x 10^{-3}	Lung cancer in humans	1
1,1,2,2–Tetrachloroethane	0.1 – 0.7	Hepatocellular carcinomas in mice	3
Trichloroethylene	1 – 10	Cell tumours in testes of rats	2A
Vinyl chloride	0.1 – 10	Haemangiosarcoma in workers Liver cancer in workers	1

Table 4.2.4 *WHO guidelines (1999) for air pollutants with carcinogenic health endpoints. These substances have been classified by IARC as either human carcinogens (Group 1), probable human carcinogens (Group 2A) or possible human carcinogens (Group 2B).*

REFERENCES

1. Siemiatycki J, Richardson L, Boffetta P (2006). Occupation. In: Schottenfeld D, Fraumeni JF, eds., *Cancer epidemiology and prevention*. New York, NY: Oxford University Press. 322-354.

2. Symanski E, Kupper LL, Hertz-Picciotto I, et al. (1998). Comprehensive evaluation of long-term trends in occupational exposure: Part 2. Predictive models for declining exposures. *Occup Environ Med* 55: 310-316.

3. Levy BS, Wegman DH (1988). *Occupational health: recognizing and preventing work-related disease*. Boston, MA: Little, Brown.

4. Monson RR (1990). *Occupational epidemiology*. Boca Raton, FL: CRC Press.

5. American Conference of Governmental Industrial Hygienists (2001). *Documentation of the threshold limit values and biological exposure indices*. Cincinnati, OH: ACGIH Worldwide.

6. Corn M (1983). Regulations, standards and occupational hygiene within the U.S.A. in the 1980s. *Ann Occup Hyg* 27: 91-105.

7. Swerdlow AJ (1990). Effectiveness of primary prevention of occupational exposures on cancer risk. In: Hakama M, Beral V, Cullen JW, et al., eds., *IARC Scientific Publications, Volume 103, Evaluating effectiveness of primary prevention of cancer*. Lyon, France: International Agency for Research on cancer 23-56.

8. Boice JD (2008). Ionizing Radiation. In: Schottenfeld D, Fraumeni JF, eds., *Cancer epidemiology and prevention*. New York, NY: Oxford University Press. 259-293.

9. Boffetta P, Matisane L, Mundt KA, et al. (2003). Meta-analysis of studies of occupational exposure to vinyl chloride in relation to cancer mortality. *Scand J Work Environ Health* 29: 220-229.

10. Maher KV and DeFonso LR (1987). Respiratory cancer among chloromethyl ether workers. *J Natl Cancer Inst* 78: 839-843.

11. Magnus K, Andersen A, Hogetveit AC (1982). Cancer of respiratory organs among workers at a nickel refinery in Norway. *Int J Cancer* 30: 681-685.

12. Talaska G, Maier A, Henn S, et al. (2002). Carcinogen biomonitoring in human exposures and laboratory research: validation and application to human occupational exposures. *Toxicol Lett* 134: 39-49.

13. Vierikko T, Jarvenpaa R, Autti T, et al. (2007). Chest CT screening of asbestos-exposed workers: lung lesions and incidental findings. *Eur Respir J* 29: 78-84.

14. Pearce N, Matos E, Vainio H, et al. (1994). *Occupational cancer in developing countries*. Lyon, France: International Agency for Research on Cancer.

4.3 Vaccination

Summary

> Hepatitis B virus (HBV) vaccine has proven to be safe and effective in preventing chronic hepatitis and hepatocellular carcinoma

> Twenty-five years after having been licensed, HBV vaccination programs are now carried out in at least 158 countries. However, they have yet to obtain high penetration in many high-risk areas, such as in sub-Saharan Africa

> Two human papillomavirus (HPV) vaccines were licensed in 2007 and show high efficacy in the prevention of precancerous lesions of the cervix uteri in young women who have not already been infected by the HPV types included in the vaccine

> The duration of the efficacy of the HPV vaccine and the need for a booster are not yet known, and the vaccine price is currently unaffordable in medium- and low-income countries

> The development of vaccines against infections other than HBV and HPV has been very difficult. A more realistic goal for vaccines against hepatitis C virus (HCV), *Helicobacter pylori* (Hp) or human immunodeficiency virus (HIV) may be in the prevention of chronic infection and disease as opposed to inducing complete protection against primary infection

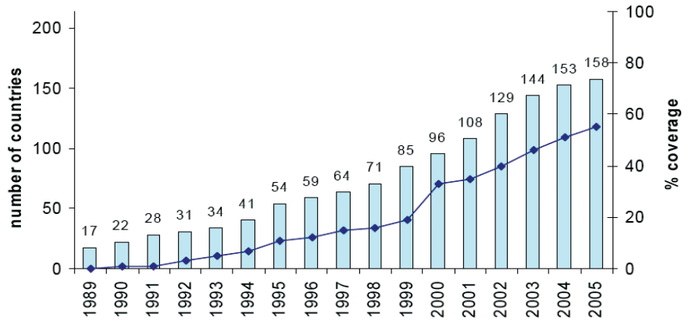


Fig. 4.3.1 *Number of countries that introduced hepatitis B virus (HBV) vaccine in children and global infant HBV vaccine coverage, 1989-2005.*
Source: WHO/UNICEF estimates 1980-2005, as of August 2006 and WHO/IVB database, 2006 192 WHO Member States.

The most important implication of our understanding that a high fraction of cancer may be caused by chronic infections (18% worldwide [1]) is the possibility of preventing the onset of these cancers through vaccination. Mass immunisation, when it has proved feasible, has resulted in some of the greatest medical successes in human history. Vaccination programmes have been implemented even in the poorest countries of the world and in fact can lead to substantial cost-saving, something that is rarely expected of healthcare interventions.

The renewed interest in vaccines that has been seen in the past few years, including those meant to prevent certain cancers, is greatly encouraging. However, there are also some major limitations in vaccine research, development and distribution in different parts of the world, which will be explored briefly in this chapter.

Cancer-causing chronic infectious agents include DNA viruses, RNA viruses, bacteria and parasites. Two vaccines against two DNA viruses, HBV and HPV, have shown efficacy in preventing the corresponding chronic infection, as well as precancerous lesions of the affected sites (liver and cervix). Progress in the design of vaccines against RNA viruses that are associated with increased cancer risk (HIV and HCV) have been hampered by the enormous genetic diversity of these agents. With respect to the bacterium (Hp) strongly associated with gastric cancer, the main obstacles to vaccine development have been insufficient understanding of the role of immunity in Hp infection. The state of the art in developing vaccines against HIV, HCV and Hp will also be briefly reviewed in this chapter.

HBV vaccine

An epidemic of jaundice due to HBV infection was reported for the first time in 1883 and was an adverse effect of a smallpox vaccination campaign in Germany (see [2] for a review). The etiology of what was formerly called "serum hepatitis" was identified in the 1960s and became better understood in the two subsequent decades following the development of laboratory markers of exposure (antibodies against hepatitis C core antigen, anti-HBc) and chronic infection (hepatitis B surface antigen, HBsAg).

HBsAg seroprevalence has marked geographic variation. Countries with high endemicity are defined as those where HBsAg seroprevalence is ≥8%. They include all of sub-Saharan Africa, the Middle East, Southeast Asia, Indonesia, China, Korea, Mongolia and, in the Americas, the northern parts of Brazil and Peru. The other extreme is embodied by low-endemicity countries (where HBsAg seroprevalence is <2%), i.e. Northern Europe, Australia, North America and the majority of South American countries. The degree of HBV endemicity often correlates with the predominant mode of transmission. In highly endemic settings, perinatal and horizontal routes, such as exposure to chronically infected household members, are responsible for most HBV transmission. Healthcare-related transmission is also common. In countries with low HBV endemicity, most new infections occur among young adults and are acquired sexually or through intravenous drug use.

The likelihood that newly infected persons will develop chronic HBV infection depends on their age at the time of infection. More than 90% of infected infants, 25–50% of children infected between 1 and 5 years of age, and 6–10% of older children and adults develop chronic infection. Immunosupressed individuals are also at higher risk of developing chronic infection [3]. Therefore, affected individuals in high-endemicity countries, where infection early in life predominates, have a disproportionally high burden of severe HBV sequelae including hepatocellular carcinoma. It has been estimated that adults who have had chronic HBV infection since childhood have a 5% incidence of hepatocellular carcinoma per decade.

HBV vaccines were first licensed in the United States in 1981. Formerly, they were plasma-derived and composed of purified HBsAg. Nowadays, HBV vaccines are predominantly produced by recombinant DNA technology. The vaccine is administered in a three-dose series and has resulted in high immunogenicity and efficacy, which to date has been monitored using short-term measures (i.e. reduction in acute HBV infection and serial seroprevalence studies in vaccinated populations). Declines in incidence and mortality rates from hepatocellular carcinoma have been reported only in children and adolescents in Taiwan, which established the first HBV immunisation program in 1984 [4].

A better estimate of the decrease in the cancer burden will be possible in approximately a decade in the two large randomised trials of HBV started in 1986 in The Gambia [5] and in 1990 in Qidong, China [6]. Despite decreases in anti-HBsAg titres to relatively low levels, immunocompetent immunised individuals have not developed chronic hepatitis infection in 10–22-year follow up. HBV vaccine injection within 12–24 hours after birth, followed by a 3-dose vaccine series, is effective in preventing vertical transmission, and the safety of the vaccine has been demonstrated in large studies. Concerns were expressed about the possibility of the vaccine having caused some cases of multiple sclerosis, diabetes mellitus and demyelinating diseases, but an expert panel dismissed these for lack of an association [7]. In addition, breakthrough infections by HBV mutant escapes among successfully vaccinated persons have been excluded.

In 1992, the World Health Organization (WHO) recommended the integration of the HBV vaccine into national immunisation campaigns. As shown in Figure 4.3.1, the number of countries that introduced the vaccine and implemented global infant coverage grew steadily from 17 in 1989 to 96 in 2000. By 2005, 158 of the 192 WHO Member States had infant HBV vaccination programs in place, with over half of these countries (62%) reporting ≥80% coverage by their programs (Figure 4.3.2). The 34 countries that have not yet introduced infant HBV vaccination notably include several highly endemic countries in sub-Saharan Africa. Several high-resource countries with low HBV endemicity, including the United Kingdom, Scandinavian countries and Japan, do not routinely vaccinate children, but have instead chosen to target high-risk groups (e.g., immigrants from high-endemicity areas, adolescents, and adults with risk factors for HBV infection).

Priorities for the future are clearly to expand the number of high-endemicity countries that

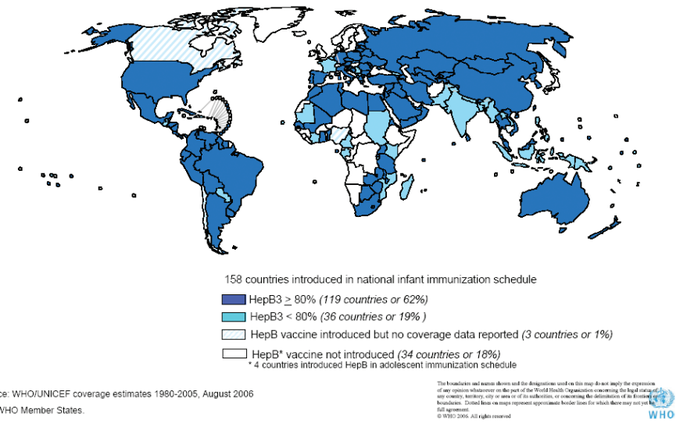


Fig. 4.3.2 *Countries having introduced hepatitis B virus (HBV) vaccine in children and infant HBV Vaccine coverage, 2005*
From WHO slide presentation Progress Toward Global Immunization Goals 2005
Summary presentation of key indicators Last update of set: 10 October 2006

include HBV vaccination in infant immunisation schedules (Figure 4.3.1) and to improve coverage in countries that have already opted to do so (Figure 4.3.2). The drop in the price of the HBV vaccine and the efforts of vaccine-donating organisations should help to make these targets possible. In addition, as policies of selective immunisation of high-risk individuals are seldom effective, routine HBV vaccination is now also advocated in low-endemicity countries on the grounds that whenever a potentially devastating disease like hepatocellular carcinoma is easily preventable, steps should be taken to achieve this outcome.

	Per protocol	By intention to treat	
	HPV-negative	Against HPV 16/18 % (CI)	Against any HPV type % (CI)
CIN2/3 or AIS	99 (93–100)	44 (31–55)	18 (7–29)
By lesion:			
CIN2	100 (93–100)	50 (34–62)	21 (7–33)
CIN3	98 (89–100)	39 (21–53)	17 (-0.1–31)
AIS	100 (31–100)	54 (-30–86)	57 (-19–87)

Table 4.3.1 *Efficacy of quadrivalent vaccine against human papillomavirus (HPV) 16/18*
Adapted from [9]. Confidence interval (CI); cervical intraepithelial neoplasia (CIN), adenocarcinoma in situ (AIS)

	Vaccine / Control	Efficacy % (CI)
HPV16/18		
CIN2 or more severe	2 / 21	90 (53–99)
CIN1 or more severe	3 / 28	89 (59–99)
Persistent infections (12 months)		
HPV16/18	11 / 46	76 (48–90)
Other high-risk types	100 / 137	27 (0.5–47)
All high-risk types	112 / 180	38 (18–54)

Table 4.3.2 *Endpoints and efficacy of bivalent vaccine against human papillomavirus (HPV) 16/18 (15,626 women, 15 months follow-up)*
Adapted from [10]. Confidence interval (CI), cervical intraepithelial neoplasia (CIN)

HPV vaccine

HPVs are DNA viruses that infect epithelial (skin or mucosal) cells. There are more than 100 known mucosal HPV types, and at least 13 of them, called high-risk types, can cause cancer of the cervix [8]. HPV16 and 18 are found in over 70% of cervical cancer worldwide and also predominate in cancer sites other than the cervix (i.e. anus, vulva, vagina, penis, and a small fraction of cancers of the head and neck). The discovery that cervical cancer was associated with sexual contact paved the way to an understanding of the role of HPV infection, which is predominantly sexually transmitted [8].

The two currently available HPV vaccines [9,10] include HPV16 and 18 and are based on L1 virus-like particles (VLPs), i.e. empty viral capsids. They were therefore expected, as has been subsequently confirmed, to be very safe, as they include neither viral oncogenes nor live or attenuated viruses. They have been licensed since 2007 for use in women aged 9–26 years in the United States, European Union and in a number of other countries. In clinical trials that included approximately 40 000 women, both vaccines were at least 90% effective in preventing persistent HPV infection and 95% effective in preventing type-specific precancerous lesions (i.e. cervical intraepithelial neoplasias (CIN) grade 2 and 3 and in situ adenocarcinoma of the cervix). One of the two vaccines also includes low-risk HPV types 6 and 11, and is therefore able to prevent genital warts, in addition to cervical HPV infections.

Available vaccines did not, however, prevent development of CIN2 and 3 in women who had been infected by HPV16 and 18 before immunisation, or CIN2 and 3 caused by other HPV types in clinical trials. [9]. Therefore, in the analyses by intention to treat, the efficacy diminished from 99% to 18% (95% confidence interval: 7–29%) when all CIN2 and 3 lesions were considered (Table 4.3.1). This efficacy profile obliges us to: 1) concentrate on the vaccination of girls before they become sexually active; 2) try to increase the number of high-risk HPV types present in the vaccine; and 3) make every possible effort to match immunisation with high-quality organised screening programs [11]. Although data on all high-risk types present in CIN2 and 3 have not yet become available, some cross-protection against persistent infection from high-risk types other than HPV16 and 18 has been reported (Table 4.3.2) [10].

However, successful prevention of cervical cancer through immunisation presents enormous challenges. The greatest of these are the lack of information on the duration of vaccine efficacy, which at this point has been evaluated for no more than five years, and by the vaccine price that is unaffordable in many medium- and low-income countries. In addition, reaching girls before puberty or in their early teens may be more difficult than delivering vaccines to newborn and infants, especially in low-resource countries. Cultural barriers and misinformation may also burden HPV vaccine acceptance.

For the moment, no plan exists to expand the use of HPV vaccine to boys, as 1) efficacy of the vaccine in the prevention of HPV infection in men is not yet proven, and 2) if good coverage is achieved, a sexually transmitted infection like HPV should be greatly reduced even by vaccinating one gender only.

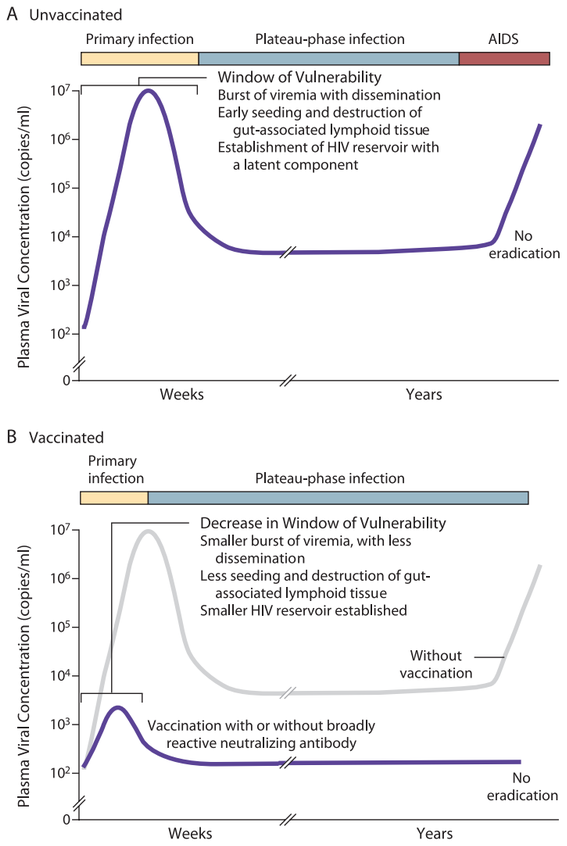


Fig. 4.3.3 Course of human immunodeficiency virus infection in unvaccinated persons and the hypothetical course of infection in vaccinated persons

Panel A shows the course of infection in unvaccinated persons. The primary stage of HIV infection (yellow) starts with a burst of viremia, dissemination of the virus, early seeding and destruction of gut-associated lymphoid tissue, and establishment of a viral reservoir with a latent component (window of vulnerability). HIV levels in plasma then decline to a set point that lasts from months to years. Eventually, in the absence of effective therapy, the virus escapes immune control and AIDS results (red). Panel B shows the hypothetical course of infection in vaccinated persons. A T-cell vaccine might decrease the burst of viremia and dissemination that occurs in primary infection (yellow), preserving gut-associated lymphoid tissue, diminishing the viral reservoir, decreasing virus levels at the set point, and increasing the length of time that viral levels are controlled (blue). From Johnston and Fauci, 2007

Vaccines against other cancer-causing chronic infections

Research into new prophylactic and therapeutic vaccines is also ongoing for at least three additional infections that are responsible for a large portion of the cancer burden worldwide: HCV, HIV and Hp. Although the first two agents are RNA viruses and the third is a bacterium, they all have in common some characteristics that have greatly undermined past efforts to produce efficacious vaccines: 1) they display high genetic and antigenic diversity and mutate very rapidly in the host; 2) they induce, after natural infection, strong humoral and cellular responses that seem, however, unable to eliminate the infection or prevent reinfection; and 3) no small animal model or cell culture systems were available until recently to help vaccine developments.

Several candidate vaccines (e.g. virus-like particle vaccines) against HCV, an increasingly important cause of liver cancer, were tested in chimpanzees [12], and induced a strong cellular-immune response. Vaccination did not prevent the chimpanzees from becoming infected, but the course of the infection was apparently attenuated.

Hp, a Gram-negative flagellate bacterium that is present in the stomach of more than half of the global population, is the leading cause of chronic gastritis, peptic ulcer disease and gastric adenocarcinoma and lymphoma (see

[13] for a review). A few vaccination studies involving between 6 and 42 infected or uninfected humans and based on various Hp formulations such as recombinant urease, killed whole cells, or live Salmonella vector presenting the subunit antigens, have not provided satisfactory results. One trial that used recombinant Hp urease coadministered with native Escherichia coli enterotoxin demonstrated a reduction of Hp load in infected participants [14].

HIV is not a carcinogenic virus *per se*, but it greatly increases the risk of many types of cancer (Kaposi sarcoma, non-Hodgkin lymphoma, Hodgkin lymphoma and cancer of the cervix and anogenital tract) via immunosuppression [3,15]. On account of the magnitude and severity of the HIV epidemic, enormous investment has gone into the design of HIV vaccines, but development of a vaccine has thus far proven unsuccessful (see [16] for a review).

A unique feature of HIV is that a pool of latently infected lymphocytes (resting CD4+ T cells) is

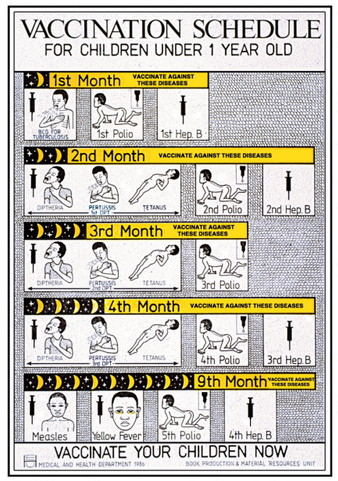


Fig. 4.3.4 *Public health poster publicizing vaccination against HBV for children under one year old in the Gambia*

Product profile of prophylactic HPV vaccine	
Cervarix, GSK	**Gardasil, Merck**
16/18 High Risk HPV types	16/18 high risk plus 6/11 low risk HPV types.
Pure Cervical Cancer Vaccine	Cervical cancer&genital warts
Women only (10-55 yrs)	Women and Men (9-45 yrs).
3 i.m. injections, 20 microg VLP	3 i.m. injections, 40 microg for HPV 11/16
Innovative AS04 adjuvant (MPL+Aluminium)	Conventional aluminium

Fig. 4.3.5 *Prophylactic HPV vaccines*

8 most common HPV types in 14,097 cases of invasive cervical cancer by region (Smith et al, 2007)

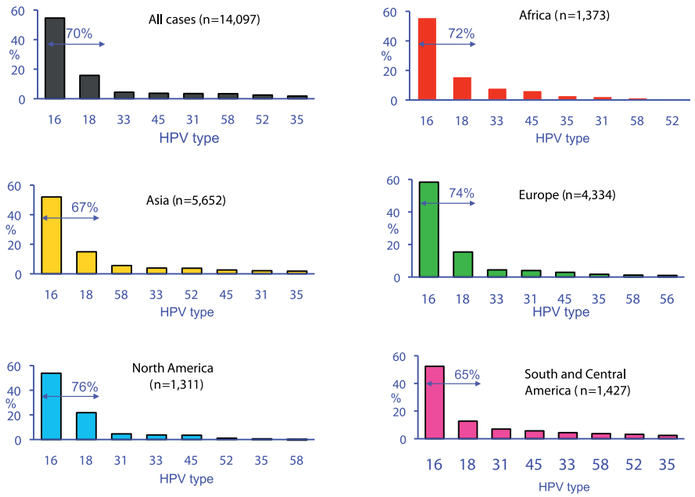


Fig. 4.3.6 *Most common types of HPV in different regions of the world*

established very early during primary infection (Figure 4.3.3). Thus, the window of opportunity for a prophylactic vaccine to clear HIV and prevent chronic infection is very small. On a positive note, HIV has some highly conserved epitopes. Initially, vaccine developers focused on recombinant forms of the viral envelope, which is the target of the virus, but later their attention moved to vaccines able to enhance T-cell immunity. However, T-cell mediated control of infection may not prove to be complete. Deciding whether the level and durability of moderated protection observed in clinical trials are sufficient to seek or grant vaccine licensing will challenge vaccine developers and regulators alike. At the moment, at least a dozen trials of candidate vaccines against HIV are under way, including a few phase II and III trials [16].

In conclusion, the development of a vaccine against infections other than HBV and HPV has been very difficult. A more realistic goal for vaccines against HCV, Hp or HIV may be preventing chronic infection and disease as opposed to inducing complete protection against primary infection. Disease-modifying vaccines represent unchartered territory, as vaccines would not be a stand-alone preventive measure, as are most classic preventive vaccines. Instead, they would need to be delivered in the context of global preventive strategies, as will be the case for HPV vaccines and cervical cancer screening [17].

Finally, it is worth bearing in mind that the private pharmaceutical sector has less incentive to invest in research and development of vaccines against cancer than anti-cancer medications [18]. The development of new cancer-preventive vaccines, as well as their accessibility to low-resource countries, is therefore crucially dependent upon the support of public and private donors such as the Bill & Melinda Gates Foundation, and those included in the Global Alliance for Vaccines and Immunization. Combined public and private research expenditures will therefore be necessary to develop important new vaccines.

REFERENCES

1. Parkin DM (2006). The global health burden of infection-associated cancers in the year 2002. *Int J Cancer* 118: 3030-3044.

2. Shepard CW, Simard EP, Finelli L, et al. (2006). Hepatitis B virus infection: epidemiology and vaccination. *Epidemiol Rev* 28: 112-125.

3. Grulich AE, van Leeuwen MT, Falster MO, et al. (2007). Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis. *Lancet* 370: 59-67.

4. Lee CL, Hsieh KS, Ko YC (2003). Trends in the incidence of hepatocellular carcinoma in boys and girls in Taiwan after large-scale hepatitis B vaccination. *Cancer Epidemiol Biomarkers Prev* 12: 57-59.

5. Viviani S, Jack A, Hall AJ, et al. (1999). Hepatitis B vaccination in infancy in The Gambia: protection against carriage at 9 years of age. *Vaccine* 17: 2946-2950.

6. Sun Z, Zhu Y, Stjernsward J, et al. (1991). Design and compliance of HBV vaccination trial on newborns to prevent hepatocellular carcinoma and 5-year results of its pilot study. *Cancer Detect Prev* 15: 313-318.

7. Stratton KR, Almario DA, McCormick MC, et al. (2002). *Immunization safety review : hepatitis B vaccine and demyelinating neurological disorders*. Washington, DC: National Academies Press.

8. IARC. (2007). *IARC monographs on the evaluation of carcinogenic risks to humans, Volume 90, Human papillomaviruses*. Lyon, France: International Agency for Research on Cancer.

9. Ault KA and Future II Study Group (2007). Effect of prophylactic human papillomavirus L1 virus-like-particle vaccine on risk of cervical intraepithelial neoplasia grade 2, grade 3, and adenocarcinoma in situ: a combined analysis of four randomised clinical trials. *Lancet* 369: 1861-1868.

10. Paavonen J, Jenkins D, Bosch FX, et al. (2007). Efficacy of a prophylactic adjuvanted bivalent L1 virus-like-particle vaccine against infection with human papillomavirus types 16 and 18 in young women: an interim analysis of a phase III double-blind, randomised controlled trial. *Lancet* 369: 2161-2170.

11. Wheeler CM and Franceschi S (2008). EUROGIN 2007 roadmap–conclusion. *Vaccine* 26 Suppl 1: A28-A31.

12. Elmowalid GA, Qiao M, Jeong SH, et al. (2007). Immunization with hepatitis C virus-like particles results in control of hepatitis C virus infection in chimpanzees. *Proc Natl Acad Sci USA* 104: 8427-8432.

13. Kabir S (2007). The current status of Helicobacter pylori vaccines: a review. *Helicobacter* 12: 89-102.

14. Smith JS, Lindsay L, Hoots B, et al. (2007). Human papillomavirus type distribution in invasive cervical cancer and high-grade cervical lesions: a meta-analysis update. *Int J Cancer* 121: 621-632.

15. Clifford GM, Polesel J, Rickenbach M, et al. (2005). Cancer risk in the Swiss HIV Cohort Study: associations with immunodeficiency, smoking, and highly active antiretroviral therapy. *J Natl Cancer Inst* 97: 425-432.

16. Johnston MI and Fauci AS (2007). An HIV vaccine–evolving concepts. *N Engl J Med* 356: 2073-2081.

17. Schiffman M, Castle PE, Jeronimo J, et al. (2007). Human papillomavirus and cervical cancer. *Lancet* 370: 890-907.

18. Barton JH (2000). Financing of vaccines. *Lancet* 355: 1269-1270.

4.4 Cancer Chemoprevention

Summary

> In healthy subjects living in well-nourished communities, current evidence does not support recommendation for any agent for chemoprevention of cancer

> There is evidence that use of some anti-oxidant supplements may increase mortality

> Folic acid supplements are suspected to increase the risk of colorectal cancer

> In women at high risk for breast cancer, tamoxifen and raloxifene may be considered for reducing the risk of developing breast cancer

> Randomised trials using ordinary doses of vitamin D (i.e. 400–600 IU per day) have shown no influence on cancer risk, although these ordinary doses seem to reduce mortality

Chemoprevention is the reduction of cancer risk through the use of pharmaceuticals or other agents such as micronutrients. Chemoprevention is an appealing low-cost and easy cancer control method, mainly for subject having an inherited predisposition to certain cancers.

Laboratory data and observational studies have suggested that higher intake of some micronutrients was associated with reduced cancer risk. Micronutrients are defined as nutrients present in the body in amounts less than 0.005% of body weight. Micronutrients usually encompass the vitamins, minerals and trace elements (e.g. selenium, zinc). Research on vitamins and cancer in humans has focused mainly on carotenoids, retinoids, vitamin A (retinol) and retinoid, vitamin E (which includes alpha-tocopherol), vitamin C and some of the group of B vitamins (folic acid). The biological basis of the interest in these vitamins is their involvement in two metabolic mechanisms commonly called an antioxidant effect through free-radical scavenger properties (carotenoids, vitamin A, C and E, retinoids) and methyl donation (folic acid).

Laboratory data and observational studies have also suggested that several commonly used pharmaceuticals could have anti-cancer activity, and could be candidates for chemoprevention of cancer of the digestive tract, such as the anti-inflammatory drugs.

Chemopreventive agents are to be considered as pharmacological compounds, that is, substances that will interact with several biological receptors which may reduce cancer risk, and also, cause other effects due to impact on other physiological activities. This notion also applies to apparently "natural" substances that can be found in usual foodstuffs, as chemoprevention will generally use doses (much) higher than those in typical dietary intakes. Also, a putative chemoprevention compound may be selected, while the average diet represents a composite mixture of hundreds of compounds. Therefore, a number of randomised trials have been mounted to verify the reality of anti-cancer activity suggested by basic research and observational studies.

Many trials tested composite intervention, mixing vitamins and trace elements, which renders it difficult, if not impossible, to disentangle the effects of individual compounds. In the remainder of the text, we have selected results from trials that provide information on effects specific to each supplement.

Anti-Oxidants

Beta-carotene

Observational epidemiological studies have consistently shown that beta-carotene is associated with decreased cancer risk, particularly of lung cancer. In contrast, randomised trials testing the effect of beta-carotene supplementation on cancer incidence and mortality generally have not been supportive [1-3]. Randomised trials did not show a change in prostate cancer risk with beta-carotene supplementation [1,4,5].

Two of these trials, the ATBC [6] and the CARET [5], yielded results suggesting the possibility of serious harmful effects of beta-carotene used as a supplement: total mortality was significantly increased in intervention groups mainly because beta-carotene given to smokers or past asbestos workers increased lung cancer incidence by 18% and 28% respectively. A meta-analysis of randomised trials concluded that beta-carotene supplementation significantly increased by 24% the risk of lung cancer among current smokers [7].

Randomised trials that tested beta-carotene for prevention of basal and squamous-cell carcinoma of the skin were negative [8,9].

Vitamin A and retinoids

Compounds related to vitamin A comprise preformed vitamin A compounds, essentially retinol and retinyl esters. These compounds were initially shown to modulate differentiation in many experimental systems [10,11]. No significant effects on mortality rates were observed for supplementation with combination of retinol and zinc [12], beta-carotene and vitamin A [5]. One large randomised trial of a vitamin A analogue, fenretinide, showed no impact on occurrence of secondary breast cancer in breast cancer survivors [13]. Vitamin A and retinols may antagonise the physiological action of Vitamin D, mainly on bone. Two studies have reported doubling of hip fracture rates among women with high retinol intakes from food or supplements (>1.5 mg per day) [14,15].

In 1998, a systematic review by a IARC Expert Group concluded that there was evidence suggesting lack of anti-cancer activity of preformed vitamin A compounds, and thus also of vitamin A (Table 4.4.1) [10].

Agent	Humans	Animals
Non-steroidal anti-inflammatory drugs		
Aspirin	Limited	Sufficient
Sulindac	Limited	Sufficient
Piroxicam	Inadequate	Sufficient
Indomethacin	Inadequate	Sufficient
Carotenoids		
beta-Carotene (high dose supplements)	Lack of activity	Sufficient
beta-Carotene (usual dietary levels)	Inadequate	Sufficient
Canthaxanthin	Inadequate	Sufficient
alpha-Carotene	Inadequate	Limited
Lycopene	Inadequate	Limited
Lutein	Inadequate	Limited
Fucoxanthin	Inadequate	Limited
Retinoids		
all-trans-Retinoic acid	Inadequate	Inadequate
13-cis-Retinoic acid	Limited	Limited
9-cis-Retinoic acid	Inadequate	Limited
Fenretinide (4-HPR)	Inadequate	Sufficient
Etretinate	Inadequate	Limited
Acitretin	Inadequate	Inadequate
N-Ethylretinamide	Inadequate	Lack of activity
Targretin	Inadequate	Inadequate
LGD 1550	Inadequate	Inadequate
Preformed vitamin A	Lack of activity	Limited

Table 4.4.1 *Evidence of cancer preventive activity: evaluations from the IARC Handbooks of Cancer Prevention series*

Retinoids are a class of compounds structurally related to vitamin A. In 1999, a systematic review by an IARC Expert Group concluded that there was inadequate or limited evidence for anti-cancer activity of nine different retinoid acid compounds, and some of them are teratogenic in humans or in animals (Table 4.4.1) [11].

Vitamin C

Vitamin C is deemed to be a free-radical scavenger, and high intakes of foodstuffs rich in vitamin C (e.g. citrus fruits) could play a role in decreasing gastric cancer incidence. Double-blind randomised trials of supplementation with ascorbic acid (1g twice per day) combined with other anti-oxidants (usually vitamin E, selenium, beta-carotene) of populations at high risk for gastric cancer in China and Venezuela did not result in higher rates of regression of dysplastic lesions in the stomach [16,17].

Vitamin E

Vitamin E exists in eight different isomers, and alpha-tocopherol is the most biologically active. Vitamin E has anti-oxidant properties that were deemed to play a role in control of cellular oxidative damage.

In the ATBC study [6], the group receiving a vitamin E supplement (50 IU per day) had no reduction in lung cancer incidence but a 34% reduction in prostate cancer incidence. However, deaths from cerebrovascular accidents doubled. A randomised placebo-controlled trial within the Women's Health Initiative Study found no effect of 600 IU per day of vitamin E on cancer risk [18].

A meta-analysis of vitamin E supplementation including 16 randomised trials suggests that high doses of vitamin E supplementation

above 200 IU per day may increase all-cause mortality [19].

Selenium

Selenium is involved in defence mechanisms against oxidative stress through the selenoproteins. Selenium at high doses is known to be toxic. Selenium supplementation with doses around 200µg per day was thought to prevent non-melanoma skin cancer, and colorectal and prostate cancer. Selenium has been part of several trials, but often mixed with vitamins, making it difficult to isolate an effect specific to this compound.

The Nutritional Prevention of Cancer (NPC) Trial [20] was a placebo-controlled randomized trial to test whether selenium supplements could reduce the incidence of non-melanoma skin cancer. The incidence of non-melanoma skin cancer remained the same in the intervention and in the placebo groups. However the group that received the supplement had statistically significant reductions of approximately 40% and 50% in overall cancer incidence and cancer mortality, respectively. Main reductions in incidence were observed for prostate, colorectal and lung cancer. Separate follow-up of lung cancer and prostate cancer showed a reduction of the incidence of these two cancers in subjects who had low serum selenium levels at baseline, and not in subjects with higher levels at baseline [21,22]. A re-analysis of trial data showed that all the protective effect was confined to males, and that selenium supplements decreased cancer risk in subjects with low serum selenium levels at baseline, whereas these supplements seemed to increase cancer risk in subjects with high selenium levels at baseline [21].

A randomised trial organised within the NPC Trial failed to show reduction of colonic polyps with selenium supplementation [23], but again a significant decrease was noticeable among subjects with low serum selenium levels at baseline, while in subjects with high serum selenium level at baseline, the frequency of polyps was greater, although statistically non significant.

Recent results of the Third National Health and Nutrition Examination Survey (NHANES III) cohort study in the USA call for caution with use of this compound, as the study suggests a U-shaped curve in associated risk with serum selenium levels and all-cause and cancer mortality, with higher mortality in subjects with low or with high serum levels of selenium, and lower mortality around optimal serum levels [24].

Hence, supplementation with selenium has little influence on cancer risk, and instead can be detrimental for subjects who have high levels of serum selenium.

Micronutrients in subjects with poor nutritional conditions

One large trial tested a combination of beta-carotene, vitamin E, selenium and trace elements (e.g. zinc) in a poorly nourished Chinese population [12]. After 5 years, the treated group experienced a statistically significant 9% reduction in total mortality, primarily as a result of a statistically significant 21% lower stomach cancer mortality rate. There was no significant reduction in oesophageal cancer, the primary endpoint of the study. Indirect evidence that beta-carotene may protect from stomach cancer in high-risk subjects comes from the randomised, controlled double-blinded chemoprevention trial in subjects with gastric dysplasia in the area with a very high gastric cancer incidence in Colombia. Gastric biopsies taken at baseline were compared with those taken after 72 months; daily use of 30mg beta-carotene (combined with vitamin C) resulted in a statistically significant increase in the frequency of rate of regression of preneoplastic lesions of the stomach [25].

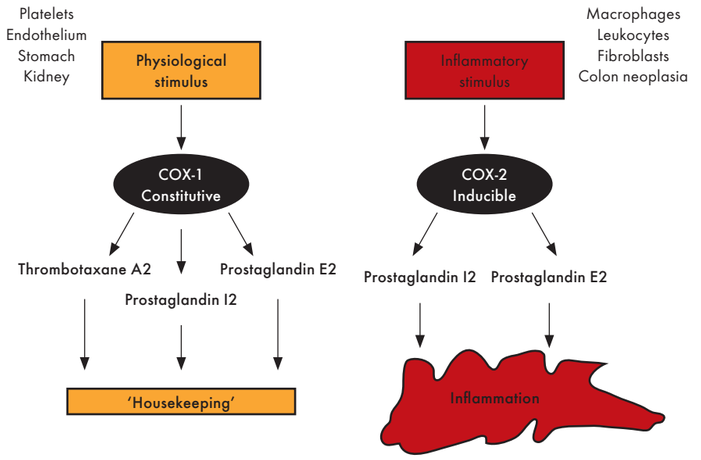


Fig. 4.4.1 *COX-1 and COX-2 cyclooxygenases: COX-1 is constitutively expressed and regulates the homeostasis of various tissues, including the generation of cytoprotective prostaglandins. Inflammatory stimuli induce COX-2, which is also highly expressed in colorectal neoplasia in the absence of stimulation*

Multivitamin preparations

A systematic review conducted under the auspices of the US National Institute for Health found no evidence that multivitamin preparations could reduce cancer risk (or the risk of other chronic diseases) [26].

Meta-analyses

A meta-analysis of randomised trials on supplementation with anti-oxidant supplements (alone or in combination) in well-nourished populations found no impact on gastro-intestinal cancer risk, but found a significantly increased risk for all-cause mortality of 6% associated with the taking of these supplements, mainly for beta-carotene (7% increase), vitamin A (16% increase), and vitamin E (4% increase) [27].

Methyl donation: Folic acid

Folic acid plays an important role in DNA repair, synthesis and methylation reactions. Two randomised placebo-controlled trials indicate that folic acid supplements may in reality increase the risk of colorectal and prostate cancer, and of adenomatous polyps [28,29].

Other micronutrients

Lycopene (from tomato), flavonoids and green tea are some examples of compounds for which anti-cancer activity is suggested by observational studies. No recommendation about the value of these substances in cancer prevention can be issued before publication of randomised trials testing their efficacy.

Vitamin D

Vitamin D is to be considered more as a hormone than as a vitamin. Furthermore, Vitamin D is not strictly speaking a vitamin, as its synthesis takes place in skin exposed to ultraviolet B radiation. Ecological studies have suggested that cancer burden increased with increasing latitude. Increasing latitude has been equated with a decrease in vitamin D status because of supposedly less sun exposure and thus less endogenous synthesis of vitamin D in the skin. Cohort studies that examined the association between serum 25-hydroxyvitamin D and cancer found weak or no association with breast and prostate cancer [30], while an inverse relationships with pancreas cancer was reported in Finish smokers [31,32]. A possible role of vitamin D in colorectal cancer is suggested by cohort studies [30]. But two randomised trials found no impact at all of ordinary doses of vitamin D supplements [33, 34] on colorectal and all-cancer risk. The trial by Trivedi et al [33] had as its primary objective the reduction of fracture risk and used 830 IU vitamin D alone per day; the WHI trial [34] used 400 IU vitamin D per day and 1g of elementary calcium.

A small 3-arm randomised trial found decreased cancer occurrence in subjects receiving vitamin D (1000 IU per day) and calcium [35]. The methodology and statistical analysis of this trial have been much criticised. For instance, subjects that received calcium supplements alone had a decrease in cancer risk of similar magnitude than subjects receiving calcium and vitamin D supplements, and thus a correct intent-to-treat analysis would have shown no significant decrease in cancer risk [36]. Also, artefacts in the placebo group severely undermined the trial's findings [37].

A meta-analysis of randomised trials on intake of vitamin D and calcium supplements found that 500–600 IU per day of vitamin D (i.e., doses similar to those tested in the WHI and in the trial by Trivedi et al. [33]) decreased all-cause mortality [38]. This result is in sharp contrast with trials on anti-oxidants showing increasing all-cause mortality. The biological mechanisms underlying the gain in life expectancy remains obscure but is probably not mediated by a reduction in cancer risk.

The question remains whether higher doses of vitamin D supplements would have more beneficial effects than ordinary doses, on cancer risk, on the risk of other non-cancerous diseases, and on mortality. The associations between high intakes or high baseline serum levels of several compounds and higher disease or mortality rate is a call for caution. It could well be that ordinary doses of vitamin D supplements may have beneficial impact on health status, as reflected by the lower all-cause mortality found by the aforementioned meta-analysis by Autier & Gandini [38]. But no data exist on the health effects of intakes of high doses of vitamin D (≥1500 IU per day) over the long term (i.e. >1 year). Therefore, before any recommendation can be made on supplementation with high doses of vitamin D, such a schedule should first be tested by large-scale double-blind placebo-controlled randomised study [32].

Nonsteroidal anti-inflammatory drugs (NSAIDs)

Numerous observational epidemiological studies have found that long-term users of aspirin or other NSAIDs have a lower risk of colorectal adenomatous polyps and colorectal cancer than nonusers [39, 40], and biological mechanisms stem from anti-cancerous properties of NSAID, in the digestive tract and also in other organs [41]. The cyclooxygenase pathway is a major target for prevention by non-steroidal anti-inflammatory drugs, primarily because the cyclooxygenase-2 (COX-2) plays a role in inflammation, apoptosis and angiogenesis, and an early potential indication of COX-2 inhibitors was the prevention of colorectal cancer.

In 1997, a systematic review by an IARC Expert Group largely based on observational studies concluded that there was limited or inadequate evidence for cancer prevention properties of aspirin, sulindac, piroxicam and indomethacin [39].

Randomised clinical trials have shown that in patients with familial adenomatous polyposis (FAP), the prodrug sulindac and the selective

Fig. 4.4.2 *The ancient Greeks chewed the bark of willow trees to alleviate pain and fever, but it was not until the last century that the active ingredient in willow bark, salicin, was isolated and commercially produced as aspirin. Observational studies have shown that regular use of aspirin reduces the risk of cancer of the colon and rectum*

cyclooxygenese (COX)-2 inhibitor celecoxib effectively inhibit the growth of familial adenomatous polyps and cause regression of existing polyps [44, 45]. However, randomised trials in patients with sporadic adenomatous polyps reduced the possibility of using this class of drug for cancer prevention because of significant cardiovascular toxicity despite effectiveness in preventing sporadic polyps [43,44]. Administration of sulindac did not result in regression of adenomas [46] or high doses required to achieve the effect may cause toxicity, which outweigh benefits of treatment [47].

Results of a large-scale, placebo-controlled long-term trial organised within the Women's Health Initiative suggested that alternate day use of low-dose aspirin (100mg) for an average 10 years of treatment did not lower risk of total, breast, colorectal or other site-specific cancers [48].

Estrogen receptor modulators

Since 1990, tamoxifen has become widely used for breast cancer treatment. Tamoxifen use has been rapidly known to increase thromboembolic events and cancer of the corpus uteri. In spite of these side effects, and tamoxifen being classified as an IARC Group I carcinogenic agent [49], it has been tested for preventing contralateral breast cancer in women with a first breast cancer. Trials started in women without a uterus, and there is conclusive evidence that tamoxifen reduces the risk for contralateral breast cancer by 38% in women with a previous diagnosis of breast cancer [50]. There was no effect for breast cancers negative for oestrogen receptors (ER-negative), but ER-positive cancers were decreased by 48% (95% CI 36-58%). Rates of endometrial cancer were increased in all tamoxifen prevention trials.

Raloxifene is a non-steroidal selective estrogen receptor modulator (SERM). One trial (the MORE trial) on treatment of osteoporosis found a reduction 72% in the incidence of breast cancer among raloxifen users [51]. A further trial (the RUTH trial) with breast cancer as a primary endpoint found a 44% decrease in breast cancer incidence among raloxifene users, but also a 49% increase of fatal stroke and 44% increase of venous thromembolism [52]. The preventive effect of raloxifene was confined to ER-positive breast tumours.

In order to better evaluate the respective properties of tamoxifen and raloxifene, a randomised trial was mounted in the USA by the National Surgical Adjuvant Breast and Bowel Project [53]. This trial showed that raloxifene and tamoxifen had a similar ability to reduce breast cancer incidence. Raloxifene induced fewer thromboembolitic events, but seemed to increase the incidence of in situ breast cancer. Death rates among women taking tamoxifen or raloxifene were similar.

Omega-3 fatty acids

Omega-3 fatty acids are mainly found in oily fish, and were deemed to protect against oxidative reactions involved in cancer and cardiovascular diseases. Systematic reviews of prospective cohort studies and of randomised trials found no evidence for a protective effect of these fatty acids on either cancer (including colorectal and breast cancer) or cardiovascular diseases [54, 55].

Dietary fibre (see also chapter on diet and cancer)

A systematic review of 13 prospective cohort studies found no effect of dietary fibre intakes on colorectal cancer incidence [56].

In five randomised trials, dietary supplementation with wheat bran or other types of fibre did not affect the rate of recurrence of colorectal adenomas [57-61]. The randomised trial by Bonithon-Kopp et al. [58] found that subject assigned in the intervention arm (ispaghula husk 3.5g per day) had in fact a significant increased risk of adenoma recurrence.

Calcium

One double-blind, placebo-controlled randomised trial [62] found that calcium supplementation (1.2 g elementary calcium per day) reduced by 15% the risk of recurrence of adenomatous polyps of the large bowel. The effect of calcium was independent of initial dietary fat and calcium intake. The same trial also found that calcium supplement seemed more likely to decrease the risk for more advanced polyps, suggesting that such supplements could decrease the incidence of colorectal cancer [63].

Another double-blind, placebo controlled randomised trial concluded that a moderate reduction of adenomatous colonic polyps with calcium supplements 1.2 g elementary calcium per day was only seen in subjects with above average serum 25-hydoxyvitamin D levels [64]. The randomised trial of Bonithon-Kopp et al [58] found a decrease of colorectal polyp recurrence in subjects assigned to calcium 2g per day, but the difference with the placebo group was statistically non-significant.

Calcium supplements (1g elementary calcium per day) were associated with a 17% increase in kidney stone formation in the WHI trial [34].

Conclusions

Most of these trials testing chemopreventive properties of many compounds found to possibly have anti-cancer properties in observational studies turned out to be negative or to show serious adverse events. Therefore no recommendation for use of a compound (even "natural substances" found in the diet) for cancer chemoprevention should be made before a large randomised trial (preferably double-blind and placebo-controlled) has evaluated both the efficacy as well as adverse effects of ingestion of the compound.

In healthy subjects living in well-nourished communities, current evidence does not support recommendation for any agent for chemoprevention of cancer, and there is evidence that use of antioxidant supplements may increase mortality (beta-carotene, vitamin E), or increase mortality in subject with high baseline serum levels of the compound (selenium), or may increase the risk of fracture (Vitamin A). Folic acid supplements are suspected to increase the risk of colorectal cancer. In communities with sub-optimal nutritional status, supplements with anti-oxidants may reduce mortality and stomach cancer risk.

In women at high risk for breast cancer, tamoxifen and raloxifene may be considered for reducing the risk of developing a second breast cancer (e.g. contralateral other breast). In subjects with familial adenomatous polyposis, the non steroidal anti-inflammatory drug sulindac may eventually be considered for prevention of adenoma recurrence although gastrointestinal and cardiovascular toxicity may be limiting. In the future, low-dose combinations of effective agents may serve to mitigate toxicity.

Randomised trials conducted so far using ordinary doses of vitamin D (i.e. 400–600 IU per day) have shown no influence of vitamin D supplements on colorectal cancer risk. However, these ordinary doses seem to reduce all-cause mortality. The effects of intakes of high doses of vitamin D (≥1500 IU per day) over the long term are unknown, and such schedule should be first tested by a placebo-controlled randomised study [32].

REFERENCES

1. Cook NR, Lee IM, Manson JE, et al. (2000). Effects of beta-carotene supplementation on cancer incidence by baseline characteristics in the Physicians' Health Study (United States). *Cancer Causes Control* 11: 617-626.

2. IARC (1998). *IARC handbooks of cancer prevention, Volume 2, Carotenoids*. Lyon, France: International Agency for Research on Cancer.

3. Vainio H and Rautalahti M (1998). An international evaluation of the cancer preventive potential of carotenoids. *Cancer Epidemiol Biomarkers Prev 7*: 725-728.

4. Heinonen OP, Albanes D, Virtamo J, et al. (1998). Prostate cancer and supplementation with alpha-tocopherol and beta-carotene: incidence and mortality in a controlled trial. *J Natl Cancer Inst* 90: 440-446.

5. Omenn GS, Goodman GE, Thornquist MD, et al. (1996). Effects of a combination of beta-carotene and vitamin A on lung cancer and cardiovascular disease. *N Engl J Med* 334: 1150-1155.

6. The Alpha-Tocopherol Beta-carotene Cancer Prevention Study Group (1994). The effect of vitamin E and beta-carotene on the incidence of lung cancer and other cancers in male smokers. *N Engl J Med* 330: 1029-1035.

7. Tanvetyanon T and Bepler G (2008). Beta-carotene in multivitamins and the possible risk of lung cancer among smokers versus former smokers: a meta-analysis and evaluation of national brands. *Cancer* 113: 150-157.

8. Green A, Williams G, Neale R, et al. (1999). Daily sunscreen application and betacarotene supplementation in prevention of basal-cell and squamous-cell carcinomas of the skin: a randomised controlled trial. *Lancet* 354: 723-729.

9. Greenberg ER, Baron JA, Stukel TA, et al. (1990). A clinical trial of beta-carotene to prevent basal-cell and squamous-cell cancers of the skin. The Skin Cancer Prevention Study Group. *N Engl J Med* 323: 789-795.

10. IARC (1998). *IARC handbooks of cancer prevention, Volume 3, Vitamin A*. Lyon, France: International Agency for Research on Cancer.

11. IARC (1999). *IARC handbooks of cancer prevention, Volume 4, Retinoids*. Lyon, France: International Agency for Research on Cancer.

12. Blot WJ, Li JY, Taylor PR, et al. (1993). Nutrition intervention trials in Linxian, China: supplementation with specific vitamin/mineral combinations, cancer incidence, and disease-specific mortality in the general population. *J Natl Cancer Inst* 85: 1483-1492.

13. Veronesi U, De Palo G, Marubini E, et al. (1999). Randomized trial of fenretinide to prevent second breast malignancy in women with early breast cancer. *J Natl Cancer Inst* 91: 1847-1856.

14. Melhus H, Michaelsson K, Kindmark A, et al. (1998). Excessive dietary intake of vitamin A is associated with reduced bone mineral density and increased risk for hip fracture. *Ann Intern Med* 129: 770-778.

15. Rothman KJ, Moore LL, Singer MR, et al. (1995). Teratogenicity of high vitamin A intake. *N Engl J Med* 333: 1369-1373.

16. Plummer M, Vivas J, Lopez G, et al. (2007). Chemoprevention of precancerous gastric lesions with antioxidant vitamin supplementation: a randomized trial in a high-risk population. *J Natl Cancer Inst* 99: 137-146.

17. You WC, Brown LM, Zhang L, et al. (2006). Randomized double-blind factorial trial of three treatments to reduce the prevalence of precancerous gastric lesions. *J Natl Cancer Inst* 98: 974-983.

18. Lee IM, Cook NR, Gaziano JM, et al. (2005). Vitamin E in the primary prevention of cardiovascular disease and cancer: the Women's Health Study: a randomized controlled trial. *JAMA* 294: 56-65.

19. Miller ER, Pastor-Barriuso R, Dalal D, et al. (2005). Meta-analysis: high-dosage vitamin E supplementation may increase all-cause mortality. *Ann Intern Med* 142: 37-46.

20. Clark LC, Combs GF, Turnbull BW, et al. (1996). Effects of selenium supplementation for cancer prevention in patients with carcinoma of the skin. A randomized controlled trial. Nutritional Prevention of Cancer Study Group. *JAMA* 276: 1957-1963.

21. Duffield-Lillico AJ, Reid ME, Turnbull BW, et al. (2002). Baseline characteristics and the effect of selenium supplementation on cancer incidence in a randomized clinical trial: a summary report of the Nutritional Prevention of Cancer Trial. *Cancer Epidemiol Biomarkers Prev* 11: 630-639.

22. Reid ME, Duffield-Lillico AJ, Garland L, et al. (2002). Selenium supplementation and lung cancer incidence: an update of the nutritional prevention of cancer trial. *Cancer Epidemiol Biomarkers Prev* 11: 1285-1291.

23. Reid ME, Duffield-Lillico AJ, Sunga A, et al. (2006). Selenium supplementation and colorectal adenomas: an analysis of the nutritional prevention of cancer trial. *Int J Cancer* 118: 1777-1781.

24. Bleys J, Navas-Acien A, Guallar E (2008). Serum selenium levels and all-cause, cancer, and cardiovascular mortality among US adults. *Arch Intern Med* 168: 404-410.

25. Correa P, Fontham ET, Bravo JC, et al. (2000). Chemoprevention of gastric dysplasia: randomized trial of antioxidant supplements and anti-helicobacter pylori therapy. *J Natl Cancer Inst* 92: 1881-1888.

26. United States. National Institutes of Health (2006). NIH State-of-the-Science Conference Statement on Multivitamin/Mineral Supplements and Chronic Disease Prevention. *NIH Consens State Sci Statements* 23: 1-30.

27. Bjelakovic G, Nikolova D, Gluud LL, et al. (2007). Mortality in randomized trials of antioxidant supplements for primary and secondary prevention: systematic review and meta-analysis. *JAMA* 297: 842-857.

28. Lonn E, Yusuf S, Arnold MJ, et al. (2006). Homocysteine lowering with folic acid and B vitamins in vascular disease. *N Engl J Med* 354: 1567-1577.

29. Cole BF, Baron JA, Sandler RS, et al. (2007). Folic acid for the prevention of colorectal adenomas: a randomized clinical trial. *JAMA* 297: 2351-2359.

30. Giovannucci E (2008). Vitamin D and cancer incidence in the Harvard cohorts. *Ann Epidemiol* In press.

31. Stolzenberg-Solomon RZ, Vieth R, Azad A, et al. (2006). A prospective nested case-control study of vitamin D status and pancreatic cancer risk in male smokers. *Cancer Res* 66: 10213-10219.

32. IARC (2008). Vitamin D and Cancer. IARC Working Group Reports Vol.5, International Agency for Research on Cancer, Lyon, France.

33. Trivedi DP, Doll R, Khaw KT (2003). Effect of four monthly oral vitamin D3 (cholecalciferol) supplementation on fractures and mortality in men and women living in the community: randomised double blind controlled trial. *BMJ* 326: 469.

34. Wactawski-Wende J, Kotchen JM, Anderson GL, et al. (2006). Calcium plus vitamin D supplementation and the risk of colorectal cancer. *N Engl J Med* 354: 684-696.

35. Lappe JM, Travers-Gustafson D, Davies KM, et al. (2007). Vitamin D and calcium supplementation reduces cancer risk: results of a randomized trial. *Am J Clin Nutr* 85: 1586-1591.

36. Ojha RP, Felini MJ, Fischbach LA (2007). Vitamin D for cancer prevention: valid assertion or premature anointment? *Am J Clin Nutr* 86: 1804-1805.

37. Schabas R (2008). Artifact in the control group undermines the conclusions of a vitamin D and cancer study. *Am J Clin Nutr* 87: 792-794.

38 Autier P and Gandini S (2007). Vitamin D supplementation and total mortality: a meta-analysis of randomized controlled trials. *Arch Intern Med* 167: 1730-1737.

39. IARC (1997). *IARC handbooks of cancer prevention, Volume 1, Non-steroidal anti-inflammatory drugs*. Lyon, France: International Agency for Research on Cancer.

40. Vainio H, Morgan G, Kleihues P (1997). An international evaluation of the cancer-preventive potential of nonsteroidal anti-inflammatory drugs. *Cancer Epidemiol Biomarkers Prev* 6: 749-753.

41. Thun MJ, Henley SJ, Patrono C (2002). Nonsteroidal anti-inflammatory drugs as anticancer agents: mechanistic, pharmacologic, and clinical issues. *J Natl Cancer Inst* 94: 252-266.

42. Giardiello FM, Hamilton SR, Krush AJ, et al. (1993). Treatment of colonic and rectal adenomas with sulindac in familial adenomatous polyposis. *N Engl J Med* 328: 1313-1316.

43. Steinbach G, Lynch PM, Phillips RK, et al. (2000). The effect of celecoxib, a cyclooxygenase-2 inhibitor, in familial adenomatous polyposis. *N Engl J Med* 342: 1946-1952.

44. Arber N, Eagle CJ, Spicak J, et al. (2006). Celecoxib for the prevention of colorectal adenomatous polyps. *N Engl J Med* 355: 885-895.

45. Bertagnolli MM, Eagle CJ, Zauber AG, et al. (2006). Celecoxib for the prevention of sporadic colorectal adenomas. *N Engl J Med* 355: 873-884.

46. Ladenheim J, Garcia G, Titzer D, et al. (1995). Effect of sulindac on sporadic colonic polyps. *Gastroenterology* 108: 1083-1087.

47. Calaluce R, Earnest DL, Heddens D, et al. (2000). Effects of piroxicam on prostaglandin E2 levels in rectal mucosa of adenomatous polyp patients: a randomized phase IIb trial. *Cancer Epidemiol Biomarkers Prev* 9: 1287-1292.

48. Cook NR, Lee IM, Gaziano JM, et al. (2005). Low-dose aspirin in the primary prevention of cancer: the Women's Health Study: a randomized controlled trial. *JAMA* 294: 47-55.

49. IARC. (1996). *IARC monographs on the evaluation of carcinogenic risks to humans, Volume 66, Some pharmaceutical drugs*. Lyon, France: International Agency for Research on Cancer.

50. Cuzick J, Powles T, Veronesi U, et al. (2003). Overview of the main outcomes in breast-cancer prevention trials. *Lancet* 361: 296-300.

51. Cauley JA, Norton L, Lippman ME, et al. (2001). Continued breast cancer risk reduction in postmenopausal women treated with raloxifene: 4-year results from the MORE trial. Multiple outcomes of raloxifene evaluation. *Breast Cancer Res Treat* 65: 125-134.

52. Barrett-Connor E, Mosca L, Collins P, et al. (2006). Effects of raloxifene on cardiovascular events and breast cancer in postmenopausal women. *N Engl J Med* 355: 125-137.

53. Vogel VG, Costantino JP, Wickerham DL, et al. (2006). Effects of tamoxifen vs raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 trial. *JAMA* 295: 2727-2741.

54. Hooper L, Thompson RL, Harrison RA, et al. (2006). Risks and benefits of omega 3 fats for mortality, cardiovascular disease, and cancer: systematic review. *BMJ* 332: 752-760.

55. MacLean CH, Newberry SJ, Mojica WA, et al. (2006). Effects of omega-3 fatty acids on cancer risk: a systematic review. *JAMA* 295: 403-415.

56. Park Y, Hunter DJ, Spiegelman D, et al. (2005). Dietary fiber intake and risk of colorectal cancer: a pooled analysis of prospective cohort studies. *JAMA* 294: 2849-2857.

57. Alberts DS, Martinez ME, Roe DJ, et al. (2000). Lack of effect of a high-fiber cereal supplement on the recurrence of colorectal adenomas. Phoenix Colon Cancer Prevention Physicians' Network. *N Engl J Med* 342: 1156-1162.

58. Bonithon-Kopp C, Kronborg O, Giacosa A, et al. (2000). Calcium and fibre supplementation in prevention of colorectal adenoma recurrence: a randomised intervention trial. European Cancer Prevention Organisation Study Group. *Lancet* 356: 1300-1306.

59. MacLennan R, Macrae F, Bain C, et al. (1995). Randomized trial of intake of fat, fiber, and beta-carotene to prevent colorectal adenomas. *J Natl Cancer Inst* 87: 1760-1766.

60. McKeown-Eyssen GE, Bright-See E, Bruce WR, et al. (1994). A randomized trial of a low fat high fibre diet in the recurrence of colorectal polyps. *J Clin Epidemiol* 47: 525-536.

61. Schatzkin A, Lanza E, Corle D, et al. (2000). Lack of effect of a low-fat, high-fiber diet on the recurrence of colorectal adenomas. Polyp Prevention Trial Study Group. *N Engl J Med* 342: 1149-1155.

62. Baron JA, Beach M, Mandel JS, et al. (1999). Calcium supplements for the prevention of colorectal adenomas. Calcium Polyp Prevention Study Group. *N Engl J Med* 340: 101-107.

63. Wallace K, Baron JA, Cole BF, et al. (2004). Effect of calcium supplementation on the risk of large bowel polyps. *J Natl Cancer Inst* 96: 921-925.

64. Grau MV, Baron JA, Sandler RS, et al. (2003). Vitamin D, calcium supplementation, and colorectal adenomas: results of a randomized trial. *J Natl Cancer Inst* 95: 1765-1771.

4.5 Screening for Cervical Cancer

Summary

> In most developed countries, cytological screening (Pap test) has led to a significant reduction in the incidence of and mortality from cervical cancer, particularly in countries that have implemented population-based screening programmes. In countries with lower participation compliance and a less developed healthcare system, screening has been much less effective in reducing mortality

> In developing countries, the cost of infrastructure and initial investments for organised cytological screening may be prohibitive. Alternative methods such as visual inspection with acetic acid (VIA) or with Lugol's iodine solution (VILI) are effective in preventing cervical cancer in low-resource countries

> HPV testing is an alternative but currently expensive method for screening and preventing cervical cancer. There is a need to develop simple, affordable and accurate methods of HPV testing with comprehensive guidelines for its use in screening programmes

> Screening should be implemented in the context of an organised programme following comprehensive quality assurance guidelines, with adequate attention paid to planning and training, resources for management of detected lesions, and coordination, monitoring and evaluation of performance and effectiveness

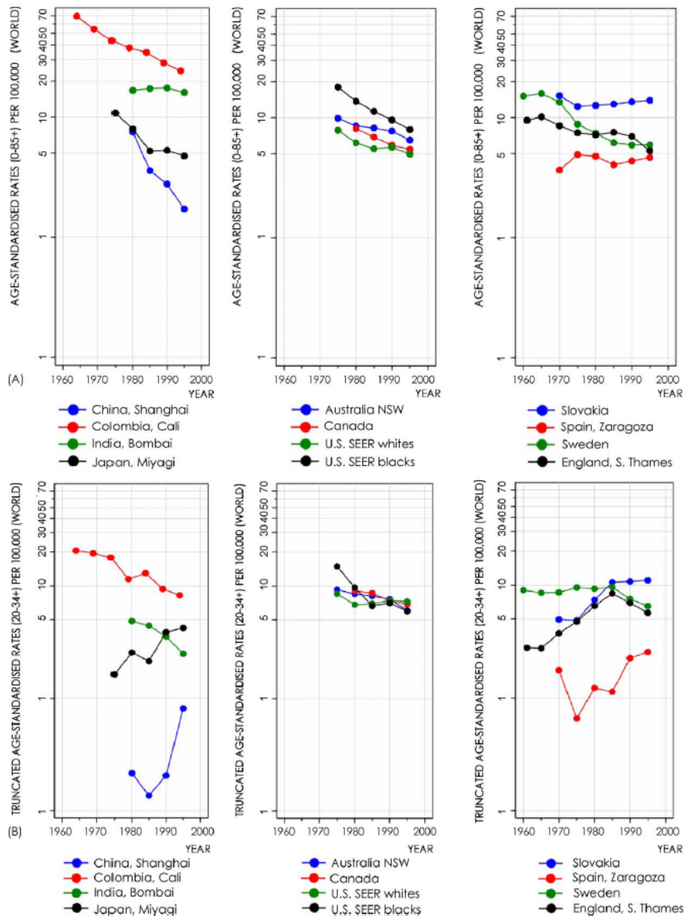


Fig. 4.5.1 *(A) Time trends in age-standardised (World) incidence rates of cervical cancer incidence based on data from selected cancer registries accepted in successive Volumes of Cancer Incidence in Five Continents [Parkin DM, Whelan S, Ferlay J, Storm H. Cancer Incidence in Five Continents, vol. I–VIII. Lyon: IARC CancerBase No. 7; 2005.]. (B) Time trends in age-truncated (World, ages 20–34) incidence rates of cervical cancer incidence based on data from selected cancer registries accepted in successive volumes of Cancer Incidence in Five Continents [Parkin DM, Whelan S, Ferlay J, Storm H. Cancer incidence in five continents, vol. I–VIII. Lyon: IARC CancerBase No. 7; 2005.]*
(Parkin et al. (2006): [28])

Invasive cervical cancer is preceded for several years by asymptomatic and slowly progressing precancerous lesions such as high-grade cervical intraepithelial lesions (CIN grade 2 and 3) or adenocarcinoma ***in situ***. The early detection of CIN by screening and their effective treatment leads to prevention of invasive cervical cancer. Following the introduction of cervical screening programmes in many developed countries a decline in incidence of and mortality from cervical cancer has been observed in the past 5 decades (Figure 4.5.1).

Persistent infection with one or more of the oncogenic types of human papillomaviruses (HPV) is the cause for cervical neoplasia [1], and cervical cancer is a rare long-term outcome of a common viral infection of the cervical epithelium. This knowledge has opened up new avenues of prevention such as HPV vaccination and HPV testing for cervical screening. While HPV vaccination is an exciting and emerging preventive option in the long run, currently screening remains the principal strategy to prevent cervical cancer globally. CIN 2–3 lesions represent a "preclinical" stage of cervical squamous-cell carcinoma that has high prevalence and is detectable in the course of population-based screening. On the other hand, screening is often not effective in detecting the pre-invasive glandular lesions of the cervical canal; thus screening has limited impact in preventing adenocarcinoma of the cervix.

Conventional cervical cytology (Pap smear, Figure 4.5.2), the most commonly and widely used cervical screening test, has been largely responsible for the early detection of cervical precancerous lesions and subsequent decline of invasive cervical cancer incidence and mortality in many developed regions of the world where successful screening programmes have been introduced. However, certain limitations of the Pap smear, in terms of the subjective nature of the test, resources required and low sensitivity in most routine settings, have led to the development and evaluation of alternative screening tests such as liquid based cytology, HPV testing and visual screening tests.

The efficacy of Pap smear screening

Cytology screening involves collection of cervical cells from the cervical epithelium using a wooden spatula or a brush, preparation and fixation of the smear by a doctor or a nurse followed by staining and reading and reporting of the results by a cytotechnician and a cytopathologist. Cytology requires a laboratory infrastructure, with internal and external quality control measures to process slides and microscopy, and a system to communicate the results to the women. High-quality training, continuing education and proficiency testing of personnel are essential to ensure reliable and efficient testing. Population-based Pap smear screening programmes were initiated in British Columbia in 1949 and in regions of Norway in 1959 and Scotland in 1960. Since then, programmes have been introduced in many developed countries. These programmes vary in their organisation, differing in the balance between public and private health care, whether the programme is systematic and population-based or opportunistic (based upon self-presentation), the age range of the women to whom screening is offered, the recommended interval between successive screens and the follow-up and management of women found to have cervical abnormalities.

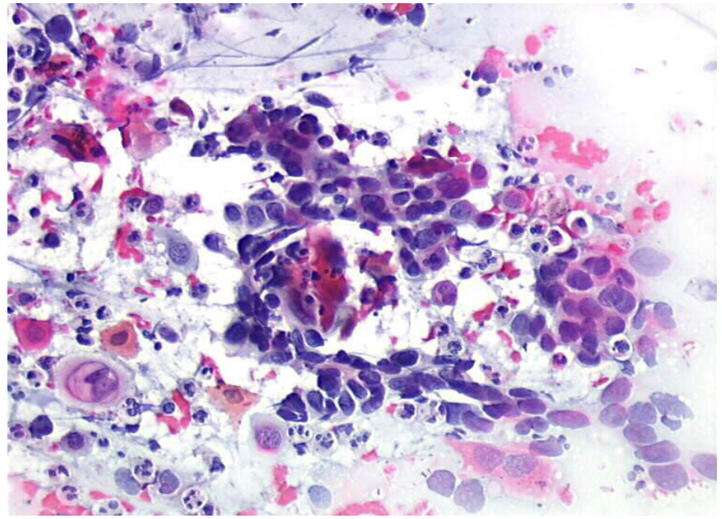


Fig. 4.5.2 *Pap smear suggestive of invasive squamous-cell carcinoma*

In most routine settings, Pap smear has a wide range in sensitivity in detecting cervical neoplasia. The sensitivity to detect CIN 2 and 3 lesions ranged from 47–62% and the specificity from 60–95% in reviews of several studies [2,3]. The sensitivity of Pap smear ranged from 31–78% and the specificity from 91–96% in studies in developing countries [4].

Large-scale population-based cytology screening programmes have resulted in a marked reduction in the incidence of and mortality from cervical cancer in the past five decades in the developed countries of Europe, North America, Japan, Australia and New Zealand [4]. Organised screening with systematic call, recall, follow-up and surveillance systems have shown the greatest effect (e.g. Finland, Iceland), while using fewer resources than the less organized programmes (e.g. USA, France). In the UK,

	Control group	Intervention group (VIA)
Eligible individuals	30,958	49,311
Cervical cancer incidence		
Cancer cases	158	167
	Hazard ratio (95% CI)	
Overall	1.00	0.75 (0.59 -0.95)
30-39 years	1.00	0.62 (0.40-0.96)
40-49 years	1.00	0.82 (0.55-1.24)
50-59 years	1.00	0.76 (0.50-1.16)
Cervical cancer mortality		
Cancer deaths	92	83
	Hazard ratio (95% CI)	
Overall	1.00	0.65 (0.47-0.89)
30-39 years	1.00	0.34 (0.18-0.66)
40-49 years	1.00	0.55 (0.31-1.00)
50-59 years	1.00	0.99 (0.58-1.66)

Table 4.5.1 *Cervical cancer incidence and mortality in the cluster randomized controlled trial in Tamil Nadu, India. R. Sankaranarayanan et al. (2007) [24]*

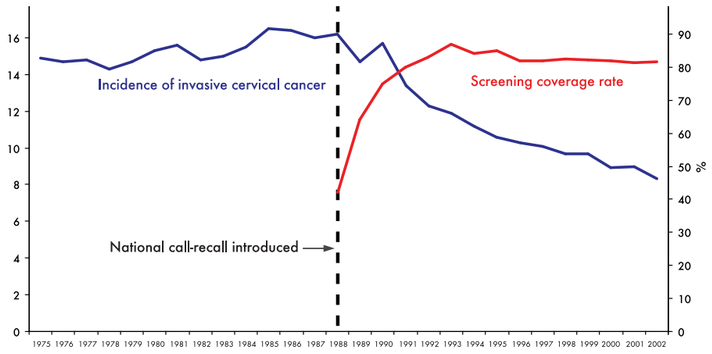


Fig. 4.5.3 *Age-standardised incidence of invasive cervical cancer and screening coverage rate England, 1975-2002. M. Quinn et al. (1999) [29], B.J. Willoughby et al. (2006) [30] Cancer Research UK (http://info.cancerresearchuk.org/)*

cervical cancer incidence rates started declining after coverage for screening was improved (Figure 4.5.3) Cervical cancer incidence has been reduced by as much as 80% where the cytology screening quality, coverage and follow-up of women are high. The highest reduction in cervical cancer incidence was in the 30–49 age group, where the focus of screening was the most intense.

Pap smear screening has been very sparsely implemented in most developing countries. Establishing quality-assured cytology screening programmes with national coverage is a challenging task in many developing countries, in view of the infrastructure for testing, trained personnel for reading, quality assurance and the resources and organisation required. Cytology screening programmes in Latin American countries such as Cuba, Brazil, Mexico, Peru and Colombia, among others, have not resulted in a significant reduction in the cervical cancer burden in these countries [5]. Possible reasons for the lack of success in these countries include a combination of sub-optimal cytology testing, lack of quality assurance, poor coverage of women at risk and inadequate follow-up of screen-positive women with diagnosis and treatment.

A critical appraisal of reasons for the sub-optimal performance of cytology screening in low- and medium-resourced countries has prompted the reorganisation of programmes in many Latin American countries and the evaluation of alternative screening tests, such as HPV DNA testing, visual screening with 3–5% acetic acid or Lugol's iodine, and paradigms that require one or two visits to complete the screening and diagnosis/treatment processes [4,6]. Following the reorganisation of the Pap smear programme in Chile, incidence and mortality started to decline [7].

Alternatives to the Pap smear

Liquid-based cytology

Liquid-based cytology (LBC) relies on a uniform thin layer of cervical cells (Figure 4.5.4) without debris prepared from processing a fluid medium containing the cervical cells, leading to improved sample adequacy and microscopic readability of the smear. It is a more expensive test than conventional cytology, and requires additional instrumentation to prepare the smears. Although earlier reviews claimed improved sensitivity to detect high-grade CIN [3,8], results from a recent review [9] and a randomised trial [10] do not support claims of better performance by LBC.

HPV testing

The fact that cervical neoplasia are caused by persistent infection with oncogenic types of HPV has led to the evaluation of HPV testing as a primary screening test for cervical neoplasia.

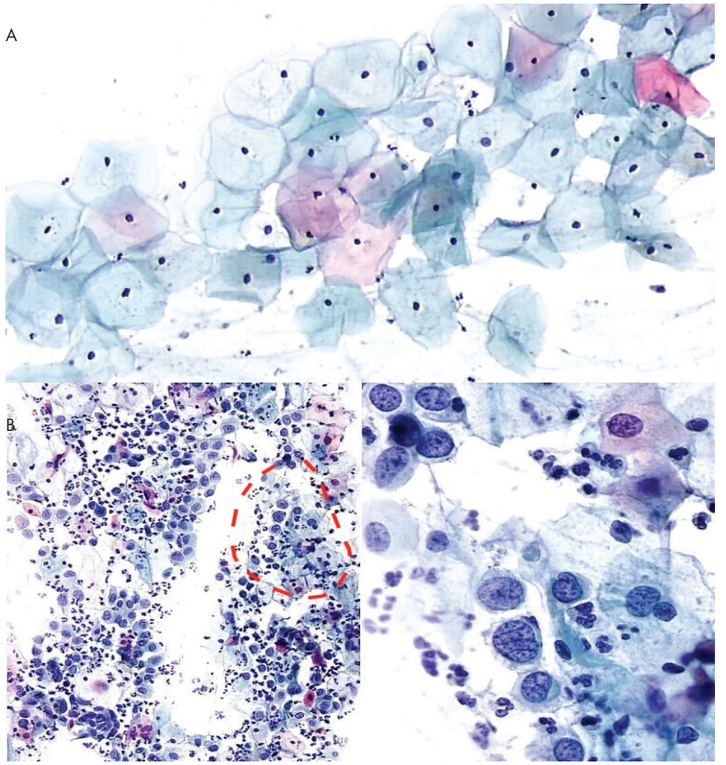


Fig. 4.5.4 *Liquid-based cytology smears showing A. normal cervical cytology B. high-grade squamous intraepithelial lesion (HSIL)*

HPV testing is the most objective and reproducible of all currently available cervical screening tests. In several cross-sectional studies the sensitivity of HPV testing in detecting CIN 2 and 3 lesions varied from 66–100% and the specificity varied from 62–96% [4,11,12]. The sensitivity of HPV testing reported by studies in developing countries has been somewhat lower than that reported by studies in developed countries. Recently reported randomised trials indicate that HPV testing has higher sensitivity for the detection of CIN as compared with Pap smear [13-15].

Although self-sampling for HPV DNA testing seems to be a viable screening option, and potentially promising for use in under-resourced areas or for women who are reluctant to participate in screening programmes, further definitive research is needed to provide a solid evidence base to inform on the use of self-sampling for HPV DNA testing for the purpose of increasing screening rates, especially in women who are never or seldom screened [16].

In low-resource settings, where repeated screening of women is not feasible, HPV testing may provide an objective method of identifying and investing the limited resources on women at risk for disease [4]. However, it is currently more expensive (US$20–30) than other screening tests and requires sophisticated laboratory infrastructure including testing equipment, storage facilities for samples and trained technicians. Further developments in terms of less expensive testing and less sophisticated infrastructure and equipment requirements are essential to make HPV testing feasible in low-resource settings. Efforts are now under way to develop simple, affordable, rapid and accurate HPV testing methods for use in low- and medium-resource settings.

In summary, compared to cytology, HPV testing is substantially more sensitive for prevalent CIN 2 or worse lesions, but significantly less specific. Whether this gain represents overdiagnosis or protection against future high-grade CIN or cervical cancer is not clear. Reduced incidence

of or mortality from invasive cervical cancer among HPV-screened subjects compared with cytologically-screened subjects has not yet been demonstrated; this issue is being addressed in a randomised trial in India [17]. Interim results from this trial show similar detection rates of CIN 2 and 3 lesions per 1000 screened women among those screened by cytology, HPV testing or visual screening with 4% acetic acid. HPV testing reportedly does not add significant psychological distress when combined with cytology in routine primary cervical screening [18].

Visual inspection

Visual screening is carried out after application of dilute acetic acid or Lugol's iodine solution. Visual inspection with acetic acid (VIA) involves naked-eye inspection of the cervix using a bright torch light or a halogen focus lamp, 1–2 minutes after the application of 3–5% acetic acid using a cotton swab or a spray. A positive test is characterised by well-defined acetowhite areas close to the squamo-columnar junction (SCJ), to the external os, on the entire cervix or a cervical growth turning acetowhite (Figure 4.4.5) [19]. Immediate results following VIA allow diagnostic investigations and/or treatment in the same session as screening. However, VIA is a subjective test that suffers from high false-positive rates and low to moderate specificity and reproducibility. Quality assurance procedures for VIA are yet to be standardised and assuring consistent high performance can be challenging under field conditions, requiring constant monitoring and frequent re-training of test providers.

The sensitivity of VIA to detect CIN 2 and 3 lesions and invasive cervical cancer varied from 37–95% and the specificity varied from 49–97% in several cross-sectional studies in developing countries [4]. The wide range in the accuracy of VIA underscores the subjective nature of the test, the varying competency of test providers, and the varying quality of reference standards used to establish the true positive disease. When Pap smear was concurrently evaluated, the sensitivity of VIA was found to be higher than or similar to that of Pap smear, but had lower specificity. It appears that a good quality VIA has an average sensitivity of around 50% and specificity of around 85% to detect high-grade CIN in experimental study settings.

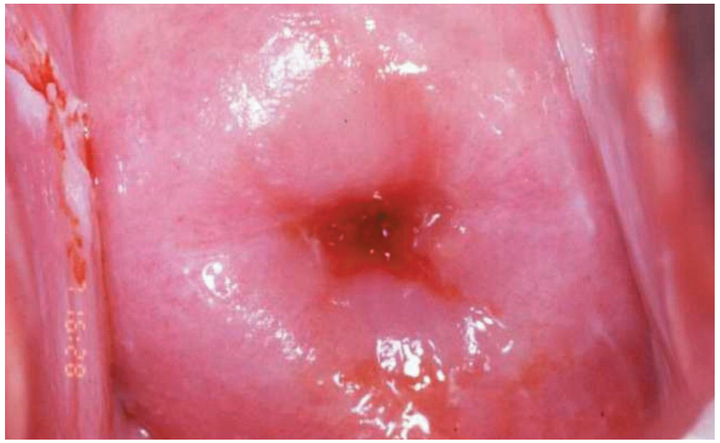


Fig. 4.5.5 *Visual inspection of the cervix with 4% acetic acid. In the normal cervix, after the application of acetic acid, no definite acetowhite areas are seen*

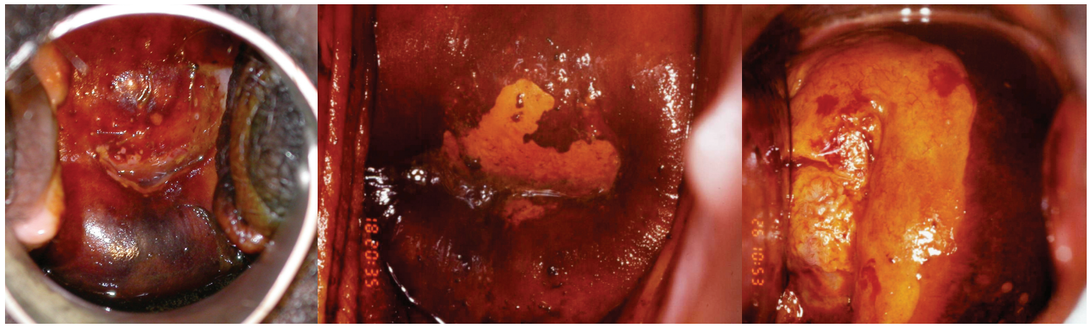


Fig. 4.5.6 *Visual inspection of the cervix with Lugol's iodine (VILI) A. VILI negative B. VILI positive C. VILI positive, invasive cancer*

The immediate availability of test results following visual testing has opened up the option of "screen and treat" or "single-visit" approach to ensure a high compliance to the treatment of screen-positive women, in which those women, with no clinical evidence of invasive cancer and satisfying the criteria for ablative therapy, are immediately treated with cryotherapy, without confirmatory investigations such as colposcopy or histology. The safety, acceptability and feasibility of combining VIA and cryotherapy in a single-visit approach have been demonstrated in rural Thailand [20], Ghana [21], Guatemala [22] and South Africa [23]. In a randomised controlled trial in South Africa, VIA followed by cryotherapy resulted in 37% and 46% lower prevalences of CIN 2–3 lesions at 6 and 12 months follow-up compared with a control group [23]. Cryotherapy for HPV test-positive women resulted in much higher declines in the prevalence of CIN 2–3 at 6 and 12 months (77% and 74% respectively) in this study.

Currently, the efficacy and effectiveness of VIA screening in reducing cervical cancer incidence and mortality are being addressed in randomised controlled trials in India [17,24]. A 25% reduction in cervical cancer incidence and a 35% reduction in mortality have been observed 7 years from the beginning of VIA screening in one of the trials (Table 1)[24].

Visual inspection with Lugol's iodine

Visual inspection with Lugol's iodine (VILI) involves naked-eye examination of the cervix to identify mustard-yellow lesions in the transformation zone after application of Lugol's iodine (Figure 4.5.6) [19]. The sensitivity of VILI varied from 44–92% and specificity from 75–85% in cross-sectional studies [25-27].

Fig. 4.5.7 *Training materials and technical reports*

Fig. 4.5.8 *Women at a clinic in India participating in a study of early detection of cervical cancer*

Conclusions

Cervical cancer reflects striking global health inequities, resulting in deaths of women in their most productive years, resulting in devastating effects on the society at large. It is the largest single cause of years of life lost to cancer in the developing world. The major barrier to prevention of cervical cancer is failure to be screened at all.

Organised screening is generally considered to be substantially more effective and efficient than opportunistic screening. The long natural history of cervical cancer presents several opportunities in terms of prevention, screening, early detection and treatment of CIN to prevent invasive cancer. Both screening and vaccination have the potential to save many lives. At the public health level, health care infrastructure, affordability and capacity to initiate and sustain vaccination and screening programmes are critical factors in cervical cancer control. Substantial evidence now exists on implementation of screening programs based on cytology, visual screening tests or HPV testing, and such action has the potential for profound public health benefit, if appropriate screening policies are implemented in earnest. It is time to focus attention on provision of adequate resources for putting in place the important programmatic components of coordination, education, and quality assurance of participation, testing, diagnosis, treatment, follow-up care and evaluation.

To screen successfully in low-resource settings the following requirements must be met:

- Adequate and timely investments to assure sufficient infrastructure for screening, diagnosis and treatment and to train screening staff;
- Screening, diagnosis and treatment provided on-site in clinics that are accessible to the majority of eligible, target women;
- An affordable, low-cost/low-technology screening test that can lead to immediate treatment of abnormalities;
- High coverage of at-risk women;
- Appropriate educational efforts directed towards health workers and women to ensure correct implementation and high participation; and
- A built-in mechanism for monitoring and evaluation of the program and adequate coordination and quality assurance.

Delaying investments in screening in low-resource countries means that many women will continue to miss opportunities for preventing cervical cancer for several decades to come. While HPV vaccination provides the hope for the future, screening provides the means for the present.

REFERENCES

1. Munoz N, Bosch FX, de Sanjose S, et al. (2003). Epidemiologic classification of human papillomavirus types associated with cervical cancer. *N Engl J Med* 348: 518-527.

2. Fahey MT, Irwig L, Macaskill P (1995). Meta-analysis of Pap test accuracy. *Am J Epidemiol* 141: 680-689.

3. Nanda K, McCrory DC, Myers ER, et al. (2000). Accuracy of the Papanicolaou test in screening for and follow-up of cervical cytologic abnormalities: a systematic review. *Ann Intern Med* 132: 810-819.

4. Sankaranarayanan R, Gaffikin L, Jacob M, et al. (2005). A critical assessment of screening methods for cervical neoplasia. *Int J Gynaecol Obstet* 89 Suppl 2: S4-S12.

5. Sankaranarayanan R, Budukh AM, Rajkumar R (2001). Effective screening programmes for cervical cancer in low- and middle-income developing countries. *Bull World Health Organ* 79: 954-962.

6. IARC (2005). *IARC handbooks of cancer prevention, Volume 10, Cervix cancer screening*. Lyon, France: International Agency for Research on Cancer.

7. Sepulveda C and Prado R (2005). Effective cervical cytology screening programmes in middle-income countries: the Chilean experience. *Cancer Detect Prev* 29: 405-411.

8. Klinkhamer PJ, Meerding WJ, Rosier PF, et al. (2003). Liquid-based cervical cytology. *Cancer* 99: 263-271.

9. Davey E, Barratt A, Irwig L, et al. (2006). Effect of study design and quality on unsatisfactory rates, cytology classifications, and accuracy in liquid-based versus conventional cervical cytology: a systematic review. *Lancet* 367: 122-132.

10. Ronco G, Cuzick J, Pierotti P, et al. (2007). Accuracy of liquid based versus conventional cytology: overall results of new technologies for cervical cancer screening: randomised controlled trial. *BMJ* 335: 28.

11. Franco EL (2003). Chapter 13: Primary screening of cervical cancer with human papillomavirus tests. *J Natl Cancer Inst Monogr* 89-96.

12. Koliopoulos G, Arbyn M, Martin-Hirsch P, et al. (2007). Diagnostic accuracy of human papillomavirus testing in primary cervical screening: a systematic review and meta-analysis of non-randomized studies. *Gynecol Oncol* 104: 232-246.

13. Bulkmans NW, Berkhof J, Rozendaal L, et al. (2007). Human papillomavirus DNA testing for the detection of cervical intraepithelial neoplasia grade 3 and cancer: 5-year follow-up of a randomised controlled implementation trial. *Lancet* 370: 1764-1772.

14. Mayrand MH, Duarte-Franco E, Rodrigues I, et al. (2007). Human papillomavirus DNA versus Papanicolaou screening tests for cervical cancer. *N Engl J Med* 357: 1579-1588.

15. Naucler P, Ryd W, Tornberg S, et al. (2007). Human papillomavirus and Papanicolaou tests to screen for cervical cancer. *N Engl J Med* 357: 1589-1597.

16. Stewart DE, Gagliardi A, Johnston M, et al. (2007). Self-collected samples for testing of oncogenic human papillomavirus: a systematic review. *J Obstet Gynaecol Can* 29: 817-828.

17. Sankaranarayanan R, Nene BM, Dinshaw KA, et al. (2005). A cluster randomized controlled trial of visual, cytology and human papillomavirus screening for cancer of the cervix in rural India. *Int J Cancer* 116: 617-623.

18. Kitchener HC, Fletcher I, Roberts C, et al. (2008). The psychosocial impact of human papillomavirus testing in primary cervical screening-a study within a randomized trial. *Int J Gynecol Cancer* 18: 743-748.

19. Sankaranarayanan R, Wesley RS (2003). *IARC Technical Publication, No. 41, A practical manual on visual screening for cervical neoplasia*. Lyon, France: International Agency for Research on Cancer.

20. Gaffikin L, Blumenthal PD, Emerson M, et al. (2003). Safety, acceptability, and feasibility of a single-visit approach to cervical cancer prevention in rural Thailand: a demonstration project. *Lancet* 361: 814-820.

21. Blumenthal PD, Gaffikin L, Deganus S, et al. (2007). Cervical cancer prevention: safety, acceptability, and feasibility of a single-visit approach in Accra, Ghana. *Am J Obstet Gynecol* 196: 407-408.

22. Mathers LJ, Wigton TR, Leonhardt JG (2005). Screening for cervical neoplasia in an unselected rural Guatemalan population using direct visual inspection after acetic acid application: a pilot study. *J Low Genit Tract Dis* 9: 232-235.

23. Denny L, Kuhn L, De Souza M, et al. (2005). Screen-and-treat approaches for cervical cancer prevention in low-resource settings: a randomized controlled trial. *JAMA* 294: 2173-2181.

24. Sankaranarayanan R, Esmy PO, Rajkumar R, et al. (2007). Effect of visual screening on cervical cancer incidence and mortality in Tamil Nadu, India: a cluster-randomised trial. *Lancet* 370: 398-406.

25. Sangwa-Lugoma G, Mahmud S, Nasr SH, et al. (2006). Visual inspection as a cervical cancer screening method in a primary health care setting in Africa. *Int J Cancer* 119: 1389-1395.

26. Sankaranarayanan R, Basu P, Wesley RS, et al. (2004). Accuracy of visual screening for cervical neoplasia: Results from an IARC multicentre study in India and Africa. *Int J Cancer* 110: 907-913.

27. Sarian LO, Derchain SF, Naud P, et al. (2005). Evaluation of visual inspection with acetic acid (VIA), Lugol's iodine (VILI), cervical cytology and HPV testing as cervical screening tools in Latin America. This report refers to partial results from the LAMS (Latin AMerican Screening) study. *J Med Screen* 12: 142-149.

28. Parkin DM and Bray F (2006). Chapter 2: The burden of HPV-related cancers. *Vaccine* 24 Suppl: S3/11-S3/25.

29. Quinn M, Babb P, Jones J, et al. (1999). Effect of screening on incidence of and mortality from cancer of cervix in England: evaluation based on routinely collected statistics. *BMJ* 318: 904-908.

30. Willoughby BJ, Faulkner K, Stamp EC, et al. (2006). A descriptive study of the decline in cervical screening coverage rates in the North East and Yorkshire and the Humber regions of the UK from 1995 to 2005. *J Public Health (Oxf)* 28: 355-360.

4.6 Screening for Breast Cancer

Summary

> Breast cancer is the most frequent cancer in women and accounts for over one in five new cancer cases in women worldwide. Due to an overall aging of the world population, the number of cases is expected to increase in the coming years

> The large randomised trials performed from 1976–1990 have shown that an invitation to breast cancer screening based on mammography can reduce mortality from breast cancer averaging 25% in women aged 50–69 years. More recently, analysis of population-based service screening programmes in women aged 40–69 years has demonstrated that regular mammography screening attendance can provide 40–45% reduction in breast cancer mortality

> There is only indirect evidence that screening by clinical breast examination will reduce the number of breast cancer deaths

> Screening should be implemented in the context of an organised, population-based programme following comprehensive quality assurance guidelines. Adequate attention should be paid to planning and training, identification and invitation of the target population, multidisciplinary management of detected lesions, as well as to coordination, monitoring and evaluation.

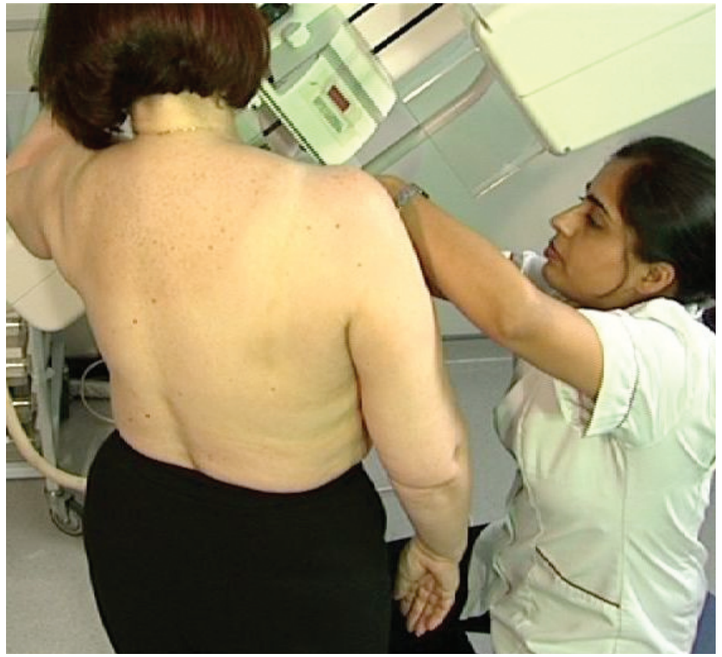


Fig. 4.6.1 *Positioning of the breast for screening mammography. Image provided by Dr ARM Wilson, Dept of Academic Oncology, Guy's Hospital, London, United Kingdom.*

Cancer of the breast is the most common cancer in women worldwide, and in many regions it is the most common cause of death from cancer in women. Breast cancer is characterised by a preclinical detectable phase lasting from 1–7 years, depending on the specific disease subtype. Mammography (X-ray examination of the breasts) can detect preclinical cancer, that is, detect the tumour before it is palpable and before it causes symptoms. Tumours detected and treated at an early stage are associated with a better survival rate than those detected symptomatically. Early diagnosis may permit breast-conserving surgery (Stage I disease), reduce the need for adjuvant therapy and decrease complications related to intensive treatment and recurrence [1-5].

The impact of screening

The incidence of breast cancer worldwide has been on the rise for at least the past half century. Factors such as diminished and delayed childbearing are partly responsible for this increase. Improved diagnostic methods are also generally considered to influence the increase. However, the introduction of screening mammography occurred several decades after the documented increase in incidence and can account for only a minor part of the increase. On the other hand, the marked increase in the incidence of *in situ* breast carcinoma appears to be directly related to the availability of mammography, as this form of breast cancer is difficult to detect by clinical methods [4-6].

In many developed countries mortality rates have been rather stable despite the steady increase in incidence. No clear overall decline in mortality was observed in any place before the late 1980s, when a gradual downturn occurred in Europe, North America and Australia. These decreases in breast cancer mortality have been attributed to a combination of earlier detection and improved treatment, but the relative contribution of each has not been determined [3,4,7,8].

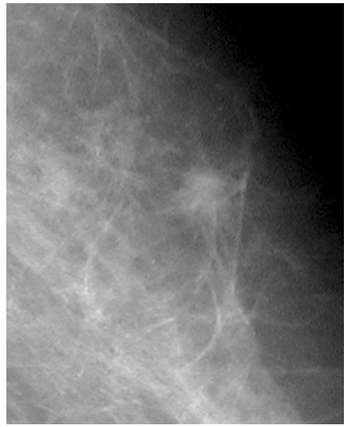


Fig. 4.6.2 *Detailed view of a mammogram from a patient revealing a small breast cancer. Image provided by Dr Margrit Reichel, Screening Reference Team, Koenigstein and Meinhard, Germany*

Protocols for screening

Breast cancer screening is delivered in a variety of ways, including organised programmes and "opportunistic" activities which involve referral to mammography facilities by clinicians and self-referral by women themselves. Organised programmes are recommended because they include an administrative structure responsible for implementation, quality assurance and evaluation. The screening process begins with information and invitation of the eligible women to attend screening and extends from performance of the screening test (in most cases mammography) to the diagnostic assessment of women with suspicious test results and, if necessary, treatment of women with screen-detected lesions. Overall screening outcome and quality depend on the performance at each step in the screening process. Population-based programmes generally require a high degree of organisation in order to identify and personally invite each woman in the eligible target population. The population-based approach to programme implementation is recommended because it provides an organisational framework conducive to effective management and continuous improvement of the screening process, such as through linkage with population and cancer registries for optimisation of invitation to screening and for evaluation of screening performance and impact.

Fig. 4.6.3 *The evaluation of mammograms requires appropriate expertise and performance standardisation. Image provided by Prof Peter B Dean, Dept of Diagnostic Radiology, University of Turku, Turku, Finland*

By the mid-1990s at least 22 countries had established national, sub-national or pilot population breast cancer screening programmes [9]. Currently, most of the 27 member states of the European Union are running or establishing population-based breast cancer screening programmes based on mammography [10]. Many programmes target the age group 50–69 years for mammography screening. The youngest age targeted for screening is generally 40 years. Some opportunistic programmes do not set an upper age limit for eligibility, whereas some population-based screening programmes target women up to age 74 or, in at least one case (The Netherlands) age 75. The upper age limit for three-yearly population-based invitation to attend the NHS Breast Screening Programme in the United Kingdom is 70 years; older women can also request to attend screening. Most screening programmes have adopted a two-year screening interval; shorter intervals of 12 or 18 months have been adopted by programmes targeting women under age 50 which is consistent with the shorter mean sojourn time of breast tumours in younger women [11].

Mammography screening is performed on large numbers of predominantly asymptomatic women. The potential harm caused by mammography includes the creation of unnecessary anxiety and morbidity, inappropriate economic cost and the use of ionizing radiation. The strongest possible emphasis on quality assur-

Fig. 4.6.4 *A positive mammogram requires comprehensive follow-up, often including percutaneous core needle biopsy under ultrasound or stereotactic guidance. Image provided by Dr ARM Wilson, Dept of Academic Oncology, Guy's Hospital, London, United Kingdom.*

ance and physico-technical quality control is required to maintain an appropriate balance between harm and benefit of screening. The evaluation of individual mammograms requires appropriate expertise and performance standardisation (Figure 4.6.3). Independent double reading of mammograms with a protocol for resolution of discrepant interpretations, and use of two views (mediolateral oblique and craniocaudal) is recommended to increase accuracy in detection of lesions [12-14]. It is also essential to adhere to adequate standards of diagnostic assessment of women with abnormal results of the initial screening evaluation, as well as standards of multidisciplinary management of lesions detected in screening. Failsafe mechanisms should be established to ensure that all women with abnormalities are contacted and recalled or referred for diagnostic assessment, which may involve repeat and/or more comprehensive mammography, clinical breast examination, ultrasonography and biopsy, if suspicion of malignancy cannot otherwise be ruled out (Figure 4.6.4). Women with a diagnosis of breast cancer should be offered an appointment for treatment within a reasonably short period of time.

Numerous countries have adopted regulations and guidelines on quality assurance of mammography screening [13]. In the United States, the Mammography Quality Standards Act (MQSA) has made certification of mammography facilities mandatory [15].

Comprehensive multidisciplinary guidelines for quality assurance in breast cancer screening and diagnosis have been developed by experts and published by the European Commission [14]. The Council of the European Union has recommended implementation of population-based breast cancer screening programmes according to the EU guidelines to all EU member states [16].

There is currently insufficient evidence from studies in high-resource countries to support the efficacy of clinical breast examination or the teaching of self-examination of the breast as a public health strategy to lower the number of breast cancer deaths in the population. These methods are being evaluated for screening in low-resource countries in which most patients currently present for treatment at very late stages [17]. A study aiming to reduce the proportion of newly diagnosed advanced stage breast cancer from 80% to 60% using breast awareness, breast self-examination, clinical breast examination and centralised assessment of abnormalities is currently underway in India.

Cancers diagnosed in the interval between two routine screening examinations, or within the time period corresponding to the regular screening interval after a negative screening examination, are known as "interval" cancers. Mammographic breast density appears to be a major risk factor for interval cancer, with the highest risk being associated with extremely dense breasts [18]. Clinical examination and self-examination, whilst not proven to show a benefit in terms of reduction in breast cancer mortality [19], may aid in the detection of interval cancers in mammography-based screening programmes.

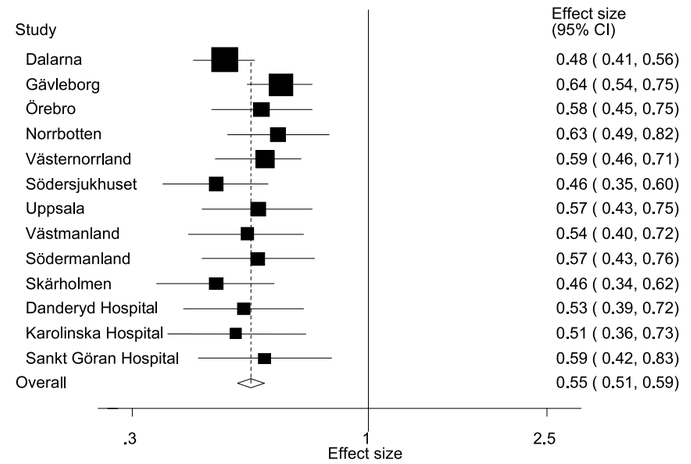


Fig. 4.6.5 *Relative risk of incidence-based breast cancer mortality for screened women in the screening epoch compared with the prescreening epoch, adjusted for self-selection bias [29]. Figure reproduced from Cancer Epidemiol Biomarkers Prev 15: 45-51 with permission of the American Association for Cancer Research, Inc.*

Evaluation of screening

Screening by mammography began to be widely adopted in the late 1980s following the demonstration of its effectiveness in two major randomised trials [20,21].

Inconclusive results were found in two trials in Canada in which annual mammography and breast physical examination were compared with single breast physical examination and subsequent care in 40–49-year-old women [22], and with annual breast physical examination in women aged 50–59 years [23]. Additional randomised controlled trials have also demonstrated a significant decrease in breast cancer mortality in the invited populations compared to the non-invited control populations. The principal factors influencing the magnitude of this decrease include the participation rates of the invited women, the performance of mammography in the control population, and the diagnostic accuracy of mammography in each particular trial [19].

Most of the existing randomised controlled trials have been criticized for putative methodological weaknesses by critics who also argued that breast cancer mortality is not a valid endpoint for screening trials [24,25]. These critics dismissal of all the positive randomized trials is generally considered to be inappropriate because, essentially, it is based on a mechanistic evaluation of technical criteria that are of questionable relevance to the results [26].

A re-appraisal of the randomised controlled trials, conducted by a working group of experts convened by the International Agency for Research on Cancer, concluded that the exclusion of the positive randomised controlled trials was unjustified and that there is sufficient evidence for the efficacy of screening women aged 50–69 years by mammography as the sole screening modality in reducing mortality from breast cancer. Women who were invited to be screened showed a reduction in breast cancer mortality averaging 25%, with the degree of benefit depending on the particular trial. Since not all women accepted the invitation, the reduction among those who chose to participate in screening is somewhat higher, being estimated at 35% [19].

None of the population screening trials had sufficient statistical power to evaluate the results by 10-year age cohorts, and attempts to determine the efficacy of mammography screening in the 40–49 year age cohort have yielded less promising results [19]. The lower incidence of breast cancer, and a somewhat greater radiopacity of the premenopausal breast at mammography, combined with a more rapid progression of breast cancer in premenopausal women may be contributing factors, but the current evidence is far from complete [1,5,27].

The effect of up to seven years of annual mammographic screening is under investigation in a randomised controlled trial in the UK which recruited women 39–41 years of age at study entry. The recently reported results at 10-year follow-up are not statistically significant but are consistent with other findings showing a significant but lesser impact of screening in women aged 40–49 years than in older women. The authors pointed out that the non-significant effect was much larger (ca. 24% mortality reduction) in the women actually exposed to screening (participants) than in the entire group of women invited to attend screening (ca. 15%). Due to the study protocol, sensitivity was reduced after the initial screening examination, which may have reduced the observed effect of screening [28].

Organized service mammography screening has been evaluated in Sweden by combining individual breast cancer patient data with screening invitation data to document the impact upon the individual woman of actually receiving the screening mammography examination. In this large study involving women in the age range 40–69 years in nearly half of the country, data were collected on 542 187 women in the pre-screening era and 566 423 women in the screening era. Approximately two thirds of the study population was from regions with invitation to screening in the age-

range 40-69 and approximately one third was from regions with invitation to screening in the age range 50-69. Some counties also offered screening to women in the age range 70-74, but the analysis was restricted to women <70. In an average follow-up period of 13 years, the observed mortality reduction to the population of 27% (screened and non-screened women combined) corresponded to a mortality reduction of 40–45% in the women actually screened (Figure 4.6.5).

Approximately 472 women (95% CI 418–554) needed to be screened by mammography to save one life from breast cancer. The number needed to screen to save one life ranged from 188 to 862 in the various regions covered by the study and was inversely related to the respective length of follow-up, which varied between 22 and 11 years due to uneven rollout of screening across the country [29].

For effective quality management, screening should be implemented in the context of an organized, population-based programme following comprehensive quality assurance guidelines. Adequate attention should be paid to planning and training, identification and invitation of the target population, multidisciplinary management of detected lesions, as well as to coordination, monitoring and evaluation. Due to the favourable prognosis of breast cancer in high-resource countries, long-term follow-up is required to assess the full impact of service screening programmes [29,30].

WEBSITES

Information from the US NCI on testing for various cancers, including breast:
http://www.cancer.gov/cancerinfo/screening

FDA's Mammography Programme:
http://www.fda.gov/cdrh/mammography/mqsa-rev.html

European Cancer Network
(breast, cervical and colorectal cancer screening, diagnosis and management)
See: IARC Screening Quality Control Group (ECN)

European Guidelines for Quality Assurance in Breast Cancer Screening and Diagnosis (pdf version):
http://bookshop.eu.int/eGetRecords?Template=Test_EUB/en_publication_details&CATNBR=ND7306954ENC

IARC Screening Quality Control Group (ECN):
http://www.iarc.fr/en/Research-Groups/Clusters-Groups/Pathogenesis-and-Prevention-Cluster/Screening-Quality-Control-Group

International Cancer Screening Network:
http://appliedresearch.cancer.gov/icsn/

REFERENCES

1. Chen HH, Duffy SW, Tabar L, et al. (1997). Markov chain models for progression of breast cancer Part I: tumour attributes and the preclinical screen-detectable phase. *J Epidemiol Biostat* 2: 9-23.

2. Ferlay J, Bray F, Pisani P, et al. (2004). GLOBOCAN 2002: Cancer incidence, mortality and prevalence worldwide. *IARC CancerBase* No. 5 Version 2.0. Lyon, France: International Agency for Research on Cancer.

3. Fletcher SW and Elmore JG (2003). Clinical practice. Mammographic screening for breast cancer. *N Engl J Med* 348: 1672-1680.

4. Parkin DM and Fernandez LM (2006). Use of statistics to assess the global burden of breast cancer. *Breast J* 12 Suppl 1: S70-S80.

5.Tabar L, Fagerberg G, Chen HH, et al. (1996). Tumour development, histology and grade of breast cancers: prognosis and progression. *Int J Cancer* 66: 413-419.

6. Barchielli A, Paci E, Giorgi D (1999). Recent trends of in situ carcinoma of the breast and mammographic screening in the Florence area, Italy. *Cancer Causes Control* 10: 313-317.

7. Berry DA, Cronin KA, Plevritis SK, et al. (2005). Effect of screening and adjuvant therapy on mortality from breast cancer. *N Engl J Med* 353: 1784-1792.

8. Hery C, Ferlay J, Boniol M, et al. (2008). Quantification of changes in breast cancer incidence and mortality since 1990 in 35 countries with Caucasian-majority populations. *Ann Oncol* 19: 1187-1194.

9. Shapiro S, Coleman EA, Broeders M, et al. (1998). Breast cancer screening programmes in 22 countries: current policies, administration and guidelines. International Breast Cancer Screening Network (IBSN) and the European Network of Pilot Projects for Breast Cancer Screening. *Int J Epidemiol* 27: 735-742.

10. Karsa Lv, Anttila A, Ronco G, et al. (2008). Cancer screening in the European Union. Report on the implementation of the Council Recommendation on cancer screening – First Report. European Communities, Luxembourg, 2008. Available from: http://www.ec.europa.eu/health/ph_determinants/genetics/documents/cancer_screening.pdf/ Date Accessed: October 12, 2008.

11. Duffy SW, Chen HH, Tabar L, et al. (1996). Sojourn time, sensitivity and positive predictive value of mammography screening for breast cancer in women aged 40-49. *Int J Epidemiol* 25: 1139-1145.

12. Nass SJ, Ball J, National Cancer Policy Board (U.S.), et al. (2005). *Improving breast imaging quality standards*. Washington, D.C: National Academies Press.

13. Yankaskas BC, Klabunde CN, Ancelle-Park R, et al. (2004). International comparison of performance measures for screening mammography: can it be done? *J Med Screen* 11: 187-193.

14.Perry N, Broeders M, de WC, et al. (2008). European guidelines for quality assurance in breast cancer screening and diagnosis. Fourth edition–summary document. *Ann Oncol* 19: 614-622.

15. US Food and Drug Administration, Center for Devices and Radiological Health. *Mammography*. Available from: http://www.fda.gov/CDRH/mammography/ Date Accessed: October 12, 2008.

16. Council of the European Union (2003). Council Recommendation of 2 December 2003 on cancer screening 2003/879/EC. *Official Journal of the European Union* 46: 34-38.

17. Anderson BO, Shyyan R, Eniu A, et al. (2006). Breast cancer in limited-resource countries: an overview of the Breast Health Global Initiative 2005 guidelines. *Breast J* 12 Suppl 1: S3-15.

18. Mandelson MT, Oestreicher N, Porter PL, et al. (2000). Breast density as a predictor of mammographic detection: comparison of interval- and screen-detected cancers. *J Natl Cancer Inst* 92: 1081-1087.

19. IARC (2002). *IARC handbooks of cancer prevention, Volume 7, Breast cancer screening*. Lyon, France: International Agency for Research on Cancer.

20.Shapiro S, Strax P, Venet L (1971) Periodic breast cancer screening in reducing mortality from breast cancer. JAMA. 215:1777-85.

21. Tabar L, Fagerberg G, Duffy SW, et al. (1992). Update of the Swedish two-county program of mammographic screening for breast cancer. *Radiol Clin North Am* 30: 187-210.

22. Miller AB, To T, Baines CJ, et al. (2002). The Canadian National Breast Screening Study-1: breast cancer mortality after 11 to 16 years of follow-up. A randomized screening trial of mammography in women age 40 to 49 years. *Ann Intern Med* 137: 305-312.

23. Miller AB, To T, Baines CJ, et al. (2000). Canadian National Breast Screening Study-2: 13-year results of a randomized trial in women aged 50-59 years. *J Natl Cancer Inst* 92: 1490-1499.

24. Olsen O and Gotzsche PC (2001). Screening for breast cancer with mammography. *Cochrane Database Syst Rev* CD001877.

25. Gotzsche PC and Olsen O (2000). Is screening for breast cancer with mammography justifiable? *Lancet* 355: 129-134.

26. Hakama M, Coleman MP, Alexe DM, et al. (2008). Cancer screening. In: Coleman MP, Alexe DM, Albreht T, et al., eds., *Responding to the challenge of cancer in Europe*. Ljubljana, Slovenia: Institute of Public Health of the Republic of Slovenia. 69-92.

27. Armstrong K, Moye E, Williams S, et al. (2007). Screening mammography in women 40 to 49 years of age: a systematic review for the American College of Physicians. *Ann Intern Med* 146: 516-526.

28. Moss SM, Cuckle H, Evans A, et al. (2006). Effect of mammographic screening from age 40 years on breast cancer mortality at 10 years' follow-up: a randomised controlled trial. *Lancet* 368: 2053-2060.

29. Swedish Organised Service Screening Evaluation Group (2006). Reduction in breast cancer mortality from organized service screening with mammography: 1. Further confirmation with extended data. *Cancer Epidemiol Biomarkers Prev* 15: 45-51.

30. Gabe R and Duffy SW (2005). Evaluation of service screening mammography in practice: the impact on breast cancer mortality. *Ann Oncol* 16: ii153-ii162.

4.7 Screening for Colorectal Cancer

Summary

> Early detection of colorectal cancer increases surgical curability. Several screening modalities exist, including the faecal occult blood test (FOBT), flexible sigmoidoscopy, colonoscopy and virtual colonoscopy

> Population-based FOBT screening may reduce CRC mortality by 16%, but cannot much reduce CRC incidence. The use of rehydrated FOBT in one trial did decrease CRC incidence by about 20% after 18 years, but this could be due to the high rate of colonoscopies induced by the low specificity of rehydrated FOBT

> Observational non-randomised studies suggest that endoscopic methods would decrease both CRC incidence and mortality, with much larger gains in mortality reduction than with FOBT

> Offering FOBT screening to a population must take into consideration the logistics of screening and the burden CRC screening will represent in terms of colonoscopy

In 2002, the worldwide burden of colorectal cancer (CRC) was estimated as 550 000 new cases and 278 000 deaths for men and 472 600 new cases and 255 000 deaths for women [1]. Colorectal cancer is most frequent in North America, Australia, New Zealand and parts of Europe. Benign or malignant neoplastic lesions of the large bowel are termed superficial when their depth is limited to the mucosa or the submucosa. These superficial CRCs are assumed to be completely curable by surgical means (laparotomy, laparoscopy) or by endoscopic removal. These superficial CRCs and advanced adenomas typically defined as adenomas 1cm or greater, or with villous components (tubulovillous or villous), or with high-grade or severe dysplasia, are the targets of screening.

Most CRCs arise from adenomatous polyps, and their removal is likely to decrease both CRC incidence and mortality. The likelihood that a polyp will evolve into CRC is correlated to its size. Adenomatous polyps less than 0.5 or 1cm are unlikely to give rise to a CRC. Hence, adenomatous polyps 1cm in size or larger are an important target for screening. Autopsy and colonoscopy studies confirm a prevalence of adenomatous polyps in the range of 30% in the adult populations above 50 years old in various Western countries. This means that the majority of polypoid precursors will never progress to cancer.

The faecal occult blood test (FOBT)

Screening with the Guaiac or Immunochemical Fecal Occult Blood Test is proposed for organised mass screening to men and women from the age of 50 years, and repeated in successive campaigns. There is no benefit in prolonging screening above age 70 years for persons who have always tested negative [2]. Persons with positive FOBT tests are referred to colonoscopy. Meta-analysis by a Cochrane Review Group of combined results from randomised controlled trials [3-8] shows that participants allocated to screening had a 16% reduction in the relative risk of colorectal cancer mortality (RR 0.84, CI: 0.78–0.90) [9]. In the three studies that used biennial screening there was a 15% relative risk reduction (CI: 0.78–0.92) in colorectal cancer mortality. When adjusted for screening attendance in the individual studies, there was a 25% relative risk reduction (RR 0.75, CI: 0.66–0.84) for those attending at least one round of screening using the faecal occult blood test.

The real efficacy of FOBT as assessed in randomised trials has been debated [10,11]. Also, sensitivity of FOBT for CRC detection is low, in the order of 40–50%, and with FOBT, most CRC are still clinically detected. Usually, non-rehydrated FOBT is used. Rehydrated FOBT leads to numerous false positive results, and in the Minnesota trial, after 18 years of follow-up, 38% of subjects in the screening group had undergone colonoscopy. This high rate of colonoscopy also led to a 20% reduction in CRC incidence [12]. When the false-positive rate is lower (as when non-rehydrated FOBT is used), FOBT screening does not lower CRC incidence because this test rarely detects the presence of adenomatous polyps.

Flexible sigmoidoscopy

Rigid rectosigmoidoscopy is now abandoned in screening protocols, while flexible sigmoidoscopy is often proposed because of a better acceptance than colonoscopy. Most guidelines recommend flexible sigmoidoscopy every 5 years. A major advantage of the procedure is that it can also be performed by trained nurses. The efficacy of rigid or flexible sigmoidoscopy has been evaluated in case–control or observational studies. The Kaiser study [13] compared exposure to rigid sigmoidoscopy during the previous 10 years in cases (distal CR cancer) and in controls (no cancer); sigmoidoscopy reduced the incidence of distal colorectal cancer by 59%. In the USA, a cohort study conducted in 24 744 health professionals [14] has shown that screening with flexible sigmoidoscopy reduces mortality from colorectal cancer by 50% and incidence by 44%.

Several studies have shown that subjects with adenomatous polyps in the descending (left) colon and rectum had a greater chance of having adenomatous polyps or CRC in the transverse and ascending (right) colon [15]. Therefore, flexible sigmoidoscopy may serve as a first-line screening procedure, followed by colonoscopy when adenomatous polyps are found.

Evaluation of the efficacy of flexible sigmoidoscopy is underway: this method is included in the PLCO (Prostate, Lung, Colorectal & Ovarian cancer) randomised screening trial in the USA [16]. Trials in the UK [17] and Italy [18] are evaluating the efficacy of a once-in-a-lifetime flexible sigmoidoscopy offered at age 55–64 years.

Colonoscopy

Colonoscopy is a total endoscopic evaluation of the colon, up to the caecum. This procedure also allows removal of polyps. The chance of finding a cancer during the 5 years following a negative colonoscopy is very small [19]. Colonoscopy is less adapted to a mass screening strategy because compliance is limited, cost is high and the possibility of complications (e.g., intestinal perforation) is present. There is indirect evidence from non-randomised studies that colonoscopy and polypectomy may reduce CRC incidence and mortality. In the prospective National Polyp Study in the USA, a 75% reduction in the CRC incidence attributable to colonoscopy was observed [20].

Other screening modalities

Numerous new tests for detection of CRC biomarkers in stools are proposed, including detection of abnormal DNA in stools. Searching for abnormal DNA seems 3 to 4 times more sensitive and has similar specificity as the least sensitive non-rehydrated Guaiac-based FOBT (Hemoccult II). However, an early version of a stool DNA-based test still failed to detect three fifths of colorectal cancers detected by colonoscopy [21].

Virtual colonoscopy (computed tomographic colonography or CTC) comprises an evaluation of the colon by CT scanning and reconstruction of the colon anatomy using computer software. While appealing, virtual colonoscopy is expensive, involves low-dose radiation, requires a similar bowel preparation as colonoscopy, and requires further colonoscopy for removal of significant polyps eventually detected. Several software packages are commercially available or have been developed by academic researchers, and detailed evaluation of their respective merits is still needed. A recent multicenter trial in the USA of 2600 asymptomatic men and women aged 50 years or older confirmed the sensitivity of CTC to be equivalent (90% accurate) to optical colonoscopy for the detection of large adenomas and cancers over 1 cm in diameter [22].

Implementation of screening measures

Implementation of screening measures depends on health authorities, reimbursement policies, and compliance of the target population. Often, several CRC screening modalities coexist in the same country. Mass screening with the FOBT is proposed and reimbursed in Japan, Germany, France, Czech Republic, and the UK. Germany and Italy have organised screening protocols based on endoscopic methods. Screening with primary sigmoidoscopy is encouraged in Scandinavian countries and in the UK. In the USA, annual FOBT or sigmoidoscopy every 5 years or colonoscopy every 10 years is recommended. New guidelines in the USA also include the use of virtual colonoscopy every 5 years.

REFERENCES

1. Ferlay J, Bray F, Pisani P, et al., eds. (2004). GLOBOCAN 2002: Cancer incidence, mortality and prevalence worldwide. *IARC CancerBase* No. 5 Version 2.0. Lyon, France: International Agency for Research on Cancer. Available from: http://www-dep.iarc.fr/ Date Accessed: November 18, 2008

2. Walsh JM and Terdiman JP (2003). Colorectal cancer screening: scientific review. *JAMA* 289: 1288-1296.

3. Hardcastle JD, Chamberlain JO, Robinson MH, et al. (1996). Randomised controlled trial of faecal-occult-blood screening for colorectal cancer. *Lancet* 348: 1472-1477.

4. Kewenter J, Brevinge H, Engaras B, et al. (1994). Results of screening, rescreening, and follow-up in a prospective randomized study for detection of colorectal cancer by fecal occult blood testing. Results for 68,308 subjects. *Scand J Gastroenterol* 29: 468-473.

5. Kronborg O, Fenger C, Olsen J, et al. (1996). Randomised study of screening for colorectal cancer with faecal-occult-blood test. *Lancet* 348: 1467-1471.

6. Kronborg O, Jorgensen OD, Fenger C, et al. (2004). Randomized study of biennial screening with a faecal occult blood test: results after nine screening rounds. *Scand J Gastroenterol* 39: 846-851.

7. Mandel JS, Bond JH, Church TR, et al. (1993). Reducing mortality from colorectal cancer by screening for fecal occult blood. Minnesota Colon Cancer Control Study. *N Engl J Med* 328: 1365-1371.

8. Scholefield JH, Moss S, Sufi F, et al. (2002). Effect of faecal occult blood screening on mortality from colorectal cancer: results from a randomised controlled trial. *Gut* 50: 840-844.

9. Hewitson P, Glasziou P, Irwig L, et al. (2007). Screening for colorectal cancer using the faecal occult blood test, Hemoccult. *Cochrane Database Syst Rev* CD001216.

10. Autier P, Boyle P, Buyse M, et al. (2003). Is FOB screening really the answer for lowering mortality in colorectal cancer? *Recent Results Cancer Res* 163: 254-263.

11. Moayyedi P and Achkar E (2006). Does fecal occult blood testing really reduce mortality? A reanalysis of systematic review data. *Am J Gastroenterol* 101: 380-384.

12. Mandel JS, Church TR, Bond JH, et al. (2000). The effect of fecal occult-blood screening on the incidence of colorectal cancer. *N Engl J Med* 343: 1603-1607.

13. Selby JV, Friedman GD, Quesenberry CP, Jr., et al. (1992). A case-control study of screening sigmoidoscopy and mortality from colorectal cancer. *N Engl J Med* 326: 653-657.

14. Newcomb PA, Norfleet RG, Storer BE, et al. (1992). Screening sigmoidoscopy and colorectal cancer mortality. *J Natl Cancer Inst* 84: 1572-1575.

15. Toribara NW and Sleisenger MH (1995). Screening for colorectal cancer. *N Engl J Med* 332: 861-867.

16. Weissfeld JL, Schoen RE, Pinsky PF, et al. (2005). Flexible sigmoidoscopy in the PLCO cancer screening trial: results from the baseline screening examination of a randomized trial. *J Natl Cancer Inst* 97: 989-997.

17. Atkin WS (1998). Flexible sigmoidoscopy as a mass screening tool. *Eur J Gastroenterol Hepatol* 10: 219-223.

18. Segnan N, Senore C, Andreoni B, et al. (2005). Randomized trial of different screening strategies for colorectal cancer: patient response and detection rates. *J Natl Cancer Inst* 97: 347-357.

19. Lieberman DA, Weiss DG, Harford WV, et al. (2007). Five-year colon surveillance after screening colonoscopy. *Gastroenterology* 133: 1077-1085.

20. Winawer SJ, Zauber AG, Fletcher RH, et al. (2006). Guidelines for colonoscopy surveillance after polypectomy: a consensus update by the US Multi-Society Task Force on Colorectal Cancer and the American Cancer Society. *Gastroenterology* 130: 1872-1885.

21. Imperiale TF, Ransohoff DF, Itzkowitz SH, et al. (2004). Fecal DNA versus fecal occult blood for colorectal cancer screening in an average-risk population. *N Engl J Med* 351: 2704-2714.

22. Johnson CD, Chen MH, Toledano AY, et al. (2008). Accuracy of CT colonography for detection of large adenomas and cancers. *N Engl J Med* 359: 1207-1217.

4.8 Screening for Oral Cancer

Summary

> Oral cancer and its precancerous lesions can be readily detected by visual inspection of the oral cavity by health care providers.

> Oral cancer screening leads to the diagnosis of an increased proportion of early stage oral cancers and improves 5-year survival.

> A statistically significant 33% reduction in oral cancer mortality following oral visual screening has been demonstrated in a large population-based randomised controlled trial.

> The assessment of the oral cavity during routine health care interactions and improved awareness among health care providers and seekers provide excellent opportunities for implementing oral cancer screening.

Oral cancer is a major health problem worldwide, accounting for 274 000 new cases and 145 000 deaths annually, of which two thirds occur in developing countries. [1] Oral cancer is often preceded by precancerous lesions such as leukoplakia, erythroplakia, lichen planus and submucous fibrosis. Oral leukoplakia refers to the presence of flat, predominantly white lesions in the lining of the mouth that cannot be characterised as any other disease. White lesions with a uniform smooth, corrugated or wrinkled surface are referred to as homogeneous leukoplakia (Figure 4.8.1), and those with irregularly flat, nodular, white or red exophytic and white lesions are referred to as non-homogeneous leukoplakia (Figure 4.8.2). Erythroplakia refers to velvety red, non-removable lesions in the oral mucosa (Figure 4.8.3) and they often harbour early invasive cancers. Oral submucous fibrosis (Figure 4.8.4) is characterised by recurrent inflammation and stiffness of the oral mucosa with progressive limitation in opening the mouth and protrusion of the tongue.

The natural history of oral precancerous lesions is not as extensively documented as that of the precursors to cervical cancer. Thus, for example, it is not known whether the different types of leukoplakia and erythroplakia constitute a continuum similar to the different stages evident during the development of cervical intraepithelial neoplasia. Although only a small fraction of subjects with these lesions may progress to invasive cancer, around 30-80% of invasive cancers are associated with pre-existing oral precancerous lesions (Figure 4.8.5). In hospital-based studies, a malignant transformation rate of 4.4–17.5% for leukoplakia, and in population based studies transformation rates of 0.13–2.2% over several years have been reported [2]. The risk of malignant transformation varies with sex (higher in women), type and location of leukoplakia (higher with non-homogeneous types and those located on the tongue or the floor of the mouth), presence of candida albicans and presence of epithelial dysplasia. The proportion of leukoplakias which regress has been reported to vary between 5 and 20% per year. It is difficult to determine to what extent the above findings are due to variations in case selection or are a true reflection of the natural history.

Early detection of oral cancer

Early oral cancers clinically present as small indurated ulcers, surface thickenings, nodules (Figure 4.8.6), reddish velvety areas (Figure 4.8.7) or ulceroproliferative growths (Figure 4.8.8), often with no symptoms. Pain is usually absent with these early lesions. Careful assessment of oral precancerous lesions for any suspicious areas, and directed biopsies, is important in the early detection of underlying invasive oral cancers. Both oral precancerous and early suspicious cancerous lesions can be readily detected by trained clinicians, nurses and auxiliary health workers, by a systematic visual oral inspection and by palpation [3]. A high level of awareness among health care providers can lead to a high degree of clinical suspicion and appropriate diagnostic follow-up (such as referral), directed biopsies and histopathological examination. It is possible to diagnose such lesions in subjects during routine healthcare interactions, particularly at the primary healthcare level. Although other methods of early detection such as mouth self examination, adjunctive tests like toludine blue application, oral cytology and fluorescence imaging exist, systematic naked eye visual inspection of the oral cavity and neck coupled with palpation of oral mucosa and neck are the most useful and readily applicable early detection procedures.

Oral visual inspection

The evidence supporting the routine use of oral visual inspection in the early detection of oral cancer is based on the performance characteristics of the test in cross-sectional studies, evaluation of routine screening programmes in health services and from a randomised controlled trial.

Oral visual inspection has been shown to be a sensitive and specific test to detect oral precancerous lesions and early asymptomatic oral cancers in several studies; the sensitivity of visual examination for detecting oral lesions varied from 58 to 94% and the specificity from 76 to 98% [3-10].The frequency of positive screening tests ranged between 1.3 and 7.3% of screened subjects and the frequency of adherence to referral among screen-positive subjects was sub-optimal, ranging from 54% to 72%.

An oral cancer screening programme in Cuba, initiated 1984, involved annual oral examination of subjects aged 15 and above by dentists. Although the proportion of stage I cancers increased from 24% in 1983 to 49% in 1989, no reduction in oral cancer mortality has been observed since the introduction of screening, due to sub-optimal coverage of target populations both for participation and treatment. [11]. A case-control study in the context of the programme revealed a 33% reduction (odds ratio 0.67 [95% CI: 0.46-0.95]) in the risk of advanced oral cancer [12]. The programme has been reorganised to cover subjects aged 30 years and above with oral visual inspection once in 3-years and with an improved referral pathway for diagnosis and treatment.

In a community-based cluster randomised controlled oral cancer screening intervention trial involving three rounds of oral visual inspection at 3-year intervals provided by trained health workers during 1995–2004 in Trivandrum, South India, a shift towards early stage at diagnosis (41% vs. 23%) and a higher 5-year survival frequency (50% vs. 34%) were observed

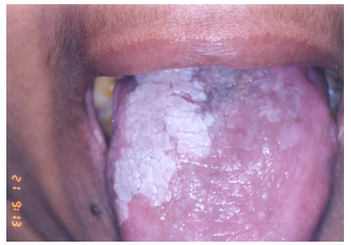


Fig. 4.8.1 *Homogenous leukoplakia on the right side of dorsum tongue*

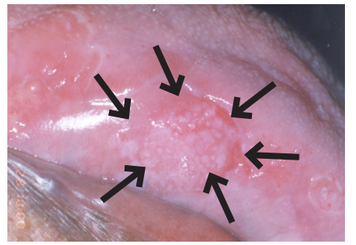


Fig. 4.8.2 *Nodular leukoplakia right lateral margin of the tongue: note the small nodules (yellow arrows) on an erythematous base (red arrows)*

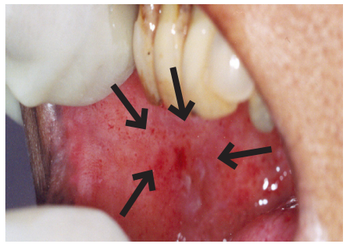


Fig. 4.8.3 *Erythroplakia with petechiae in the right buccal mucosa*

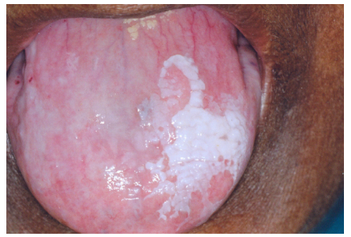


Fig. 4.8.4 *Oral submucous fibrosis, with a co-existing homogenous leukoplakia on the left side of dorsum tongue*

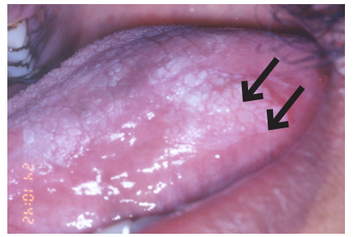


Fig. 4.8.5 *Homogenous leukoplakia on the dorsum and left lateral margin of the tongue, showing malignant transformation. Directed biopsy from the white plaques with erythematous margin posteriorly (arrows) revealed well differentiated squamous-cell carcinoma*

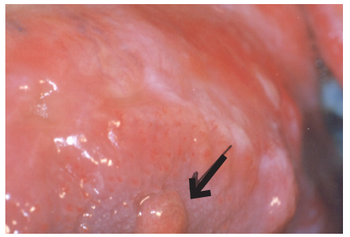


Fig. 4.8.6 *Early invasive cancer presenting as a nodule arising in a non-homogeneous, nodular leukoplakia in the left lateral margin of the tongue*

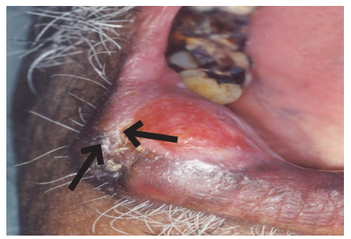


Fig. 4.8.7 *Directed biopsy from ulcerated and crusted area (thick arrow) in the red, velvety erythroplakia of the lower lip (thin arrow) revealed well differentiated squamous-cell carcinoma*

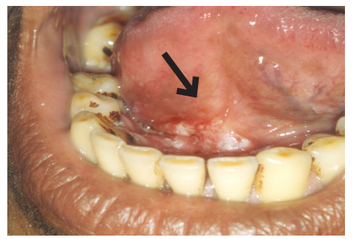


Fig. 4.8.8 *Early invasive oral cancer in the floor of mouth presenting as an ulceroproliferative growth and erythematous area around the Wharton's duct (arrow)*

in the screened population (Table 4.8.1) [8]. A 21% reduction in oral cancer mortality was observed in the intervention group compared to the control group 9-years from the initiation of screening in this study, which did not reach statistical significance. However, a statistically significant 34% reduction in mortality was observed among tobacco and/or alcohol users as compared to similar control subjects (Table 4.8.2). In summary, evidence from the Indian study shows that oral visual screening can reduce mortality in high-risk individuals. The cost-effectiveness of oral visual inspection is currently being addressed in the context of this trial.

Stage	Intervention	Control
I (<2 cm)	51 (25%)	20 (13%)
II (2-4 cm)	34 (17%)	17 (11%)
III (>4 cm)	37 (18%)	35 (22%)
IV (adjacent structures involved)	67 (33%)	70 (44%)
Not known	16 (8%)	16 (10%)
Total	205 (100%)	158 (100%)

Table 4.8.1 *Oral cancer cases according to stage (and percentage distribution), detected during an Indian screening trial (1995-1999), compared with an unscreened control population*

	Intervention group	Control group	Rate ratio (95%CI)	
Overall				
Eligible individuals (number)	96,517	95,356		
Oral cancer cases (number)	205	158		
Stage I and II cancer cases (%)	41	23		
Oral cancer deaths (number)	77	87		
5-year survival (%)	50	34		
Oral cancer mortality rate (per 100 000)	16	21	0.79	(0.51 – 1.22)
Among tobacco or alcohol users, or both				
Oral cancer deaths (number)	70	85		
Oral cancer mortality rate (per 100 000)	30	45	0.66	(0.45 – 0.95)
People with no habits				
Oral cancer deaths (number)	7	2		
Oral cancer mortality rate (per 100 000)	3	1	3.47	(0.12 – 96.51)

Table 4.8.2 *Oral cancer incidence, stage distribution and mortality in a randomised control trial of oral cancer screening in Trivandrum District, India*
Ref: Sankaranarayanan et al., Lancet 2005; 365: 1927-33 [8]

Visual inspection after toluidine blue staining

Toluidine blue dye has been predominantly used as an adjunct for early detection of oral cancer in subjects with precancerous lesions, in order to provide better demarcation of possible malignant and dysplastic changes so as to help select sites for biopsies [13]. This test has been evaluated only in a few specified clinical settings where the reported false negative and false positive rates ranged from 20–30%. The value of visual examination after toluidine blue application as a primary screening test in the early detection of oral cancer is not known.

Mouth self examination

There is very little information on self-screening for oral cancer or on health education to promote mouth self-examination, especially in high-risk population groups. In a study to evaluate the feasibility of mouth self-examination in India, 36% of 22 000 subjects who were taught mouth self-examination reportedly practised the test and in the 247 subjects visiting the clinic within two weeks of a promotion campaign, 89 precancers and 7 oral cancers were detected [14]. There is no information available on long-term feasibility and detection rates of oral cancer with self-screening.

Oral cytology

Screening by oral cytology has never achieved the same recognition or efficacy as cervical cytology screening, and its role as a primary oral screening test is not yet clear. Keratinization of the oral epithelium poses a major challenge in collecting an adequate number of cells and oral lesions need to be visible before a sample can be collected. Inadequate cellular smears and the subjective nature of interpretation leads to high false negative rates for oral lesions [6,15]. New collection techniques using brush biopsy have reportedly improved the sensitivity (92.3%) and specificity (94.3%) for detection of oral cancer or dysplasia when tested on visually identified lesions [16,17]. Recently, liquid-based oral cytology has also being investigated [18].

Fluorescence spectroscopy or imaging

Fluorescence spectroscopy evaluates the physical and chemical properties of tissue by analyzing the intensity and character of light emitted in the form of fluorescence. Autofluorescence, and 5-amino levulinic acid (5-ALA) induced protoporphyrin IX (PPIX) fluorescence can be recorded using a target integrating colour CCD camera [19]. Their usefulness as screening tools remains to be established.

Saliva-based tests

The value of using genomic targets in saliva as a early detection approach for oral cancer is currently being investigated [20].

Conclusions

Based on the findings from the large Indian cluster-randomised controlled trial, routine use of oral visual screening among tobacco and/or alcohol users is an effective method of reducing oral cancer mortality in addition to primary prevention efforts to reduce tobacco and alcohol use. The very low risk of oral neoplasia among non-users of tobacco or alcohol or both justifies the restricted use of screening among high-risk individuals. Health education messages and information on the usefulness of oral visual inspection through mass media and by posters in health centres, dispensaries and other health care establishments are conducive to improving awareness to prompt subjects at high risk to avail themselves of early detection services. Considering the fact that oral cavity assessment is an integral part of a general physical examination, awareness among health care providers of the effectiveness of oral visual inspection is critical in the early detection of oral neoplasia.

REFERENCES

1. Ferlay J, Bray F, Pisani P, Parkin DM. (2004). GLOBOCAN 2002: Cancer incidence, mortality and prevalence worldwide. *IARC CancerBase* No. 5 Version 2.0. Lyon, France: International Agency for Research on Cancer.

2. Rodrigues VC, Moss SM, Tuomainen H (1998). Oral cancer in the UK: to screen or not to screen. *Oral Oncol* 34: 454-465.

3. Sankaranarayanan R (1997). Health care auxiliaries in the detection and prevention of oral cancer. *Oral Oncol* 33: 149-154.

4. Mathew B, Sankaranarayanan R, Sunilkumar KB, et al. (1997). Reproducibility and validity of oral visual inspection by trained health workers in the detection of oral precancer and cancer. *Br J Cancer* 76: 390-394.

5. Mehta FS, Gupta PC, Bhonsle RB, et al. (1986). Detection of oral cancer using basic health workers in an area of high oral cancer incidence in India. *Cancer Detect Prev* 9: 219-225.

6. Ogden GR, Cowpe JG, Wight AJ (1997). Oral exfoliative cytology: review of methods of assessment. *J Oral Pathol Med* 26: 201-205.

7. Rodrigues VC, Moss SM, Tuomainen H (1998). Oral cancer in the UK: to screen or not to screen. *Oral Oncol* 34: 454-465.

8. Sankaranarayanan R, Ramadas K, Thomas G, et al. (2005). Effect of screening on oral cancer mortality in Kerala, India: a cluster-randomised controlled trial. *Lancet* 365: 1927-1933.

9. Warnakulasuriya KA, Ekanayake AN, Sivayoham S, et al. (1984). Utilization of primary health care workers for early detection of oral cancer and precancer cases in Sri Lanka. *Bull World Health Organ* 62: 243-250.

10. Warnakulasuriya KA and Nanayakkara BG (1991). Reproducibility of an oral cancer and precancer detection program using a primary health care model in Sri Lanka. *Cancer Detect Prev* 15: 331-334.

11. Fernandez-Garrote L, Sankaranarayanan R, Lence Anta JJ, et al. (1995). An evaluation of the oral cancer control program in Cuba. *Epidemiology* 6: 428-431.

12. Sankaranarayanan R, Fernandez GL, Lence AJ, et al. (2002). Visual inspection in oral cancer screening in Cuba: a case-control study. *Oral Oncol* 38: 131-136.

13. Martin IC, Kerawala CJ, Reed M (1998). The application of toluidine blue as a diagnostic adjunct in the detection of epithelial dysplasia. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 85: 444-446.

14. Mathew B, Sankaranarayanan R, Wesley R, et al. (1995). Evaluation of mouth self-examination in the control of oral cancer. *Br J Cancer* 71: 397-399.

15. Silverman S, Bilimoria KF, Bhargava K, et al. (1977). Cytologic, histologic and clinical correlations of precancerous and cancerous oral lesions in 57,518 industrial workers of Gujarat, India. *Acta Cytol* 21: 196-198.

16. Sciubba JJ (1999). Improving detection of precancerous and cancerous oral lesions. Computer-assisted analysis of the oral brush biopsy. U.S. Collaborative OralCDx Study Group. *J Am Dent Assoc* 130: 1445-1457.

17. Scheifele C, Schmidt-Westhausen AM, Dietrich T, et al. (2004). The sensitivity and specificity of the OralCDx technique: evaluation of 103 cases. *Oral Oncol* 40: 824-828.

18. Navone R, Burlo P, Pich A, et al. (2007). The impact of liquid-based oral cytology on the diagnosis of oral squamous dysplasia and carcinoma. *Cytopathology* 18: 356-360.

19. Betz CS, Stepp H, Janda P, et al. (2002). A comparative study of normal inspection, autofluorescence and 5-ALA-induced PPIX fluorescence for oral cancer diagnosis. *Int J Cancer* 97: 245-252.

20. Zimmermann BG, Park NJ, Wong DT (2007). Genomic targets in saliva. *Ann NY Acad Sci* 1098: 184-191.

4.9 Screening for Stomach Cancer

Summary

> Stomach cancer screening has been practiced in certain high-risk areas such as Japan and the Republic of Korea

> The efficacy and effectiveness of such screening has not been shown in a randomised trial

Stomach cancer screening has been practiced in Japan since 1963 and has been public health policy in The Republic of Korea since 1996. Screening is based on early detection of stomach cancer, with surgical resection of the stomach if a tumour is detected. The two techniques used for detection are X-ray examination, after the patient swallows a barium contrast medium, and endoscopic examination, with biopsies taken to confirm the presence of cancer. Gastric cancer screening is rare in less-developed countries, although pilot schemes based on the Japanese model have been conducted in Venezuela, Chile and Costa Rica.

It is difficult to judge the efficacy of stomach cancer screening in reducing mortality from stomach cancer. No randomised trial of stomach cancer screening has ever been conducted, though case–control studies with mortality from stomach cancer as an endpoint have been carried out. However, these studies were subject to several sources of bias that reduce the quality of the evidence they provide on screening efficacy. Recently, some prospective studies have shown important reductions in mortality from gastric cancer among participants in screening programmes in Japan and Costa Rica [1-3]. These studies are not subject to the recall bias that affects case–control studies. However, since these are observational studies, they still have the problem of self-selection: individuals who choose to participate in the screening programme may have a cancer risk that differs from that of non-participants. Therefore these studies cannot substitute for randomised trials.

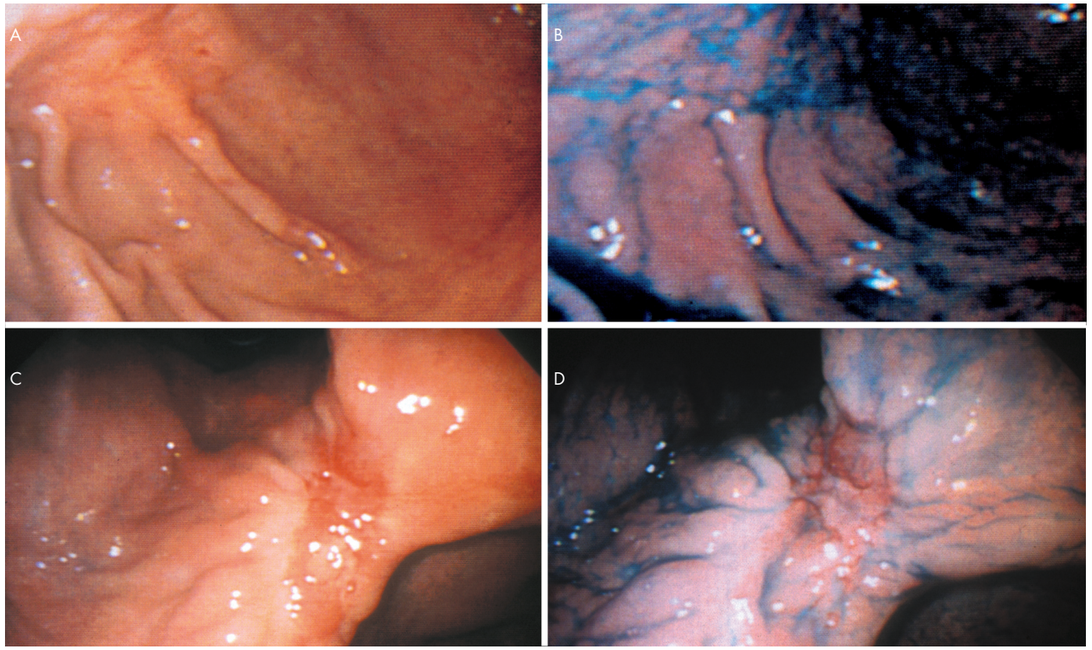


Fig. 4.9.1 *Endoscopic views of gastric cancer (A,C) and corresponding images with dye enhancement (B,D). A, B Depressed early gastric cancer. C,D Deep ulcer scar surrounded by superficial early gastric cancer infiltrating the mucosa and submucosa*

REFERENCES

1. Lee KJ, Inoue M, Otani T, et al. (2006). Gastric cancer screening and subsequent risk of gastric cancer: a large-scale population-based cohort study, with a 13-year follow-up in Japan. Int J Cancer 118: 2315-2321.

2. Mizoue T, Yoshimura T, Tokui N, et al. (2003). Prospective study of screening for stomach cancer in Japan. Int J Cancer 106: 103-107.

3. Rosero-Bixby L and Sierra R (2007). X-ray screening seems to reduce gastric cancer mortality by half in a community-controlled trial in Costa Rica. Br J Cancer 97: 837-843.

4.10 Screening for Prostate Cancer

Summary

> Prostate cancer is now the leading incident form of cancer in men in many countries

> Evidence shows harms of screening, but no evidence from randomised trials shows efficacy of prostate cancer screening with PSA (or any other modality)

> Population screening for prostate cancer cannot be recommended at present

> Testing for PSA and integrated programmes of expert multidisciplinary diagnosis and treatment are effective at reducing mortality from prostate cancer

> The availability of a cheap and safe test such as PSA has thrown up new issues and challenges for epidemiology

Among several methods that have been proposed to screen for prostate cancer, case–control studies have found conflicting results for digital rectal examination. Prostate Specific Antigen (PSA) measurement, obtained from a simple blood sample, has been widely proposed as a screening tool for prostate cancer. The PSA test was first approved in 1986 for monitoring progression in patients with prostate cancer. In 1991, William Catalona [1] published results obtained from a large series of men in whom PSA was measured and concluded that the screening [*sic*] programme was able to identify patients at high risk. For the purposes of evaluating PSA as a screening tool, the absence of a parallel control group was a major handicap: the study simply involved testing levels of PSA in a large series of consecutive male patients.

Four randomised trials have investigated or are in the process of investigating the efficacy of prostate cancer screening, mainly using the PSA test. The Quebec study [2] was claimed to be the first randomised trial to show the efficacy of screening for prostate cancer. Fernand Labrie presented the data in the plenary session at the annual meeting of the American Society of Clinical Oncology (ASCO) in Los Angeles in 1998. He reported death rates of 48.7 per 100 000 in unscreened men and 15 per 100 000 in screened men, with a claimed odds ratio of 3.25 in favour of screening. Re-analysis of these data on an *intention-to-screen* basis found a 16% excess of deaths in the group invited to screening, suggesting that the comparison of compliers with non-compliers may have been affected by selection bias. The second randomised trial to be published came from Norrköping in Sweden [3] and reported a 47% higher rate of diagnosis in screened men than in controls. The intention-to-screen analysis on the data calculated the relative risk of death from prostate cancer to be 1.04: that is, a 4% increase in the risk of death from prostate cancer in the group offered screening. A recent Cochrane collaboration review concluded that both of these randomised trials had significant limitations in their methods, and a pooled analysis produced a relative risk of death of 1.01, with a non-significant confidence interval [4].

Results of two large randomised trials have been awaited for several years. The Prostate, Lung, Colorectal and Ovarian (PLCO) [5] cancer trial in the USA started in 1993. It recruited 37 000 men aged 55–74 years into a screening group and the same number into a parallel control group. The European randomised study of screening for prostate cancer [6] was started in 1991 and recruited 83 645 men aged 50–75 years into a screening group and 99 393 men into a control group. These trials have been ongoing for 14 and 17 years, respectively, without producing results on the efficacy of screening.

The PSA test itself is a simple blood test that involves minimal risk to study participants; the risk increases only when a patient is treated after receiving a diagnosis of prostate cancer. The availability of such a simple and cheap test has given rise to some very interesting and important consequences. The first is 'contamination' in randomised trials. The sample size for a clinical trial is calculated to give the number of events required to achieve an appropriate level of statistical power. Zelen and Parker [7] showed that the effective sample size is equal to $n(1-p)^2$, where p is the proportion of the control group who received the treatment and n is the original number of events required. In prostate screening trials, p would be the proportion of the control group who have their PSA measured outside the study. If the contamination rate is 10% then the effective sample size is 0.81 times the number of people in the study. The likely consequence of the high rate of PSA testing in the population is that contamination rates in clinical trials will be around 30–50%, and this is having a major impact on the effective sample size of studies. Since the sample size cannot be increased by entering new study subjects, more time will be required to have the (increased) number of events needed to obtain adequate statistical power. As recruitment has long since closed, considerable delays are being encountered in acquiring enough events (deaths from prostate cancer) to make comparisons between the screened and unscreened groups.

The side effects of radical therapy for all forms of prostate cancer have been well known for many years, so whether to recommend screening depends on whether any moderate reduction in mortality is offset by a decreased quality of life for the men treated [8]. In a random sample of patients in the USA, Potosky found a rate of serious adverse events (30-day postoperative mortality, incontinence, wearing pads at 6 months or a year, and an unchangeable loss of potency) of 28.6% in those treated radically [9]. Although a treatment needs to be in place for all men in the community, it could lead to a situation in which a huge loss in quality of life more than offsets a moderate reduction in mortality through screening.

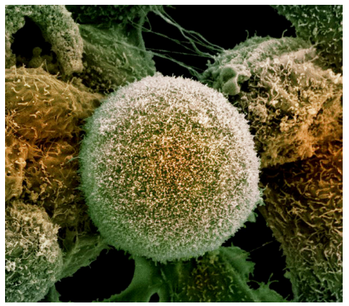


Fig. 4.10.1. *A cluster of prostate cancer cells. Scanning electron micrograph*

Even if the results of ongoing trials are null or inconclusive, however, it is clear that nothing can stop the inexorable rise in the use of PSA testing in the community. It would be helpful at this point, therefore, to introduce some method of evaluating the outcome of such an activity in a scientifically meaningful manner.

Nerve-sparing radical prostatectomy was introduced to the federal state of the Tyrol, Austria, in 1998. Unorganised cancer detection began in 1990, and PSA testing was made freely available to every man aged 45–75 years in 1993 [10]. By 2005, 86.6% of men who had passed through the age window had been screened at least once [11], and 14 000 had been screened 14 times. As this was a demonstration project in a community rather than a randomised trial, new ideas on how to treat and detect prostate cancer were incorporated into the algorithm and used throughout the state. Men in the rest of Austria were not offered PSA testing. Using the standardised mortality rate with the pre-screening era (1986–90) used as a baseline, the rate in 1991 was 113% of baseline, though this has gradually reduced to just 46% of baseline in 2005. In the rest of Austria, a gradual evolution in the uptake of PSA (as in most countries) has been accompanied by a 3% annual reduction in mortality since 1993 (similar to the reduction in the USA), while a 7.2% reduction was observed in the Tyrol [11].

Reassuringly, the screening did not result in a deferral of prostate cancers until after the age of 80 years, as there was a reduction of 64% in the number of cancer deaths expected in the Tyrol and 93% in the rest of Austria. When the age-standardised mortality was analysed with a different smoothing trend, a larger and more rapid reduction was seen in the Tyrol than in the rest of Austria. The entire state of the Tyrol has outstanding urological services for every patient, with free immediate access to many different types of treatment. Study of morbidity and mortality after radical prostatectomy in a series of 1663 patients in 1998–2004 showed no mortality at 30 days, no ureteral injury, and incidences of 0.6% for rectal injury (which has decreased to 0.1% since 2000), 0.7% for rectal bleeding that required intervention, 80.6% for continence at 3 months and 95.1% for continence at 12 months [11].

Since 2000 the potency status, defined as the ability of having intercourse 2 years after surgery with or without PDE5 inhibitors, of 512 men who were potent prior to the operation and younger than 65 years was assessed by an independent investigator; 78.9% preservation of erectile potency was observed. Continence was defined as no need for protective pads; 95.1 % urinary continence was recorded after 12 months in men under 65 years of age [11].

Randomised, controlled trials evaluating the effectiveness of PSA and digital rectal screening in reducing prostate cancer mortality are underway [5,6], but the results will not be available for several years. Furthermore, the randomised design of these trials may be compromised if non-adherence to the assigned intervention group is extensive, i.e. widespread contamination of the control group due to members seeking PSA testing. The consequences on the statistical power of these trials could be considerable.

Overall, these results from Tyrol confirm that, in the best of circumstances, a programme of PSA testing and rapid evaluation and specialised treatment can be effective. A paradox seen in many studies in the USA is that men diagnosed with prostate cancer live as long as, or longer than, men who have not been given such a diagnosis. Walsh and Thompson [12] sought an explanation for this paradox by studying a consecutive series of surgical patients treated at the Veterans Association Hospital in San Antonio. After surgery, 72% of men had a change of medical regimen, 61% had a change of drug treatment and 29% received a new medical diagnosis. Walsh and Thompson proposed that changes of such magnitude would be expected to affect survival outcomes of men recently diagnosed with prostate cancer. [12]

Since the introduction of PSA testing, the reported incidence of low-grade prostate cancer has declined [13]. A population-based cohort of 1858 prostate cancers diagnosed during 1990–92 was assembled at the Connecticut cancer registry. Histological slides were reread between 2002 and 2004 by an experienced prostate pathologist blinded to the original Gleason scores. Worryingly, the contemporary Gleason score readings were significantly higher than the original readings (the mean score increased from 5.95 to 6.8). The contemporary Gleason score-standardised mortality for prostate cancer (1.50 deaths per 100 person-years) seemed to be 28% lower than the standardised historical rate (2.08 deaths per 100 person-years), even though the overall outcome was unchanged. The authors concluded that the decline in reported incidence of low-grade prostate cancers seems to be the result of reclassification of Gleason scores over the past decade, which resulted in an apparent improvement in clinical outcome.

In a cohort of over half a million men aged ≥70 years assembled from 104 US Veterans Hospitals during 2002 and 2003, 56% of elderly men had a PSA test in 2003: 64% of men aged 70–74 years and 36% of men aged ≥85 years [14]. The US Preventive Services Task Force [15] claimed that men with a life expectancy of less than 10 years are unlikely to benefit from screening even under favourable assumptions, concluding that: "although potential harms of screening for prostate cancer can be established, the presence or magnitude of potential benefits cannot. Therefore, the net benefit of screening cannot be determined." They recommend that if physicians opt to perform screening for individual patients, they should first discuss uncertain benefits and possible harms.

The real impact and tragedy of widespread prostate cancer testing is the doubling of the lifetime risk of a diagnosis of prostate cancer without any effect on the risk of dying from this disease. In 1985, an American man had an 8.7% lifetime risk of being diagnosed with prostate cancer and a 2.5% risk of dying from prostate cancer [16]. Twenty years later, in 2005, an American man had a 17% lifetime risk of being diagnosed with prostate cancer and a 3% risk of dying from prostate cancer [17]. Despite this, the increase in PSA testing will be impossible to stop.

Trial results for and against testing have always been contentious among supporters and opponents of screening. In the case of breast cancer, even with data available from nine randomized trials with reasonable methods, claims have been made that there is no evidence to support mammographic screening. With fewer trials available for evaluating prostate cancer screening and with contamination rates in the control group likely to be very high, questions will undoubtedly be posed about the reliability of the findings.

REFERENCES

1. Catalona WJ, Smith DS, Ratliff TL, et al. (1991). Measurement of prostate specific antigen in serum as a screening test for prostate cancer. *N Engl J Med* 324: 1156-1161.

2. Labrie F, Dupont A, Candas B, et al. (1998). Decrease of prostate cancer death by screening: first data from the Quebec prospective and randomized study. *1998 ASCO Annual Meeting* 17: Abstract no. 4

3. Sandblom G, Varenhorst E, Lofman O, et al. (2004). Clinical consequences of screening for prostate cancer: 15 years follow-up of a randomised controlled trial in Sweden. *Eur Urol* 46: 717-723.

4. Ilic D, O'Connor D, Green S, et al. (2006). Screening for prostate cancer. *Cochrane Database Syst Rev* 3: CD004720.

5. Gohagan JK, Prorok PC, Kramer BS, et al. (1995). The prostate, lung, colorectal, and ovarian cancer screening trial of the National Cancer Institute. *Cancer* 75: 1869-1873.

6. de Koning HJ, Auvinen A, Berenguer SA, et al. (2002). Large-scale randomized prostate cancer screening trials: program performances in the European Randomized Screening for Prostate Cancer trial and the Prostate, Lung, Colorectal and Ovary cancer trial. *Int J Cancer* 97: 237-244.

7. Zelen M and Parker RA (1986). Case-control studies and Bayesian inference. *Stat Med* 5: 261-269.

8. Boyle P (2003). Screening for prostate cancer: have you had your cholesterol measured? *BJU Int* 92: 191-199.

9. Potosky AL, Legler J, Albertsen PC, et al. (2000). Health outcomes after prostatectomy or radiotherapy for prostate cancer: results from the Prostate Cancer Outcomes Study. *J Natl Cancer Inst* 92: 1582-1592.

10. Bartsch G, Horninger W, Klocker H, et al. (2001). Prostate cancer mortality after introduction of prostate specific antigen mass screening in the Federal State of Tyrol, Austria. *Urology* 58: 417-424.

11. Bartsch G, Horninger W, Klocker H, et al. (2008). Tyrol Prostate Cancer Demonstration Project: early detection, treatment, outcome, incidence and mortality. *BJU Int* 101: 809-816.

12. Walsh RM and Thompson IM (2007). Prostate cancer screening and disease management: how screening may have an unintended effect on survival and mortality-the camel's nose effect. *J Urol* 177: 1303-1306.

13. Albertsen PC, Hanley JA, Barrows GH, et al. (2005). Prostate cancer and the Will Rogers phenomenon. *J Natl Cancer Inst* 97: 1248-1253.

14. Walter LC, Bertenthal D, Lindquist K, et al. (2006). PSA screening among elderly men with limited life expectancies. *JAMA* 296: 2336-2342.

15. Harris R and Lohr KN (2002). Screening for prostate cancer: an update of the evidence for the U.S. Preventive Services Task Force. *Ann Intern Med* 137: 917-929.

16. Seidman H, Mushinski MH, Gelb SK, et al. (1985). Probabilities of eventually developing or dying of cancer–United States, 1985. *CA Cancer J Clin* 35: 36-56.

17. Jemal A, Siegel R, Ward E, et al. (2007). Cancer statistics, 2007. *CA Cancer J Clin* 57: 43-66.

4.11 Screening for Ovarian Cancer

Summary

> There is at present no established method for early detection of ovarian cancer

> Methods proposed to date yield many false-positive results requiring unnecessary laparatomy or are not sensitive enough for detection of ovarian cancer when in a early stage of development

> Randomised trials of potential screening methods are underway

Ovarian cancer is the fourth most common cancer in females, with annual incidence rates ranging between 8.5 and 21.5 per 100 000 in female populations of European countries. The International Agency for Research on Cancer estimated that in 2002 there were 204 499 ovarian cancer cases and 124 860 ovarian cancer deaths worldwide [1]. Ovarian cancer is a heterogeneous group of malignancies that can remain asymptomatic despite being at an advanced stage, or cause non-specific symptoms. In about 70% of patients, ovarian cancer is diagnosed at an advanced stage, leading to a poor prognosis: in Europe, the average 5-year survival of ovarian cancer patients is around 40% [2].

The ability to non-invasively distinguish between non-cancerous and cancerous ovarian process and to detect ovarian cancers at an earlier stage would be major benefit in the management of women with symptomatic pelvic conditions. Many methods, used alone or in combination, for distinguishing between non-cancerous and cancerous ovarian process have been investigated, including transvaginal sonography (TVS), Doppler ultrasonography, measurement of serum CA 125, computed tomography scan (CT), magnetic resonance imaging (MRI), fluorodeoxyglucose (FDG) and positron emission tomography (PET) scan (the FDG-PET scan) and radioimmunoscintigraphy [3-7]. However, for a number of reasons, from lack of sensitivity or specificity to cost issues, TVS remains the major detection tool. The use of the Risk of Malignancy Index (RMI), which incorporates menopausal status, CA 125 and TVS, has also been proposed. The RMI version developed by IJ Jacob and co-workers has a pooled sensitivity of 78% (95% CI 72–84%) and pooled specificity of 90% (95% CI 81–95%), with an inverse correlation between sensitivity and specificity [8,9]. Other computerised expert systems and a variety of scoring systems based on the combination of ultrasound image characteristics, serum CA 125 level and various other clinical and patient-related parameters have also been tried, but have proven to be less effective than RMI (7) or TVS performed by expert ultrasonographers [10].

Various serum biomarkers have been proposed, like the CA 125, or some blood protein profiles that would represent biological signatures of ovarian cancer, but none of these biomarkers has shown superiority to echography, and furthermore their large-scale application leads to many false positive results and unnecessary laparatomy procedures [11].

On-going trials in the USA [12] and in the UK [8] aim at assessing the value of ultrasound and biomarker-based tests. Their results will not be available for several years. In the meantime, currently available methods prove quite unable to detect ovarian cancer early [13], and new technologies are eagerly awaited.

REFERENCES

1. Ferlay J, Bray F, Pisani P, et al. (2004). GLOBOCAN 2002: Cancer incidence, mortality and prevalence worldwide. *IARC CancerBase* No. 5 Version 2.0. Lyon, France: International Agency for Research on Cancer.

2. Engel J, Eckel R, Schubert-Fritschle G, et al. (2002). Moderate progress for ovarian cancer in the last 20 years: prolongation of survival, but no improvement in the cure rate. *Eur J Cancer* 38: 2435-2445.

3. The role of the generalist obstetrician-gynecologist in the early detection of ovarian cancer (2003). *Int J Gynaecol Obstet* 80: 235-238.

4. Grab D, Flock F, Stohr I, et al. (2000). Classification of asymptomatic adnexal masses by ultrasound, magnetic resonance imaging, and positron emission tomography. *Gynecol Oncol* 77: 454-459.

5. Huber S, Medl M, Baumann L, et al. (2002). Value of ultrasound and magnetic resonance imaging in the preoperative evaluation of suspected ovarian masses. *Anticancer Res* 22: 2501-2507.

6. Kurtz AB, Tsimikas JV, Tempany CM, et al. (1999). Diagnosis and staging of ovarian cancer: comparative values of Doppler and conventional US, CT, and MR imaging correlated with surgery and histopathologic analysis-report of the Radiology Diagnostic Oncology Group. *Radiology* 212: 19-27.

7. Myers ER, Bastian LA, Havrilesky LJ, et al. (2006). Management of adnexal mass. *Evid Rep Technol Assess (Full Rep)* 1-145.

8. Jacobs I, Oram D, Fairbanks J, et al. (1990). A risk of malignancy index incorporating CA 125, ultrasound and menopausal status for the accurate preoperative diagnosis of ovarian cancer. *Br J Obstet Gynaecol* 97: 922-929.

9. van Trappen PO, Rufford BD, Mills TD, et al. (2007). Differential diagnosis of adnexal masses: risk of malignancy index, ultrasonography, magnetic resonance imaging, and radioimmunoscintigraphy. *Int J Gynecol Cancer* 17: 61-67.

10. Timmerman D (2004). The use of mathematical models to evaluate pelvic masses; can they beat an expert operator? *Best Pract Res Clin Obstet Gynaecol* 18: 91-104.

11. Nossov V, Amneus M, Su F, et al. (2008). The early detection of ovarian cancer: from traditional methods to proteomics. Can we really do better than serum CA-125? *Am J Obstet Gynecol* 199: 215-223.

12. Gohagan JK, Prorok PC, Hayes RB, et al. (2000). The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial of the National Cancer Institute: history, organization, and status. *Control Clin Trials* 21: 251S-272S.

13. Bast RC, Brewer M, Zou C, et al. (2007). Prevention and early detection of ovarian cancer: mission impossible? *Recent Results Cancer Res* 174: 91-100.

4.12 Screening for Lung Cancer

Summary

- Lung cancer is a good candidate for screening, but early attempts based on X-rays and cytology did not prove to be effective
- The search for serological biomarkers for early detection of lung cancer is an active area of research
- Pulmonary spiral CT-scan results in the identification of early lesions with good prognosis, but the possibility of lead-time bias and over-diagnosis cannot yet be ruled out
- Currently, no methods can be recommended for population-based screening of lung cancer

Lung cancer has one of the poorest survival rates of all cancers, mainly due to the lack, in the majority of patients, of symptoms and signs during the early phases of neoplastic growth. This fact, together with the high risk in specific groups of the population, namely smokers (the cumulative risk at age 75 reaches 15% or more in continuous smokers [1]), workers exposed to occupational carcinogens, and women exposed to high level of indoor air pollution, make lung cancer a good candidate for targeted pre-clinical detection.

Early efforts to identify an effective approach to screen pre-clinical cases of lung cancer concentrated on X-ray examinations, search of abnormal cells in expectorate, and the combination of the two (see [2] for a review). Unfortunately, although screen-detected cases had a longer survival than clinically detected cases, the difference was accounted for by lead-time bias, that is, the fact that an earlier detection of a cancer would generate a longer survival even if the natural history of the disease is not altered (i.e. mortality is not affected), and by over-diagnosis, that is, the fact that the screening detected slow-growing lesions that by their nature have a long survival [2].

In the past decade, two new approaches have been proposed for screening lung cancer in high-risk populations. First, efforts are being made to identify disease biomarkers, typically in serum, using novel molecular techniques, notably proteomics (i.e. the systematic analysis of proteins and protein fragments). Although promising, this approach has not yet led to the identification of a valid biomarker [3].

The second approach relies on CT-assisted, low-energy X-rays, notably the so-called spiral CT-scan, which generates a high-resolution, tridimensional image of the lungs. Non-randomised studies of spiral CT scan in high-risk populations have resulted in the identification of a relatively large number of nodules in the lungs, which can be removed surgically, and in the majority of cases are shown to be early forms of lung cancer [4]. The survival of the patients whose early cancers are removed is excellent, but two issues remain to be elucidated before one can conclude that spiral CT scan should be implemented in population-based screening [5]. First, the occurrence of spiral CT scan-detected nodules is higher than that of clinically diagnosed cancers in a comparable population, suggesting that a proportion of the nodules are 'false positives', i.e. represent slow-growing neoplastic lesions that would not have become clinically relevant (so-called over-diagnosis). Second, a reduction in mortality in a screening population has not yet been demonstrated (i.e. the possibility of lead-time bias has not been excluded). These two possible biases are illustrated in Figure 4.12.1.

Randomised trials ongoing in the United States and Europe should provide the final evidence on the effectiveness of spiral CT scan as screening method for lung cancer. In the meantime, national and international authorities generally recommend against the implementation of population-based screening programs for lung cancer [6].

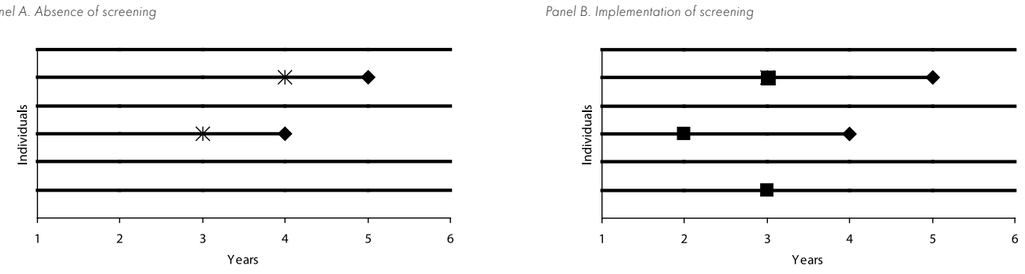


Fig. 4.12.1 *Illustration of lead-time bias and over-diagnosis in a hypothetical screening program of six individuals*
Asterisk: clinical diagnosis; squares: screening-based diagnosis; diamonds: death
In panel A, two cancers with 1-year survival are diagnosed
In panel B, the diagnosis of the two cases is anticipated by one year and one additional case is diagnosed. Mortality, however, is not affected. The screening program apparently increases survival of cases (lead-time bias) and leads to the identification of clinically irrelevant cases (over-diagnosis)

REFERENCES

1. Peto R, Darby S, Deo H, et al. (2000). Smoking, smoking cessation, and lung cancer in the UK since 1950: combination of national statistics with two case-control studies. *BMJ* 321: 323-329.

2. Parkin DM and Moss SM (2000). Lung cancer screening: improved survival but no reduction in deaths–the role of "over-diagnosis". *Cancer* 89: 2369-2376.

3. Massion PP and Caprioli RM (2006). Proteomic strategies for the characterization and the early detection of lung cancer. *J Thorac Oncol* 1: 1027-1039.

4. Henschke CI, Yankelevitz DF, Libby DM, et al. (2006). Survival of patients with stage I lung cancer detected on CT screening. *N Engl J Med* 355: 1763-1771.

5. Black WC (2007). Computed tomography screening for lung cancer: review of screening principles and update on current status. *Cancer* 110: 2370-2384.

6. Bach PB, Silvestri GA, Hanger M, et al. (2007). Screening for lung cancer: ACCP evidence-based clinical practice guidelines (2nd edition). *Chest* 132: 69S-77S.

4.13 Screening for Cutaneous Melanoma

Summary

> There is at present no established method for detection of cutaneous melanoma

> Methods proposed to date are poorly cost-effective and result in identification and expensive treatment of melanoma that would likely never have become life-threatening

The goal of screening is to prevent deaths from cutaneous melanoma through detection of the cancer at an early, curable stage. The commonest methods for early detection of melanoma are whole-body skin examinations (WBSE) and skin self-examination (SSE)[1].

Cutaneous melanoma has two characteristics of a good candidate for screening: the absence of treatment for advanced disease while detection at an early stage may guarantee cure with surgery; the screening method is an (apparently) simple skin examination.

In spite of the apparent simplicity of screening for cutaneous melanoma, no randomised trial has ever shown that such screening could save lives or indicated how many. Other factors fuel controversies regarding population screening of this cancer.

1. Cutaneous melanoma remains a rare disease in many light-skinned populations, and screening for rare cancer is known to be poorly cost-effective;

2. The nodular type (about 10–15% of all cutaneous melanoma) is a fast-growing, aggressive type of cancer, and screening will most probably not be able to detect it at a curable stage;

3. In practice, WBSE is a luxury for most health care systems, as WBSE takes time and health professional have little extra time available for such screening;

4. Many individuals will have nevi or in situ melanoma removed instead of invasive melanoma, and this will contribute to further increasing costs of screening, lead to disfiguring scars and finally negatively impact quality of life;

5. Many screen-detected cutaneous melanoma will consist of indolent cancer that would most probably never have become life-threatening;

6. Mortality from cutaneous melanoma concentrates in the elderly, mainly in men over 60 years of age, because of delay to consult a doctor when a pigmented lesion develops, or because the melanoma develops on a hidden skin area such as the back and the shoulders. Also, it is known that elderly men would have low compliance to skin screening [2].

7. Evaluation of pilot programmes have shown that individuals attending screening often constitute a selected fraction of the population that are more concerned about their health, and also are healthier than non-attendees [3,4].

8. Following logically from the previous point, costs of screening may be considerable in comparison to eventual health benefits. It may appear more appropriate to test the efficacy of screening for melanoma in a subset of high-risk subjects, for instance individuals with a strong family history of cutaneous melanoma or siblings of melanoma patients [5], or of patients with numerous nevi or atypical nevi, or sun-sensitive individuals living in sunny climates. It remains to be shown (ideally via randomised trials) whether a targeted screening strategy may be efficient. In Queensland, Australia, where the incidence of cutaneous melanoma is the highest in the world, a randomised trial of WBSE is ongoing [6,7]. This trial devotes much effort toward having men 50 years old and older participating in the screening programme [8].

A form of screening requiring fewer resources than WBSE is the promotion of regular skin self-examination (SSE) for self-detection of changes in nevi appearance [9]. Promotion of SSE requires ensuring rapid accessibility to medical services for checking (and eventually removing) self-detected suspected lesions. Simply disseminating a message about SSE and the importance of early detection without providing opportunities to have lesions examined and excised will seriously hamper preventive efforts and lead to reduced reliability in health messages given to the population. One case–control study found that SSE could reduce de development of advanced cutaneous melanoma [10], but results on screening efficacy from this kind of study design require verification by more robust designs such as a randomised trial.

REFERENCES

1. Koh HK, Geller AC, Miller DR, et al. (1995). The early detection of and screening for melanoma. International status. *Cancer 75*: 674-683.

2. Geller AC, Sober AJ, Zhang Z, et al. (2002). Strategies for improving melanoma education and screening for men age >or= 50 years: findings from the American Academy of Dermatological National Skin Cancer Sreening Program. *Cancer* 95: 1554-1561.

3. Koh HK, Lew RA, Prout MN (1989). Screening for melanoma/skin cancer: theoretic and practical considerations. *J Am Acad Dermatol* 20: 159-172.

4. McGee R, Elwood M, Williams S, et al. (1994). Who comes to skin checks? *N Z Med J* 107: 58-60.

5. Geller AC, Emmons KM, Brooks DR, et al. (2006). A randomized trial to improve early detection and prevention practices among siblings of melanoma patients. *Cancer* 107: 806-814.

6. Aitken JF, Youl PH, Janda M, et al. (2006). Increase in skin cancer screening during a community-based randomized intervention trial. *Int J Cancer* 118: 1010-1016.

7. Lowe JB, Ball J, Lynch BM, et al. (2004). Acceptability and feasibility of a community-based screening programme for melanoma in Australia. *Health Promot Int* 19: 437-444.

8. Janda M, Youl PH, Lowe JB, et al. (2006). What motivates men age > or =50 years to participate in a screening program for melanoma? *Cancer* 107: 815-823.

9. Weinstock MA, Risica PM, Martin RA, et al. (2007). Melanoma early detection with thorough skin self-examination: the "Check It Out" randomized trial. *Am J Prev Med* 32: 517-524.

10. Berwick M, Begg CB, Fine JA, et al. (1996). Screening for cutaneous melanoma by skin self-examination. *J Natl Cancer Inst* 88: 17-23.

4.14 Genetic Testing

Summary

> Genetic testing of high-risk cancer susceptibility genes is becoming an important part of clinical cancer genetics in some high-income countries, but is not often available in middle- or low-income countries

> The main beneficiaries of the genetic information gleaned from this type of genetic testing are the unaffected relatives of the individuals who are tested

> The most commonly tested high-risk susceptibility genes are BRCA1 and BRCA2 (primarily for breast and ovarian cancer) and MLH1 and MSH2 (primarily for colon and endometrial cancer). However, there are many other genes for which testing is available under specific circumstances

> Medical and surgical interventions have been developed for the carriers of high-risk mutations in the more-often tested genes. Although the interventions involve quality of life tradeoffs, they do, on average, add years to the lives of these at-risk patients

In North America, Europe, Japan and Australia, genetic testing of high-risk cancer susceptibility genes is becoming an increasingly important component of the clinical management of at-risk patients and their close relatives. In 1996, the American Society of Clinical Oncology [1] developed recommendations covering when genetic testing should be offered to patients; these recommendations were updated in 2003. The fundamental ASCO recommendations are "that genetic testing be offered when 1) the individual has personal or family history features suggestive of a genetic cancer susceptibility condition, 2) the test can be adequately interpreted, and 3) the results will aid in diagnosis or influence the medical or surgical management of the patient or family members at hereditary risk of cancer." In addition, ASCO recommends that testing only be performed in a setting where patients can receive counselling both before the decision to request testing is taken and after test results become available [1].

The vast majority of genetic testing of cancer susceptibility genes is directed towards the established high-risk breast cancer and colon cancer susceptibility genes. De novo testing of an at-risk patient usually involves a mutation screen of the whole open reading frame of the underlying susceptibility gene(s), often augmented with a screen for duplications or deletions of individual exons [2]; consequently, the tests are technologically demanding and relatively expensive. In order to maximise testing efficiency, the first individual from an at-risk family to be tested will usually be a cancer case considered to have a high prior probability of carrying a mutation based on age at diagnosis, family history, and perhaps tumour immunohistochemical profile. If the index case is found to be a mutation carrier, the genotype information may well influence their subsequent medical and surgical management. Two further consequences flow from the identification of a specific mutation in an index case. First, it must be understood and emphasised that the main beneficiaries of the genetic information will be the unaffected relatives of the index case. This is because for unaffected mutation carriers there are medical and surgical interventions that can either reduce the risk of disease or aid in early detection thus improving survival. Second, with very few exceptions, the at-risk relatives of the index case need only be tested with a specific test targeting the exact mutation that was identified in the index case. Mutation-specific tests are much less expensive, and have higher sensitivity and specificity, than do de novo whole gene tests.

Breast cancer

The principal high-risk breast cancer susceptibility genes are BRCA1 and BRCA2; predisposition due to inherited mutations in either of these genes is often referred to as Hereditary Breast-Ovarian Cancer Syndrome (HBOC). The genes were first characterised in 1994 and 1995, respectively [3-5]. Although the absolute risks conferred by inheritance of high-risk mutations in these genes have been somewhat controversial, a combined analysis of 22 studies estimated that BRCA1 mutation carriers have a cumulative risk of 65% and a cumulative ovarian cancer risk of 39% by age 70. For BRCA2 carriers, the cumulative breast cancer and ovarian cancer risks by age 70 were 45% and 11%, respectively [6]. Because these risks are very high, women who carry mutations in these genes will often opt for surgical intervention as a form of primary prevention. At this time, the preferred approach is probably prophylactic bilateral salpingo-oophorectomy. Removing the ovaries and fallopian tubes directly and dramatically reduces the risk of ovarian cancer, and can also reduce the risk of breast cancer by approximately 50% [7,8]. At the same time, tantalising new evidence suggests that tumours arising in BRCA1 and BRCA2 carriers have an Achilles heel that can be exploited to improve their treatment. Specifically, these tumours appear to be differentially sensitive to chemotherapeutic agents that induce DNA-crosslinks, and even more sensitive to poly-ADP ribose polymerase (PARP) inhibitors [9-11]. If these laboratory pharmaco-genetic observations can be converted to effective treatments, then data from the BRCA1 and BRCA2 genetic tests will provide important benefits to both unaffected and affected mutation carriers.

Colon cancer

The two best-understood colon cancer susceptibility syndromes are familial adenomatous polyposis (FAP) and hereditary non-polyposis colon cancer (HNPCC or Lynch syndrome). The majority of cases of FAP are due to germline mutations in the colon cancer susceptibility gene APC, identified as such by Groden et al. and Nishisho et al. in 1991 [12,13]. Patients who carry fully penetrant mutations in FAP will typically present with hundreds or even thousands of colon polyps by their mid-20s, and the incidence of colon cancer in these individuals is essentially 100%. Accordingly, the preferred treatment for these patients is prophylactic colectomy, which can add decades to the lives of patients who are detected and treated early as compared to patients who are not diagnosed with FAP until they present with colon cancer [14-16]. For this syndrome, the genetic concept that the first-degree relatives of FAP patients and APC mutation carriers need to be assessed very early is the key to adding years to their lives.

HNPCC is due to germline mutations in the DNA mismatch repair genes MLH1, MSH2, MSH6 and PMS2, with about 90% of explained cases attributed to mutations in one of the first two of these four genes. The proteins encoded by these genes help repair small single-strand DNA lesions that occur constantly due to endogenous and exogenous mutagenesis. Tumours arising due to loss of function in these genes exhibit increased frequencies of point mutations and instability in the length of microsatellite repeats, termed microsatellite instability. Cumulative risk of colon cancer due to germline mutations in these genes has not been studied as thoroughly as has been the case for BRCA1 and BRCA2. However, a recent population based case-family study concluded that the cumulative risk of colon cancer for carriers of mutations in one of these four genes is slightly greater than 40%, with greater risk to males than females (45% vs. 38%, respectively) [17]. In contrast to FAP patients, the preferred medical management of HNPCC patients focuses on colonoscopy beginning in their early to mid 20s, at intervals of 1 to 2 years [15,18]. This approach should reduce the incidence of invasive colorectal cancer in HNPCC carriers by more than 50% compared to carriers who do not receive routine screening [19-21]. Identification of unaffected HNPCC carriers by age ~25 requires that an older index case from the patient's family underwent testing and was found to be a mutation carrier, hence the role of genetic testing. But to whom should testing be offered? For some time, the decision of who to test for mutations in these genes has been guided by a combination of the family history-based Amsterdam criteria and assessment of tumour microsatellite instability under the Bethesda Guidelines [22,23]. However, new models that make a more detailed analysis of family history, perhaps supplemented with detailed assessment of tumour pathology features, may supplant these criteria [24-26]. In addition, antibodies against MLH1, MSH2, MSH6, and PMS2 that work well in immunohistochemical staining procedures are now available and may be used to prioritise patients for gene mutation screening [27].

While genetic testing for cancer susceptibility is dominated by testing for germline mutations in the HBOC and HNPCC susceptibility genes, there are many less common cancer susceptibility syndromes for which at least some of the underlying susceptibility genes are known. Many of these are summarised in Table 4.14.1. Genetic testing can be conducted for mutations in any of these genes, though in many cases the testing is done on a research basis rather than an established clinical or commercial basis.

Returning to the ASCO recommendations for when genetic testing should be offered, there are important caveats to each of the three criteria. First, with respect to personal and family history, identification of at-risk patients has, to date, depended heavily on family history criteria. However, at least for BRCA1 and BRCA2, the majority of breast cancer cases who carry mutations do not have sufficient family history to suggest that they are likely to be mutation carriers [28]. Thus, strict adherence to family history criteria for testing will deny the benefits of this genotype information to a large fraction of mutation carriers. However, it is now becoming evident that tumours in many BRCA and mismatch repair mutation carriers can be recognised by immunohistochemical, expression profiling, or array CGH criteria [27,29,30]. Thus, in the sense that a patient's personal history includes the molecular characteristics of their tumour, personal history is set to become an increasingly important component of the decision of whom to recommend for genetic testing.

Second, with respect to interpretation of test results, roughly 90% of the high-risk mutations present in the BRCA and mismatch repair genes can be recognised directly from the mutation screening data. However, a significant fraction of sequence variants observed during clinical mutation screening, mostly missense substitutions, are initially unclassified. Further analysis of the individual unclassified variants to determine which are clinically important is a multi-disciplinary problem that is attracting considerable research interest [31-33].

Third, at the time that a susceptibility gene is first identified, the requirement of aiding in diagnosis or influencing treatment presents a circular problem: one cannot know for sure that the test results will meet this requirement until a cohort of mutation carriers have been identified; however, one cannot identify a cohort of mutation carriers without doing some testing! To date, the natural process has been that most genetic testing carried out on a newly identified susceptibility gene takes place in a research setting, and growth of the scale of testing (or not) has depended on the perceived utility of the initial results. With high-risk susceptibility genes, genotype-phenotype relationships have almost by definition been fairly clear. However, as cancer genetics research moves towards either intermediate-risk susceptibility genes or complex genotypes based on panels of modest-risk SNPs, genotype-phenotype relationships will become less clear and questions of clinical utility more challenging to answer.

A decade ago, the scale of genetic testing for mutations in cancer susceptibility genes was very modest, and most testing was either carried out in academic labs or in hospital based testing services that had grown out of academic labs. Driven by positive feedback loops between evidence that the clinical decisions based on results from genetic cancer susceptibility tests can add years to patient's lives, public health service interest, and commercial testing interest, the scale of genetic testing has grown dramatically. Still, this growth is limited almost entirely to the practice of medical genetics in high-income

SYNDROMES	GENES	GENE SYMBOLS	CHROMOSOMAL LOCATION
Dominant inheritance			
Familial retinoblastoma	Retinoblastoma, osteosarcoma	RB1	13q14
Familial adenomatous polyposis (FAP)	Colorectal cancer	APC	5q21
Hereditary nonpolyposis colorectal cancer (HNPCC)	Colorectal, endometrial, ovarian, and gastric cancer	MLH1	3p
		MSH2	2p
		MSH6	2p
		PMS1	2q
Hereditary breast and ovarian cancer (HBOC)	Breast, ovarian, prostate, and colon cancer	BRCA1	17q
		BRCA2	13q
Li-Fraumeni syndrome (LFS)	Sarcomas, breast cancer, brain tumors, leukemia	TP53	17p13
Li-Fraumeni syndrome 2 (LFS2) (the syndrome assignment controversial, however, increased cancer risk is clear)	Breast cancer+ weak LFS-like spectrum	CHEK2	22q12
Cowden syndrome and Bannayan-Ruvalcaba-Riley syndrome	Breast, thyroid	PTEN	10q22
Neurofibromatosis, type 1	Neural tumors, leukemia, soft tissue sarcoma, bone tumors	NF1	17q11
Neurofibromatosis, type 2	Acoustic neuromas, meningiomas	NF2	22q2
Multiple endocrine neoplasia (MEN) type 1	Pancreatic islet cell cancer, parathyroid, hyperplasia, pituitary adenomas	MEN1	11q13
Multiple endocrine neoplasia (MEN) type 2a and 2b	Medullary thyroid cancer; pheochromocytoma	RET	10q11
Von Hippel-Lindau syndrome (VHL)	Renal cancer, vascular tumors	VHL	3p25
Familial melanoma	Melanoma, other tumors	INK4A	9p
		CDK4	6q
Gorlin syndrome	Basal cell carcinoma	PTCH	9q31
Hereditary leiomyomatosis and renal cell cancer (HLRCC)	Leiomyomatosis, renal cell tumors	FH	1q42.3-q43
Peutz-Jeghers syndrome	gastrointestinal hamartomatous polyps, gastric, colon, breast, ovarian cancer	STK11	19p

Table 4.14.1 *Cancer susceptibility syndromes and underlying high-risk susceptibility genes*

SYNDROMES	GENES	GENE SYMBOLS	CHROMOSOMAL LOCATION
Recessive Inheritance			
Ataxia telangiectasia	Lymphoma, leukemia, breast cancer	ATM	11q22
MYH associated polyposis	Colon	MYH	1p32-34
Nijmegen breakage syndrome	Lymphoma, leukemia, breast cancer, prostate cancer	NBS1	8q21
Bloom's syndrome	Solid tumours	BLM	15q26
Familial Wilms tumour	Kidney	WT1	11q
Xeroderma pigmentosum	Basal cell carcinoma, squamous-cell carcinoma, melanoma (skin)	XPA	9p34
		XPB	2q21
		XPC	3p25
		XPD	19q13
		DDB2 (XPE)	11p11-12
		ERCC1 (XPF)	16p13
		XPG	13q32-33
		XPV (Pol n)	6p21
Fanconi Anemia		FANCA	16q24
		FANCB	Xp22
		FANCC	9q22
		FANCD2	3p25
		FANCE	6p21
		FANCF	11p15
		FANCG	9p13
		BRIP1 (FANCJ)	17q22-24
		FANCL	2p16
		FANCF	14q21
X-linked lymphoproliferative disorder	Lymphoma	XLP	Xq25

Table 4.14.1 *(cont.)*

countries. For the most part, middle- and low-income countries lack some combination of the laboratory infrastructure required to carry out clinical-quality genetic testing, the medical infrastructure of physicians and/or genetic counsellors who are trained in medical genetics and able to communicate concepts of genetic risk to patients, and the medical insurance infrastructure required to pay for these activities. Consequently, it may be many years before our current knowledge of the genetics of cancer susceptibility begins to provide noticeable benefit to genetically high-risk patients and their close relatives in middle- or low-resource countries.

REFERENCES

1. ASCO (2003). American Society of Clinical Oncology policy statement update: genetic testing for cancer susceptibility. *J Clin Oncol* 21: 2397-2406.

2. Tavtigian SV, Le Calvez-Kelm F (2008). Molecular Diagnostics: Methods and Limitations. In: Isaacs C, Rebbeck TR, eds., *Hereditary breast cancer.* New York: Informa Healthcare.

3. Miki Y, Swensen J, Shattuck-Eidens D, et al. (1994). A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1. *Science* 266: 66-71.

4. Tavtigian SV, Simard J, Rommens J, et al. (1996). The complete BRCA2 gene and mutations in chromosome 13q-linked kindreds. *Nat Genet* 12: 333-337.

5. Wooster R, Bignell G, Lancaster J, et al. (1995). Identification of the breast cancer susceptibility gene BRCA2. *Nature* 378: 789-792.

6. Antoniou A, Pharoah PD, Narod S, et al. (2003). Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case Series unselected for family history: a combined analysis of 22 studies. *Am J Hum Genet* 72: 1117-1130.

7. Kauff ND and Barakat RR (2007). Risk-reducing salpingo-oophorectomy in patients with germline mutations in BRCA1 or BRCA2. *J Clin Oncol* 25: 2921-2927.

8. Nusbaum R and Isaacs C (2007). Management updates for women with a BRCA1 or BRCA2 mutation. *Mol Diagn Ther* 11: 133-144.

9. Bryant HE, Schultz N, Thomas HD, et al. (2005). Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase. *Nature* 434: 913-917.

10. Bryant HE, Ying S, Helleday T (2006). Homologous recombination is involved in repair of chromium-induced DNA damage in mammalian cells. *Mutat Res* 599: 116-123.

11. Farmer H, McCabe N, Lord CJ, et al. (2005). Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. *Nature* 434: 917-921.

12. Groden J, Thliveris A, Samowitz W, et al. (1991). Identification and characterization of the familial adenomatous polyposis coli gene. *Cell* 66: 589-600.

13. Nishisho I, Nakamura Y, Miyoshi Y, et al. (1991). Mutations of chromosome 5q21 genes in FAP and colorectal cancer patients. *Science* 253: 665-669.

14. Heiskanen I, Luostarinen T, Jarvinen HJ (2000). Impact of screening examinations on survival in familial adenomatous polyposis. *Scand J Gastroenterol* 35: 1284-1287.

15. Lynch HT, Lynch JF, Lynch PM, et al. (2008). Hereditary colorectal cancer syndromes: molecular genetics, genetic counseling, diagnosis and management. *Fam Cancer* 7: 27-39.

16. Nugent KP, Spigelman AD, Phillips RK (1993). Life expectancy after colectomy and ileorectal anastomosis for familial adenomatous polyposis. *Dis Colon Rectum* 36: 1059-1062.

17. Jenkins MA, Hayashi S, O'Shea AM, et al. (2007). Pathology features in Bethesda guidelines predict colorectal cancer microsatellite instability: a population-based study. *Gastroenterology* 133: 48-56.

18. Lindor NM, Petersen GM, Hadley DW, et al. (2006). Recommendations for the care of individuals with an inherited predisposition to Lynch syndrome: a systematic review. *JAMA* 296: 1507-1517.

19. de Vos tot Nederveen Cappel WH, Nagengast FM, Griffioen G, et al. (2002). Surveillance for hereditary nonpolyposis colorectal cancer: a long-term study on 114 families. *Dis Colon Rectum* 45: 1588-1594.

20. Jarvinen HJ, Mecklin JP, Sistonen P (1995). Screening reduces colorectal cancer rate in families with hereditary nonpolyposis colorectal cancer. *Gastroenterology* 108: 1405-1411.

21. Jarvinen HJ, Aarnio M, Mustonen H, et al. (2000). Controlled 15-year trial on screening for colorectal cancer in families with hereditary nonpolyposis colorectal cancer. *Gastroenterology* 118: 829-834.

22. Boland CR, Thibodeau SN, Hamilton SR, et al. (1998). A National Cancer Institute Workshop on Microsatellite Instability for cancer detection and familial predisposition: development of international criteria for the determination of microsatellite instability in colorectal cancer. *Cancer Res* 58: 5248-5257.

23. Vasen HF, Watson P, Mecklin JP, et al. (1999). New clinical criteria for hereditary nonpolyposis colorectal cancer (HNPCC, Lynch syndrome) proposed by the International Collaborative group on HNPCC. *Gastroenterology* 116: 1453-1456.

24. Balmana J, Stockwell DH, Steyerberg EW, et al. (2006). Prediction of MLH1 and MSH2 mutations in Lynch syndrome. *JAMA* 296: 1469-1478.

25. Chen S, Wang W, Lee S, et al. (2006). Prediction of germline mutations and cancer risk in the Lynch syndrome. *JAMA* 296: 1479-1487.

26. Jenkins MA, Baglietto L, Dowty JG, et al. (2006). Cancer risks for mismatch repair gene mutation carriers: a population-based early onset case-family study. *Clin Gastroenterol Hepatol* 4: 489-498.

27. Southey MC, Jenkins MA, Mead L, et al. (2005). Use of molecular tumor characteristics to prioritize mismatch repair gene testing in early-onset colorectal cancer. *J Clin Oncol* 23: 6524-6532.

28. Cui J and Hopper JL (2000). Why are the majority of hereditary cases of early-onset breast cancer sporadic? A simulation study. *Cancer Epidemiol Biomarkers Prev* 9: 805-812.

29. Hedenfalk I, Ringner M, Ben-Dor A, et al. (2003). Molecular classification of familial non-BRCA1/BRCA2 breast cancer. *Proc Natl Acad Sci U S A* 100: 2532-2537.

30. Jonsson G, Naylor TL, Vallon-Christersson J, et al. (2005). Distinct genomic profiles in hereditary breast tumors identified by array-based comparative genomic hybridization. *Cancer Res* 65: 7612-7621.

31. Easton DF, Deffenbaugh AM, Pruss D, et al. (2007). A systematic genetic assessment of 1,433 sequence variants of unknown clinical significance in the BRCA1 and BRCA2 breast cancer-predisposition genes. *Am J Hum Genet* 81: 873-883.

32. Goldgar DE, Easton DF, Deffenbaugh AM, et al. (2004). Integrated evaluation of DNA sequence variants of unknown clinical significance: application to BRCA1 and BRCA2. *Am J Hum Genet* 75: 535-544.

33. Ou J, Niessen RC, Lutzen A, et al. (2007). Functional analysis helps to clarify the clinical importance of unclassified variants in DNA mismatch repair genes. *Hum Mutat* 28: 1047-1054.

CANCER IN THE SOUTH-EAST ASIA REGION (SEA)

Rapidly progressing epidemiological transition taking place in the South-East Asia (SEA) Region of WHO has reached an advanced stage, characterised by predominance of chronic noncommunicable diseases (NCDs). With an age-standardised mortality rate of 111 per 100 000 and 9% share in total deaths, cancer has become an important public health priority. In 2000, there were an estimated 1.3 million cases and 0.9 million deaths from cancer in the Region, with cervix uteri, breast, oral cavity and lung cancer the most prevalent. Unlike in more developed regions of the world, where most of cancers are related to lifestyle and environmental risk factors, in the SEA Region chronic infections caused by Human papillomavirus (HPV), hepatitis B and C viruses; *Helicobacter pylori* and liver fluke are also of high importance.

Effective cancer control requires a comprehensive national cancer control policy and programme with adequate resource allocation, development of diagnostic and therapeutic capacity and good resource utilisation in palliative care. High levels of female illiteracy, gender discrimination and other socioeconomic inequalities, as well as lack of awareness of the risk factors and poor enforcement of tobacco, alcohol and food legislation, all hinder the efforts of cancer control programmes. Widespread inaccessibility of preventive, early detection and treatment services for large segments of the population in the Region due to the geographical and financial constraints contribute to poor health outcomes. As out-of-pocket payment for the treatment of cancer could economically devastate families and individuals, the creation of appropriate financing mechanisms to cover the cost of treatment needs to be addressed.

Member countries of the SEA Region are taking action to reduce the burden and risk factors of cancer and improve the quality of life of the patients and their families—thus contributing to implementation of the WHO Strategy for Prevention and Control of Cancer. To further strengthen commitment and capacity of Member countries to tackle cancer and other major NCDs (i.e. cardiovascular diseases, chronic respiratory diseases and diabetes), the Regional Framework for Prevention and Control of NCDs has been developed. The WHO Regional Committee for the South-East Region, at its Sixtieth session in September 2007 in Thimphu, Bhutan, endorsed the Regional Framework; it also adopted, for the first time in its history, a Resolution on the Prevention and Control of NCDs. The resolution urges Member countries to formulate, update and strengthen national policies, strategies and programmes for integrated prevention and control of NCDs; to establish suitable infrastructure and appropriate funding mechanisms for this purpose; and to promote multisectoral collaboration for integrated prevention and control of NCDs.

There is an increasing capacity in the Region to address the health and socioeconomic burdens of cancer. Selected information collected through the regional survey conducted by WHO in 2006–2007 is shown in Table 1. Cancer registries, either hospital or community-based such as those set up with WHO support in India, Indonesia, Sri Lanka and Thailand, serve an important role in providing information about the area-specific prevalence of different types and locations of cancer. Since 2001 when WHO began to promote the STEP-wise approach to NCD Risk Factor Surveillance (STEPS) in the Region, most countries have gathered standardised information on NCD risk factors (Table 2). Locally available data on tobacco use, unhealthy diet, physical inactivity and alcohol consumption facilitate planning, implementation and evaluation of preventive action on cancer and other NCDs.

Tobacco use remains the major preventable behavioural risk factor for lung and some other types of cancer. Member countries of the Region are taking strong anti-tobacco measures within the provisions of the WHO Framework Convention on Tobacco Control (WHO FCTC). Out of 11 SEA countries, 10 have signed and ratified the WHO FCTC, and 5 already have tobacco control legislation in place. In addition to smoking, tobacco is often chewed, leading to cancer of the oral cavity—the third most common type of cancer in the SEA Region.

Physical activity, avoidance of obesity and frequent daily intake of fresh fruit and vegetables reduce the risk of several cancers. Implementation of the WHO Global Strategy on Diet, Physical Activity and Health (DPAS) will lead to significant reduction in the mortality and morbidity of cancer and other major NCDs. In the SEA Region, the DPAS is being implemented in three countries, with five more countries in the process of initiating its implementation.

Cancer of the uterine cervix is the most common cancer among women in the Region. Though its rates are dropping in some countries as a result of improved socioeconomic conditions, further improvement requires the introduction of an active screening programme. Broad implementation of cytology-based screening and treatment for cervical cancer is hindered by financial constraints and inadequate health infrastructure and outreach. Alternate strategies such as visual inspection with acetic acid are being introduced in some countries, including India

and Thailand. Currently WHO is supporting Maldives and Thailand in engaging in the research project on delivery of HPV vaccine to adolescents.

Childhood immunisation against hepatitis B is the most cost-effective strategy to prevent adult mortality from liver cancer. Following 1992 World Health Assembly Resolution WHA45.17, most countries of the SEA Region have introduced hepatitis B vaccine in their routine national immunisation programmes. This process was further accelerated by the Global Alliance for Vaccines and Immunization (GAVI).

A majority of countries of the SEA Region already have national cancer control programmes in place. Most often these programmes are at the early stage of development. WHO is supporting the national governments in strengthening their capacity to prevent and control cancer. This is being done through advocacy for and technical support in development and strengthening of cancer control programmes and plans encompassing cancer prevention, early detection, management, palliative care and surveillance and research. Member countries are being supported in setting up surveillance systems (cancer registries) and in addressing major behavioural risk factors of cancer in line with FCTC and DPAS. Technical assistance is provided in implementing the hepatitis B immunisation and cervical cancer prevention programmes. WHO is involved in cancer control partnerships such as the Programme of Action on Cancer Therapy (PACT), aimed at strengthening diagnostic and treatment capacity of cancer in developing countries.

Technical support of WHO at the national level is being executed in close collaboration with the ministries of health, in line with long-term WHO country cooperation strategies, and focuses on strategic planning, capacity building, advocacy, networking and research. In support of the National Cancer Control Programme (NCCP), the WHO India Country Office provides technical support in the area of cancer surveillance (see the Atlas of Cancer in India, Figure 1); development of training manuals, guidelines and awareness materials; demonstration programmes for community-based cancer control; and capacity building of health personnel. It supports initiatives for pain relief and palliative care and facilitated oral morphine availability in India. The Country Office is supporting the revision of NCCP strategy to achieve an optimal mix of preventive, curative and palliative care and will continue to support the implementation and evaluation of comprehensive cancer control in India.

In Indonesia, WHO is helping to develop national policy and strategy on cancer prevention and control by bringing together policymakers, professionals and NGOs. It supports the development of hospital-based cancer registries in Jakarta and also has facilitated the development and use of guidelines for comprehensive cervical cancer prevention. In Myanmar, WHO support focuses on providing fellowships to various categories of health professionals in the areas of surveillance, prevention, early detection, effective treatment and palliative care. WHO collaborative work includes also development of information, education and communication (IEC) materials (Figure 2) and creating community awareness on early detection of cancer. Technical support to epidemiological research on cancer is also provided.

In Thailand, the WHO collaborative work includes assessment of exposure to occupational carcinogens, development of an occupational and environmental cancer surveillance system, networking of community health personnel and volunteers and strengthening of communities and local authorities to assess and tackle environmental threats. Also, in other Member States of the SEA Region, including Bangladesh, Bhutan, DPR Korea, Maldives and Sri Lanka, WHO country offices are providing technical support in development of NCCPs and in implementing specific cancer control activities.

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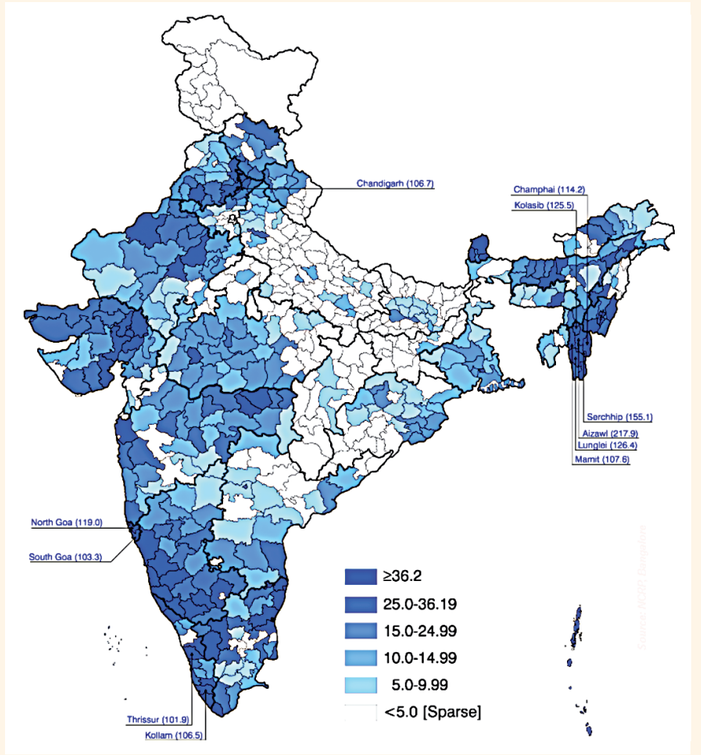


Figure 1. *Minimum incidence of all cancers in India (men)*
Source: Cancer Atlas (ICMR)

Figure 2. *IEC poster produced jointly by the Ministry of Health and WHO in Myanmar*

Area	Indicator	No. of countries (total 11)
Policy/programme	National health policy addresses cancer and other major NCDs	5
	National plan/ programme for cancer control	8
Infrastructure	Presence of a NCD unit or department in ministry of health	8
	Presence of national cancer reference centre	9
Legislation/regulation	Anti-tobacco	10
	Food and nutrition (related to NCDs)	5
Surveillance	Surveillance systems for major cancers	4
	Population- based cancer registries	3
	Hospital-based cancer registries	8
	NCD risk factor (STEPS) surveys conducted	9
Management	Availability of guidelines for cancer management	6
	Anti-neoplastic medicines accessible and affordable for low-income groups	2

Table 1. *Capacity of SEA Member countries to prevent and control cancer: select indicators*
Modified from "Scaling up prevention and control of chronic noncommunicable diseases in the SEA Region. Capacity for noncommunicable disease prevention and control in countries of the South-East Asia Region: results of a 2006-2007 survey". SEA/RC60/9 -INF DOC1

Country/site	Current smokers (%)	Current consumers of alcohol (%)	Proportion (%) eating < 5 servings of F & V	Proportion (%) physically inactive	Proportion (%) overweight and obese
Bangladesh – R	25.3	NS	NR	NR	8.6
Bangladesh – U	21.9	NS	NR	NR	36.5
DPR Korea	31.1	NS	NS	NS	NR
India – R	17.8	26.4	84.6	10.0	13.3
India – U	15.7	20.7	81.4	23.8	39.4
Indonesia*	32.0	3.3	94.5	7.8	22.3
Maldives	22.7	NS	84.6	NR	44.2
Myanmar – R	24.4	18.0	98.2	3.5	23.3
Myanmar – U	22.9	18.4	99.1	7.3	36.5
Nepal	20.6	40.5	99.1	NR	16.5
Sri Lanka	19.6	40.5	96.8	14.9	28.8
Thailand*	18.6	40.1	85.0	NR	37.5
TOTAL (range)	**16-32**	**3-41**	**81-99**	**4-24**	**9-44**

Table 2. *Prevalence of select behavioural risk-factors in the SEA Region (age 25–64; both sexes)*
Source: "Scaling up prevention and control of chronic noncommunicable diseases in the SEA Region. Risk factors: results from surveys using the STEPS approach." SEA/RC60/9 -INF DOC 2.
**Only national surveys, other are sub-national surveys; F & V – fruits and vegetables; NR – not reported; NS – not studied; R – rural; U – urban.*

5

Cancer Site by Site

5.1 Head and Neck Cancers

Summary

- Tobacco smoking, alone and in combination with alcohol, is the most important risk factor
- Tobacco chewing is also an important risk factor in some populations
- Infection of human papilloma virus is a recognised cause of some head and neck cancers
- Genes that metabolise alcohol appear to influence the risk of developing head and neck cancers

Head and neck cancers are a related group of cancers that involve the oral cavity, pharynx and larynx. Each year there are approximately 400 000 cases of cancer of the oral cavity and pharynx, with 160 000 cancers of the larynx, resulting in approximately 300 000 deaths [2]. Regions with a high incidence include much of Southern Asia as well as parts of Central and Southern Europe.

The majority of head and neck cancers are squamous-cell carcinoma (SCC) in histology, and the main risk factors for these cancers are tobacco and alcohol use. Tobacco smoking is the most important risk factor for head and neck cancer, and the risk is higher for heavy smokers, long-term smokers and smokers of black tobacco or high-tar cigarettes. Cigar and pipe smoking also pose a risk, while stopping smoking is followed by a decrease in risk [3]. Smoking of bidis (small cigarettes common in parts of Asia) appears to have a higher risk for cancer of the hypopharynx and larynx than smoking of Western type cigarettes [4]. Consumption of alcoholic beverages also increases the risk of head and neck cancer. Relative to abstainers and very light drinkers, the risk in heavy drinkers is in the order of tenfold. This increased risk is unlikely to be related to alcohol consumption *per se*, but instead it may be caused by exposure to acetaldehyde, which is an intermediate metabolite of ethanol and is a known animal carcinogen [5]. Although the effect of alcohol and tobacco may vary slightly according to the different subsites, the combined effect of both exposures accounts for the majority of all head and neck cancers that occur globally. A recent pooled analysis from the INHANCE consortium based on over 10 000 cases and 15 000 controls, shows that approximately 70% of such cancers can be explained by these two exposures, ranging from 65% for oral cavity cancer (51% for women and 65% for men) to 86% for larynx cancer (79% for women and 86% for men). Furthermore, the proportion of those cancers caused by alcohol and tobacco was reduced with decreasing age, being just 32% for cancers diagnosed prior to age 45. Strong interaction between the two exposures was also apparent (Figure 5.1.1).

Other risk factors for these cancers are therefore clearly important. Established risk factors specifically for oral cavity cancer are betel quid and areca nut in India and Taiwan [6]. Several occupational substances or circumstances such as isopropanol manufacturing, inorganic acid mists containing sulfuric acid and mustard gas are suspected risk factors for laryngeal cancer [7]. Poor oral health and frequent use of mouthwash are also potential risk factors for oral cancer, although are unlikely to be relevant for other head and neck cancers [8].

Human papilloma virus (HPV) is a recognised cause of some head and neck cancers, with substantial evidence for a role of HPV16E6 from large case-control studies. The evidence comes primarily from several large epidemiological studies that have analysed associations of various HPV markers. HPV markers studied were (i) HPV DNA in biopsy tissues or oral cell scraping analysed by southern blotting or highly sensitive PCR methods, (ii) antibodies to HPV 16 capsids analysed by ELISA using HPV 16 major capsid protein L1-derived virus-like particles as antigens, and (iii) antibodies to HPV 16 E6 and E7 analysed by ELISA. HPV capsid antibodies are a cumulative marker of past and present HPV infection [9]. Young females with new genital HPV 16 infection demonstrated by HPV 16 DNA positivity will seroconvert to only about 60 % within 6 months. Titers of HPV capsid antibody titers usually are rather low but persist for many years. Mucosal HPV capsid antibodies are more prevalent in females than in males. Antibodies to the oncoproteins E6 and E7 of HPV 16 and 18 are markers of invasive cancer expressing these viral oncoproteins [10-12]. They are rare in the general population and among women with cervical cancer precursor lesions. In patients with invasive cervical cancer, prevalence of these antibodies increases with stage [10]. Antibodies to HPV 16 E6 and E7 also develop in patients with invasive HPV 16 DNA positive head and neck squamous-cell carcinoma [10], particularly in patients with evidence of HPV 16 E6 expression [13,14].

The largest study on the association of HPV and head and neck cancer, involving 1670 case patients (1415 with cancer of the oral cavity and 255 with cancer of the oropharynx) and 1732 control subjects, reported a prevalence of HPV DNA in 3.9% of specimens from the oral cavity and 18.3% of specimens from the oropharynx [15]. Furthermore, when cases were compared to controls, a strongly increased risk was observed for antibodies against HPV 16 E6 and E7 proteins, for both cancers of the oral cavity (OR=2.9, 95% CI 1.7–4.8) and oropharynx (OR=9.2, 95% CI 4.8–17.7). In a more recent US study comprising 204 head and neck cancer cases and 326 controls, a fivefold increased risk for HPV 16 E6/E7 antibodies was observed for oral cancer (OR=5.1, 95% CI 1.2–22.4), and a 70-fold increased risk was observed for cancer of the oro-pharynx (OR=72.8, 95%CI 16.0–330) [16]. In a systematic review of presence of HPV in DNA in head and neck cancers, HPV 16 accounted for practically all of the HPV infections of the oropharynx, whereas HPV 18 was also commonly observed in the oral cavity [17].

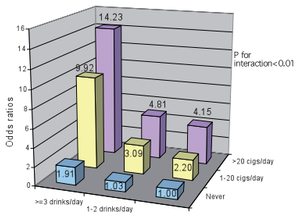
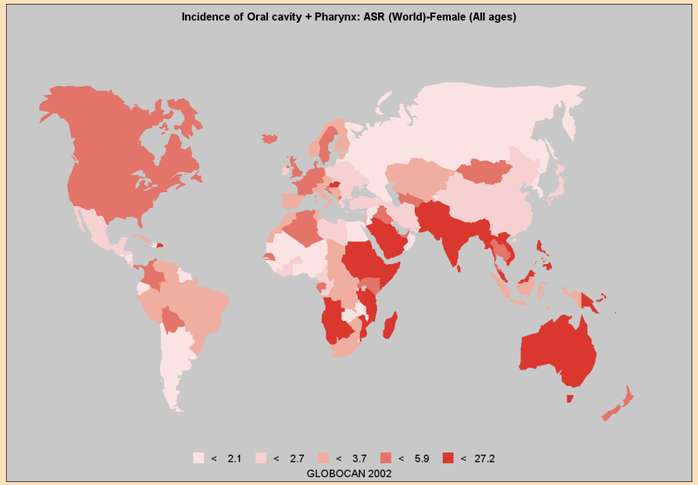


Fig. 5.1.1 *Interaction between tobacco and alcohol frequency on the risk of head and neck cancer*

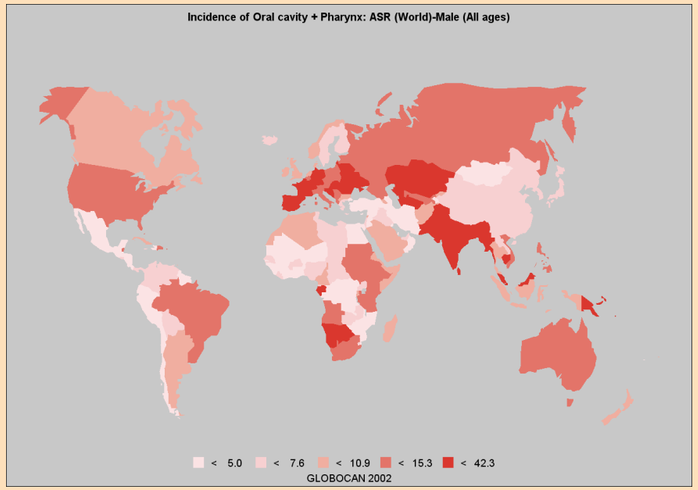
Important questions remain however regarding the role of other specific types of HPV, interaction with other risk factors, and the role of HPV in larynx cancer tumours. Furthermore, their role in determining response to treatment and survival from head and neck cancer is not well elucidated. Also, an effect between increased intake of fruits and vegetables and a reduced risk of head and neck cancers has been observed, although mostly in hospital-based case-control studies.

Treatment and survival

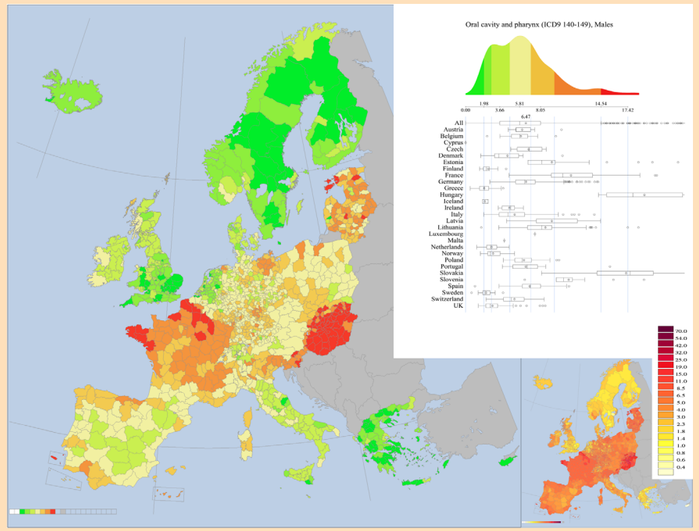
Primary treatment varies with the anatomic subsite and stage of disease. For most early cancers, surgical resection is the cornerstone of treatment [18]. However, for certain anatomic sites such as the tonsils, the base of the tongue, and the floor of the mouth, as well as for all locally advanced cancers, radiotherapy is used, either alone or combined with surgery. Occasionally, chemotherapy may be used in addition to radiotherapy. Following diagnosis of oral cavity and pharynx cancer, 5-year relative survival is close to 40% in the United States and in Europe, although it varies substantially among countries. Moreover, the prognosis is generally better for women and for malignancies of the oral cavity than for those arising in the hypopharynx. In Europe, 5-year relative survival rates remained virtually identical from 1983 to 1994, suggesting that no major progress has been made [19].



World Map 5.1.1



World Map 5.1.2



European Map 5.1.1 *The outstanding feature of this map depicting mortality from cancer of oral cavity and pharynx in the European Union in males is the higher levels of mortality in almost the whole of Hungary and Slovakia, in much of Slovenia, and in France with concentrations of excess in the north-west and north-east. There was also a belt of high rates extending across northern Germany and an aggregation of high rates in north-east Italy bordering Slovenia. Rates were generally low in the Nordic Countries, the United Kingdom and Ireland, much of Spain and Italy, and in Greece.*
The geographical distribution of areas of high cancer risk for oral cancer demonstrates that while the higher mortality rates in France end abruptly at the border with Belgium–the risk being around one half in Belgium (5.9 per 100 000) of that in France (11.3 per 100 000) - this phenomenon is not seen in the south, with rates in south-east France and in the north of Italy, and in southwest France and northern Spain being at much the same levels. This suggests that there were likely to have been comparable exposures in the south, whereas exposures and/or protective agents may have been different in the north.
Taking account of known risk factors, the high levels in males appear to be generally in regions where there is a prevalent habit in the population of drinking strong alcoholic beverages. Reduction of this, together with avoidance of cigarette smoking, would lead to a large reduction in risk [1].

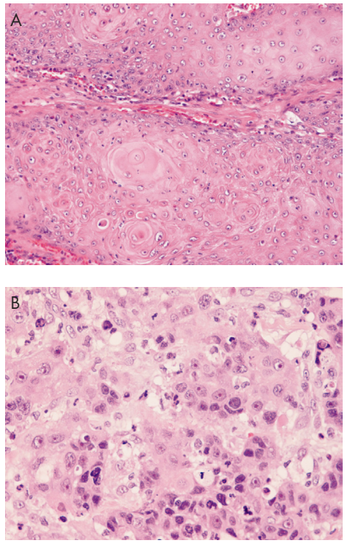


Fig. 5.1.2 *Squamous-cell carcinoma (SCC). A: Well differentiated SCC. B: Poorly differentiated SCC*

Genetic susceptibility to aerodigestive cancers

Genetic susceptibility studies for aerodigestive cancers have focused primarily on genes related to alcohol metabolism. A pooled analysis of 6 studies on the alcohol dehydrogenase 1C polymorphism comprising over 1300 cases and 1700 controls failed to identify any effect with the ADH1C variant genotype [20]. Subsequent analysis based on a collaboration of 3 large studies comprising over 3800 cases and 5000 controls has however provided extremely strong evidence for a protective effect for the ADH1B R48H variant (OR=0.54, 0.46–0.65; $p=10^{-12}$), and the ADH7 A92G variant (OR=0.68, 0.60–0.77; $p=10^{-9}$).

Furthermore, the effect of both variants was significantly modified by alcohol consumption. These results illustrate that interactions between environmental and genetic effects can be detected when (i) one has very large sample sizes, (ii) one has excellent lifestyle and environmental data, and (iii) one has identified genetic factors that have a real effect.

Larynx Cancer

It is estimated that between 25% and 30% of all cancers in developed countries are tobacco-related. For both sexes combined the proportion of cancers arising in the oesophagus, larynx and oral cavity attributable to the effect of tobacco, either acting singly or jointly with the consumption of alcohol is between 43% and 60%. Although the greatest hazard is caused by cigarette smoking, cigars can cause similar hazards if their smoke is inhaled and both cigar and pipe smoker cause comparable hazards of cancers of the oral cavity, pharynx, extrinsic larynx, and oesophagus.

Tobacco smoking has long been recognised as a major cause of cancer of the larynx and especially of the endolarynx [21,22].

Gandini et al. [23] conducted a systematic meta-analysis of observational studies on cigarette smoking and cancer from 1961 to 2003. The aim was to quantify the risk for 13 cancer sites recognised to be related to tobacco smoking by the International Agency for Research on Cancer, and to analyse the risk variation for each site in a systematic manner. Data were extracted from the 254 reports (177 case-control studies, 75 cohorts and 2 nested case-control studies) published in this period and included in the 2004 IARC Monograph on tobacco smoke and involuntary smoking [22]. The analyses were carried out on 216 studies with reported estimates for 'current' and/or 'former' smokers. Sensitivity analysis was performed, and the authors looked for publication and other types of bias. Lung (RR 8.96; 95% CI 6.73–12.11), laryngeal (RR 6.98; 95% CI 3.14–15.52) and pharyngeal (RR 6.76; 95% CI 2.86–15.98) cancers presented the highest relative risks for current smokers, followed by upper digestive tract (RR 3.57; 95% CI 2.63–4.84) and oral (RR 3.43; 95% CI 2.37–4.94) cancers. As expected, pooled relative risks for respiratory cancers were greater than the pooled estimates for other sites. The analysis of heterogeneity showed that study type, gender and adjustment for confounding factors significantly influence the risk estimates and the reliability of the studies.

Tuyns et al. [24] published results regarding tobacco and alcohol consumption from a large, multicentre, case–control study comprising 1147 male cases (cancer of the larynx and hypopharynx) and 3057 male controls. The relative risk associated with cigarette smoking was approximately 10 for all considered subsites of the larynx and hypopharynx. The risks for alcohol drinking varied by site, however, being higher for epilarynx and hypopharynx (OR = 4.3 for 80g/day or more) but lower at the same dose for endolarynx (OR = 2.1). Risk decreased within 10 years of quitting cigarette smoking, and smokers of blond tobacco were found to have about half the risk of smokers of black tobacco. The authors also reported that the risks associated with joint exposure to alcohol and tobacco were consistent with a multiplicative relative risk model [23].

The relationship between type of cigarettes smoked and the risk of cancer of the oral cavity and pharynx (excluding salivary gland and nasopharynx) was examined in a hospital-based case–control study involving 291 male cases and 1272 controls conducted in Pordenone Province and Greater Milan in Northern Italy (this is the same study base as above) [25]. As a basis for classification, the authors used tar-yield and the brand smoked for the longest time (<22mg, low to medium tar; ≥22mg, high tar). After adjustment for other risk factors, relative to non-smokers the risk among ever-smokers for oral and pharyngeal cancers were 8.5 (95% CI 3.7–19.4)) for low/medium and 16.4 (7.1–38.2) for high-tar cigarettes. For larynx cancer, the corresponding results were 4.8 (2.3–10.1) and 7.1 (3.2–15.6) relative to non-smokers. The authors concluded that these data provided further quantitative evidence of the importance of type of cigarette smoked on the risk of oral cancers as well as other cancers of the upper digestive and respiratory tract [25].

The incidence and mortality rates of laryngeal cancer in Poland and notably high and have been increasing for 25 years. Zatonski et al. [26] report a study among persons under the age of 65 in Lower Silesia, in southwest Poland, based on 249 newly-diagnosed cases and 965 controls. For smoking more than 30 cigarettes per day, the relative risk compared to non-smokers was 59.7 (95% CI 13–274) and the risk for consuming vodka regularly for 30 or more years was 10.4 (95% CI 4–27.2). Exposures to tobacco and alcohol showed a clear multiplicative effect in all categories of exposure. The risk of laryngeal cancer was shown to be reduced by quitting smoking or by having a history of intermittent smoking. Poor nutrition was identified as a strong independent risk factor in this study. It was estimated that smoking alone accounts for 95 per cent of all cases of laryngeal cancer in this population [26].

According to a large population-based case–control study in Southern Europe, about 90% of the current incidence of larynx cancer could be prevented by avoiding smoking and alcohol consumption, tobacco being responsible for the most of the risk [27,28]. A case–control study conducted in Poland estimated that smoking alone accounted for 95% of all cases of laryngeal cancer [26]. Similar conclusions have been drawn from an Italian study aimed at evaluating the impact of a reduction of cigarette smoking on mortality [29].

From a case–control study conducted in Liaoning province (China) in 1991 and 1992, smoking was the most important risk factor, with an OR of 16.8, and cigarette smoking in particular had an OR of 30.4 [30]. A different Chinese population-based case–control study, conducted in Shanghai between 1988 and 1990, confirmed that cigarette smoking was the main risk factor for laryngeal cancer accounting for 86% of the male and 54% of the female cases. The adjusted (for age and education) OR was 8.7 (95% CI 3.8–19.6) for ever versus never smoking. The risk increased with both the quantity and duration of smoking, with a 25-fold excess in the heaviest consumption categories; it declined following cessation [31].

The analysis of data from a case–control study conducted in Northern Italy between 1986 and 1992 showed a OR of 8.8 (95% CI 5.2–14.8) for heavy current smokers compared to never smokers and a OR of 3.3 (95% CI 1.9–5.5) for ex- or moderate smokers. Estimates of attributable risk implied that 77% of laryngeal cancers in men were due to smoking [31].

The risk of laryngeal cancer was shown to be reduced by smoking cessation [32]; having a history of intermittent smoking also seems to reduce the risk of laryngeal cancer compared with continued smoking, but this new finding, of considerable interest and potential importance with regard to possible mechanisms of laryngeal carcinogenesis, needs validation from further studies [26]. In a cohort of patients with laryngeal cancer, Hamzany et al. [33] observed that of 1443 patients treated for laryngeal carcinoma between 1960 and 2006, 55 (3.8%) were non-smokers: 40 (73%) had never smoked and 15 (27%) had stopped smoking 12 years or more before diagnosis.

There is convincing epidemiological evidence that the consumption of alcoholic beverages increases the risk of cancers of the oral cavity, pharynx and extrinsic larynx and of squamous-cell carcinoma of the oesophagus. The risks tend to increase with the amount of ethanol drunk, in the absence of any clearly defined threshold below which no effect is evident. There is wide variability among European Union/European Economic Area countries in terms of per-capita average alcohol consumption and preferred type of alcoholic beverage.

Alcohol drinking

The relationship between increased laryngeal cancer risk and alcohol consumption has been consistently demonstrated by a variety of epidemiological studies [34,35]. A large population-based case–control study in Southern Europe found that reducing only alcohol consumption could prevent a quarter of the cases of laryngeal carcinoma [27].

The results from a case–control study conducted in Northern Italy were an OR of 1.5 (95% CI 1.0–2.2) for drinkers of 6 to 7 alcoholic drinks per day and an OR of 2.2 (95% CI 1.6–3.0) for drinkers of 8 or more drinks per day compared to teetotallers or moderate drinkers. Estimates of attributable risk implied that alcohol intake accounted for 25% of cases [36]. Other estimates showed ORs for men and women respectively of 2.0 and 2.6 for people in the highest intake category (42 or more drinks/week in women and 42-55 drinks/week in men) as compared to light drinkers [37].

A dose-dependent effect for alcohol has often been noted [38,39]. In a case-control study conducted in New York between 1985 and 1990, estimates of the risk for heavy drinkers (207 ml or more/daily) for supraglottic and glottic cancer were respectively 9.6 and 2.5. Interestingly, binge drinkers had higher ORs: 28.4 and 8.3 for supraglottic and glottic cancer respectively [38]. Similar results were obtained by another American case-control study (Seattle, Washington): for 7 to 13, 14 to 20, 21 to 41 and 42 or more drinks per week the OR were respectively 1.9 (95% CI 1.1–3.2), 2.1 (95% CI 1.0–4.4), 2.8 (95% CI 1.4–5.7) and 3.1 (95% CI 1.2–7.9) when compared to drinkers of fewer than 7 drinks per week [40].

Epidemiological studies provide definite evidence that alcohol drinking is an independent risk factor for laryngeal cancer. This risk increases with the amount of alcohol consumed: in a meta-analysis of 20 studies conducted in North America, Europe, Japan and Korea the multivariate relative risks were about 2 for 50g (approximately 4 drinks)/day and about 4 for 100g/day compared to nondrinkers, in the absence of evidence of a threshold. Genetic polymorphisms in the alcohol-metabolising enzyme aldehyde dehydrogenases have been found to be associated with upper aerodigestive tract cancer, including the larynx [41]. Further, the risk is increased with concomitant tobacco smoking, each agent approximately multiplying the effect of the other. In the absence of smoking, the relative and absolute risks are small for moderate alcohol consumption, but there is an increased risk for elevated alcohol consumption. After stopping drinking, some decrease in risk becomes apparent only in the long term. The supraglottis is more closely related to alcohol consumption, as compared to the glottis/subglottis. In various populations, the most commonly used alcoholic beverage appears to be the one most strongly associated with laryngeal cancer risk, suggesting that no meaningful difference exists for different types of alcoholic beverages.

The relationship between alcoholism and cancer of the larynx has been evaluated by a case–control study conducted in the United States [40]. The aim of the study was to determine if alcoholism (as measured by responses to the Michigan Alcoholism Screening Test (MAST)) was a risk factor for laryngeal cancer independently from alcohol consumption. They found an OR of 1.9 (95% CI 1.1–3.4) for a score of 5 or more compared with a score of 0, after having been adjusted for age, gender, average alcohol consumption and summary cigarette use. To investigate if there were a higher association for tissues that come into more direct contact with alcohol, they evaluated different multiple logistic regression models and obtained an OR of 1.9 (95% CI 1.0–3.7) for glottic and subglottic tumours and an OR of 2.3 (95% CI 0.9–5.5) for supraglottic tumours after having been adjusted for the same factors listed above. Possible explanations for the association between alcoholism and laryngeal cancer include the possibility that the MAST score may be serving as an additional measure of alcohol consumption, that is, measure of alcoholism improves the accuracy of assessment of alcohol consumption; that alcoholism is associated with a pattern of alcohol consumption (e.g. alcoholics may gulp drinks instead of sipping them, perhaps leading to a smaller amount of alcohol being aspirated) that increases the risk of laryngeal cancer; or that alcoholism may be a marker for host susceptibility to the carcinogenic effects of alcohol.

A different study, which examined the relationship between alcoholism and cancer risk in a population-based cohort of 9353 individuals who were discharged with a diagnosis of alcoholism between 1965 and 1983 found an excess risk for larynx cancer (standardised incidence ratio 3.3, 95% CI 1.7–6.0) [42].

Combined effects of tobacco smoking and alcohol drinking

Tobacco smoking [21,22] and alcohol consumption [34,35] are the major established risk factors for laryngeal cancer, as for other neoplasms of the upper aerodigestive tract. That the relationship between cigarette smoking and laryngeal cancer risk is causal is strongly suggested by the magnitude of the relative risk estimates derived from comparisons between smokers and non-smokers, by the positive trend in these estimates with increasing cigarette usage, by the relatively reduced risk incurred by groups who do not smoke, such as Seventh Day Adventists, by the decrease in risk among ex-smokers relative to those who continue to smoke and by the consistency of these findings in epidemiological studies of a variety of different designs [21,22,43]. There are, however, some quantitative differences in the association with other upper digestive tract cancers, since cancer of the larynx, and particularly the endolarynx, is less strongly associated with alcohol and more strongly with tobacco than cancer of the oral cavity or of the oesophagus [23]. This difference is biologically plausible since the endolarynx is not in direct contact with alcohol. There is still some debate on the nature of the biological and statistical interaction between alcohol and tobacco on risk of laryngeal cancer [34,35], although most investigations have concluded that the combined risk is multiplicative [26], or at least greater than additive [43]. This further indicates the importance of intervention on at least one factor for subjects exposed to both habits. The study from Poland estimated that cigarette smoking alone accounted for an estimated 95% of laryngeal cancer in that high risk area [26].

The separate effects of alcohol and tobacco on laryngeal cancer are quite strong. The risk of extrinsic laryngeal cancer is 2.5 times greater in heavy drinkers/non-smokers and over 9 times greater among current smokers/non-drinkers. Although alcohol drinking increases the risk of upper digestive and respiratory tract neoplasms even in the absence of smoking, alcohol drinking and tobacco smoking together greatly increase the risk of these cancers, each factor approximately multiplying the effect of the other. Compared with never-smokers and non-alcohol drinkers, the relative risk of these neoplasms is increased between 10- and 100-fold in people who drink and smoke heavily. If there were total abstinence from drinking and smoking, the risk of oral, pharyngeal, laryngeal and squamous cell oesophageal cancers in European countries would be extremely low.

Dietary factors and larynx cancer

Intake of fruit and vegetables may protect against head and neck cancer incidence, although few prospective studies have examined this association. In the USA, 490 802 participants of the NIH-AARP Diet and Health cohort were observed during 2 193 751 person-years of follow-up from 1995–2000 [44]. Of these, 787 participants were diagnosed with head and neck cancer. An inverse association was found between total fruit and vegetable intake and head and neck cancer risk (per serving/day/1000 calories, hazard ratio 0.94, 95% CI 0.89–0.99). In models mutually adjusted for fruit and vegetable intake, the association was stronger for vegetables (fifth vs. first quintile: 0.65, 0.50–0.85) than for fruits (fifth vs. first quintile: 0.87, 0.68–1.11). When further subclassified into botanical groups, those in the highest tertile of leguminosae (dried beans, string beans and peas, 0.80, 0.67–0.96), rosaceae (apples, peaches, nectarines, plums, pears and strawberries, 0.60, 0.49–0.73), solanaceae (peppers and tomatoes, 0.82, 0.69–0.98) and umbelliferae (carrots, 0.73, 0.60–0.89) had decreased risk of head and neck cancer, but no significant associations were seen for nine other botanical groups [44]. Results from this large prospective observational study are consistent with previous case–control studies [45] and support the hypothesis that total fruit and vegetable intake is associated with reduced risk of head and neck cancer.

Family history and genetic susceptibility

Tobacco smoking and consumption of alcoholic beverages are established causes of cancers of the upper aerodigestive tract (UADT), whereas reduced intake of vegetables and fruits are likely causes of UADT cancers (these include cancers of the oral cavity, pharynx (other than nasopharynx), larynx and oesophagus). The role of genetic predisposition and possible interactions of genetic with exogenous factors, however, have not been adequately studied. Moreover, the role of pattern of smoking and drinking, as well as the exact nature of the implicated dietary variables, has not been clarified.

Only a few epidemiologic studies have considered the relation between UADT risk and family history of head and neck cancer (HNC) and other cancers. Negri et al [45] pooled individual-level data across 12 case–control studies including 8967 UADT cases and 13 627 controls. A family history of HNC in first-degree relatives increased the risk of HNC (OR 1.7, 95% CI 1.2–2.3). The risk was higher when the affected relative was a sibling (OR 2.2, 95% CI 1.6–3.1) rather than a parent (OR 1.5, 95% CI 1.1–1.8) and for more distal HNC anatomic sites (hypopharynx and larynx). The risk was also higher in, or limited to, subjects exposed to tobacco. The OR rose to 7.2 (95% CI 5.5–9.5) among subjects with family history, who were alcohol and tobacco users. A weak but significant association (OR 1.1, 95% CI 1.0–1.2) emerged for family history of other tobacco-related neoplasms, particularly with laryngeal cancer (OR 1.3, 95% CI 1.1–1.5). No association was observed for family history of non-tobacco-related neoplasms and the risk of HNC (OR 1.0, 95% CI 0.9–1.1). Familial factors play a role in the etiology of HNC. A clear

message is that, regardless of family history of HNC, avoidance of tobacco and alcohol exposure may be the best way to avoid HNC [46].

In 2002 the IARC initiated the Alcohol-Related Cancers and Genetic susceptibility in Europe (ARCAGE) project, with the participation of 15 centres in 11 European countries. Information and biological data from a total of 2304 cases and 2227 controls have been collected and will be used in a series of analyses. A total of 166 single nucleotide polymorphisms of 76 genes are being studied for genetic associations with UADT cancers. About 80% of cases were males, and fewer than 20% of all cases occurred before the age of 50 years [47]. Overall, the most common subsite was larynx, followed by oral cavity, oropharynx, esophagus and hypopharynx. Close to 90% of UADT cancers were squamous-cell carcinomas. A clear preponderance of smokers and alcohol drinkers was observed among UADT cases compared with controls [47].

Hashibe et al. [48] investigated six alcohol dehydroxegenase (ADH) genetic variants in over 3800 aerodigestive cancer cases and 5200 controls from three individual studies. Gene variants rs1229984 (ADH1B) and rs1573496 (ADH7) were significantly protective against aerodigestive cancer in each individual study and overall (P<0.0001 in each case). These effects became more apparent with increasing alcohol consumption (P for trend=0.0002 and 0.065, respectively). Both gene effects were independent of each other, implying that multiple ADH genes may be involved in upper aerodigestive cancer etiology.

Using epidemiologic data and biological samples previously collected in three case-control studies from US and Chinese populations, Park et al. selected and genotyped one SNP from each of three previously determined regions within the 8q24 loci, rs1447295 (region 1), rs16901979 (region 2), and rs6983267 (region 3), and examined their association with several smoking-related cancers including cancer of the larynx [49]. A noteworthy association was observed between rs6983267 and upper aerodigestive tract cancers (adjusted OR 1.69; 95% CI 1.28–2.24), particularly in the oropharynx (adjusted OR 1.80; 95% CI 1.30–2.49) and larynx (adjusted OR 2.04; 95% CI 1.12–3.72). When the analysis was stratified by smoking status, an association was observed between rs16901979 and upper aerodigestive tract cancer among never-smokers. These results suggest that variants of the 8q24 chromosome may play an important role in smoking-related cancer development.

REFERENCES

1. Boyle P, Smans M (2008). *IARC Scientific Publications, Number 156, Atlas of cancer mortality in the European Union and the European Economic Area 1993-1997*. Lyon, France: International Agency for Research on Cancer.

2. Franceschi S, Bidoli E, Herrero R, et al. (2000). Comparison of cancers of the oral cavity and pharynx worldwide: etiological clues. *Oral Oncol* 36: 106-115.

3. Kjaerheim K, Gaard M, Andersen A (1998). The role of alcohol, tobacco, and dietary factors in upper aerogastric tract cancers: a prospective study of 10,900 Norwegian men. *Cancer Causes Control* 9: 99-108.

4. Sapkota A, Gajalakshmi V, Jetly DH, et al. (2007). Smokeless tobacco and increased risk of hypopharyngeal and laryngeal cancers: a multicentric case-control study from India. *Int J Cancer* 121: 1793-1798.

5. IARC (1999). *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 71 Part 1, Re-evaluation of some organic chemicals, hydrazine and hydrogen peroxide*. Lyon, France: International Agency for Research on Cancer.

6. IARC (2004). *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 85, Betel quid and areca-nut chewing and some areca-nut derived nitrosamines*. Lyon, France: International Agency for Research on Cancer.

7. Siemiatycki J, Richardson L, Straif K, et al. (2004). Listing occupational carcinogens. *Environ Health Perspect* 112: 1447-1459.

8. Guha N, Boffetta P, Wunsch F, V, et al. (2007). Oral health and risk of squamous-cell carcinoma of the head and neck and esophagus: results of two multicentric case-control studies. *Am J Epidemiol* 166: 1159-1173.

9. Dillner J (1999). The serological response to papillomaviruses. *Semin Cancer Biol* 9: 423-430.

10. Lehtinen M, Pawlita M, Zumbach K, et al. (2003). Evaluation of antibody response to human papillomavirus early proteins in women in whom cervical cancer developed 1 to 20 years later. *Am J Obstet Gynecol* 188: 49-55.

11. Meschede W, Zumbach K, Braspenning J, et al. (1998). Antibodies against early proteins of human papillomaviruses as diagnostic markers for invasive cervical cancer. *J Clin Microbiol* 36: 475-480.

12. Zumbach K, Hoffmann M, Kahn T, et al. (2000). Antibodies against oncoproteins E6 and E7 of human papillomavirus types 16 and 18 in patients with head-and-neck squamous-cell carcinoma. *Int J Cancer* 85: 815-818.

13. Kreimer AR, Clifford GM, Snijders PJ, et al. (2005). HPV16 semiquantitative viral load and serologic biomarkers in oral and oropharyngeal squamous-cell carcinomas. *Int J Cancer* 115: 329-332.

14. Smeets SJ, Hesselink AT, Speel EJ, et al. (2007). A novel algorithm for reliable detection of human papillomavirus in paraffin embedded head and neck cancer specimen. *Int J Cancer* 121: 2465-2472.

15. Herrero R, Castellsague X, Pawlita M, et al. (2003). Human papillomavirus and oral cancer: the International Agency for Research on Cancer multicenter study. *J Natl Cancer Inst* 95: 1772-1783.

16. Smith EM, Ritchie JM, Pawlita M, et al. (2007). Human papillomavirus seropositivity and risks of head and neck cancer. *Int J Cancer* 120: 825-832.

17. Kreimer AR, Clifford GM, Boyle P, et al. (2005). Human papillomavirus types in head and neck squamous-cell carcinomas worldwide: a systematic review. *Cancer Epidemiol Biomarkers Prev* 14: 467-475.

18. Forastiere A, Koch W, Trotti A, et al. (2001). Head and neck cancer. *N Engl J Med* 345: 1890-1900.

19. Coleman MP, Gatta G, Verdecchia A, et al. (2003). EUROCARE-3 summary: cancer survival in Europe at the end of the 20th century. *Ann Oncol* 14 Suppl 5: v128-v149.

20. Brennan P, Lewis S, Hashibe M, et al. (2004). Pooled analysis of alcohol dehydrogenase genotypes and head and neck cancer: a HuGE review. *Am J Epidemiol* 159: 1-16.

20. Brennan P, Lewis S, Hashibe M, et al. (2004). Pooled analysis of alcohol dehydrogenase genotypes and head and neck cancer: a HuGE review. Am J Epidemiol 159: 1-16.

21. IARC (1986). IARC monographs on the evaluation of carcinogenic risks to humans, Volume 38, Tobacco smoking. Lyon, France: International Agency for Research on Cancer.

22. IARC (2004). IARC monographs on the evaluation of carcinogenic risks to humans, Volume 83, Tobacco smoke and involuntary smoking. Lyon, France: International Agency for Research on Cancer.

23. Gandini S, Botteri E, Iodice S, et al. (2008). Tobacco smoking and cancer: a meta-analysis. Int J Cancer 122: 155-164.

24. Tuyns AJ, Esteve J, Raymond L, et al. (1988). Cancer of the larynx/hypopharynx, tobacco and alcohol: IARC international case-control study in Turin and Varese (Italy), Zaragoza and Navarra (Spain), Geneva (Switzerland) and Calvados (France). Int J Cancer 41: 483-491.

25. La Vecchia C, Bidoli E, Barra S, et al. (1990). Type of cigarettes and cancers of the upper digestive and respiratory tract. Cancer Causes Control 1: 69-74.

26. Zatonski W, Becher H, Lissowska J, et al. (1991). Tobacco, alcohol, and diet in the etiology of laryngeal cancer: a population-based case-control study. Cancer Causes Control 2: 3-10.

27. Berrino F and Crosignani P (1992). Epidemiology of malignant tumors of the larynx and lung. Ann Ist Super Sanita 28: 107-120.

28. Lehmann W, Raymond L, Faggiano F, et al. (1991). Cancer of the endolarynx, epilarynx and hypopharynx in south-western Europe: assessment of tumoral origin and risk factors. *Adv Otorhinolaryngol* 46: 145-156.

29. Farchi G (1992). Estimation of the impact of cigarette smoking reduction on mortality from tumors of the lung and larynx. *Ann Ist Super Sanita* 28: 147-153.

30. Guo X (1993). A case-control study of the etiology of laryngeal cancer in Liaoning Province. *Zhonghua Er Bi Yan Hou Ke Za Zhi* 28: 219-21, 252.

31. Zheng W, Blot WJ, Shu XO, et al. (1992). Diet and other risk factors for laryngeal cancer in Shanghai, China. *Am J Epidemiol* 136: 178-191.

32. Boyle P, Macfarlane GJ, Zheng T, et al. (1992). Recent advances in epidemiology of head and neck cancer. *Curr Opin Oncol* 4: 471-477.

33. Hamzany Y, Hadar T, Feinmesser R, et al. (2008). Laryngeal carcinoma in nonsmoking patients. *Ann Otol Rhinol Laryngol* 117: 564-568.

34. IARC (1988). *IARC monographs on the evaluation of carcinogenic risks to humans, Volume 44, Alcohol drinking*. Lyon, France: International Agency for Research on Cancer.

35. IARC (In Press). *IARC monographs on the evaluation of carcinogenic risks to humans, Volume 92, Alcohol drinking*. Lyon, France: International Agency for Research on Cancer.

36. Tavani A, Negri E, Franceschi S, et al. (1994). Attributable risk for laryngeal cancer in northern Italy. Cancer Epidemiol Biomarkers Prev 3: 121-125.

37. Franceschi S, Bidoli E, Negri E, et al. (1994). Alcohol and cancers of the upper aerodigestive tract in men and women. *Cancer Epidemiol Biomarkers Prev* 3: 299-304.

38. Blot WJ (1992). Alcohol and cancer. *Cancer Res* 52: 2119s-2123s.

39. Muscat JE and Wynder EL (1992). Tobacco, alcohol, asbestos, and occupational risk factors for laryngeal cancer. *Cancer* 69: 2244-2251.

40. Hedberg K, Vaughan TL, White E, et al. (1994). Alcoholism and cancer of the larynx: a case-control study in western Washington (United States). *Cancer Causes Control* 5: 3-8.

41. La Vecchia C, Zhang ZF, Altieri A (2008). Alcohol and laryngeal cancer: an update. *Eur J Cancer Prev* 17: 116-124.

42. Adami HO, McLaughlin JK, Hsing AW, et al. (1992). Alcoholism and cancer risk: a population-based cohort study. *Cancer Causes Control* 3: 419-425.

43. Wynder EL, Covey LS, Mabuchi K, et al. (1976). Environmental factors in cancer of the larynx: a second look. *Cancer* 38: 1591-1601.

44. Freedman ND, Park Y, Subar AF, et al. (2008). Fruit and vegetable intake and head and neck cancer risk in a large United States prospective cohort study. *Int J Cancer* 122: 2330-2336.

45. Cattaruzza MS, Maisonneuve P, Boyle P (1996). Epidemiology of laryngeal cancer. *Eur J Cancer B Oral Oncol* 32B: 293-305.

46. Negri E, Boffetta P, Berthiller J, et al. (2008). Family history of cancer: Pooled analysis in the International Head and Neck Cancer Epidemiology Consortium. *Int J Cancer* 124: 394-401.

47. Lagiou P, Georgila C, Minaki P, et al. (2008). Alcohol-related cancers and genetic susceptibility in Europe: the ARCAGE project: study samples and data collection. *Eur J Cancer Prev* .

48. Hashibe M, McKay JD, Curado MP, et al. (2008). Multiple ADH genes are associated with upper aerodigestive cancers. *Nat Genet* 40: 707-709.

49. Park SL, Chang SC, Cai L, et al. (2008). Associations between variants of the 8q24 chromosome and nine smoking-related cancer sites. *Cancer Epidemiol Biomarkers Prev* 17: 3193-3202.

5.2 Esophageal Cancer

Summary

- Over 450 000 cases and 380 000 deaths occur each year
- Squamous cell cancer predominates in low- and middle-income countries, and is typically associated with tobacco smoking and alcohol use
- Extremely high rates have been reported in Western and Central Asia (notably parts of China and Iran)
- Adenocarcinoma is increasingly important in high-income countries, and is related to obesity and chronic gastro-esophageal reflux

Cancer of the esophagus affects more than 450 000 people globally each year, and is the sixth most common cancer among men and ninth among women [2]. Survival is uniformly low, with 5-year survival rates usually less than 10%. In regions with established cancer registries that are included in the IARC *Cancer Incidence in Five Continents* series, populations with a high incidence are found among US black populations, as well as in South America, Asia, France and Africa (Table 5.2.1). Most notable are the extremely high rates for both men and women that are recorded in Cixian, China [3].

In those high-incidence registries that provide information on histological type, approximately 90% are squamous-cell carcinomas. This is in contrast to some lower-risk populations, such as Caucasian Americans, where adenocarcinomas now predominate. For example, SEER data from the same period indicate that among Caucasian Americans, who have an age-standardised incidence for esophageal cancer of 4.7/100 000 among men and 1.2/100 000 among women, 55% of cases are coded as adenocarcinoma as opposed to 45% squamous-cell carcinoma.

The main risk factors for squamous cell esophageal cancer in western countries are alcohol and tobacco consumption, which in individual studies have been found to account for 75–90% of the disease [4]. The risk of esophageal cancer increases rapidly with the amount of both tobacco and alcohol consumption, with no evidence of any threshold effect for either. Most studies show a dose-response relation with tobacco consumption, and decreases in risk are found after quitting smoking. Similarly, a dose-response relation is observed with increasing alcohol consumption.

Although alcohol and tobacco consumption are the primary lifestyle risk factors for oesophageal cancer in Western populations, dietary factors are also likely to be important. Fresh fruit and vegetable intake appears to have a strong protective effect [5], and although the relationship for particular types of fruits and vegetables is unclear, citrus fruits and green leafy vegetables appear to possess greater chemopreventative effects than other families of fruits and vegetables. Conversely, there is some evidence that frequent dietary consumption of salted meat and fish, as well as pickled vegetables may represent a risk factor.

Regarding the intake of hot beverages, consumption of hot mate, a herbal infusion consumed in parts of Southern Brazil, Argentina and Uruguay, appears to be strongly associated with development of esophageal cancer. Three case–control studies from Uruguay and Brazil have reported an increased risk among drinkers of mate, including a dose-response relationship [2,6,7]. An IARC monograph evaluation of mate consumption concluded that hot mate was *"probably carcinogenic to humans"* (Group 2A), although confounding from other lifestyle factors could not be excluded. Although mate is traditionally drunk very hot, any information on the temperature of mate consumption has been self-reported, and it is not possible to separate out a possible carcinogenic effect due to the temperature or the composition of the beverage.

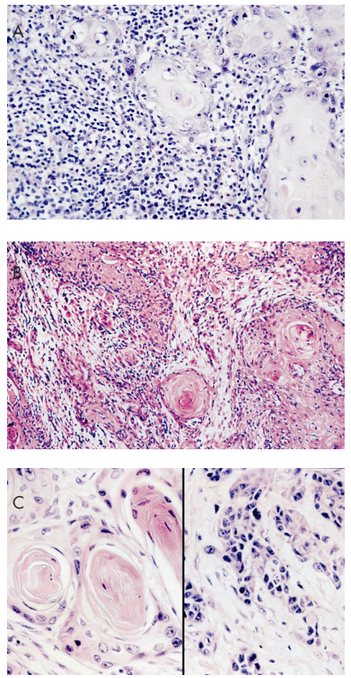


Fig. 5.2.1 *Squamous-cell carcinoma. A: Moderately differentiated. B: Well differentiated with prominent lymphoid infiltrate. C: Well differentiated areas (left) contrast with immature basal-type cells of a poorly differentiated carcinoma (right)*

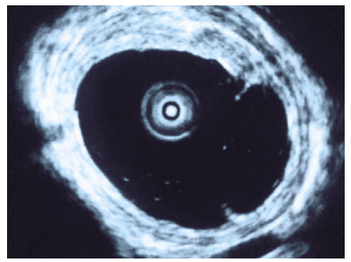
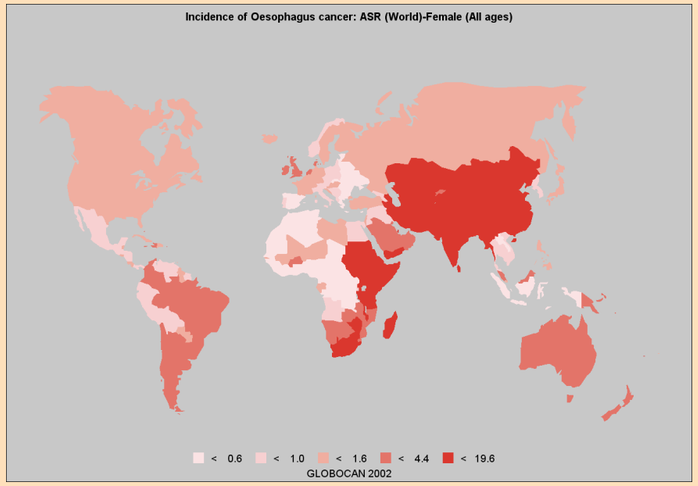


Fig. 5.2.2 *Catheter probe ultrasonograph of a squamous-cell carcinoma*

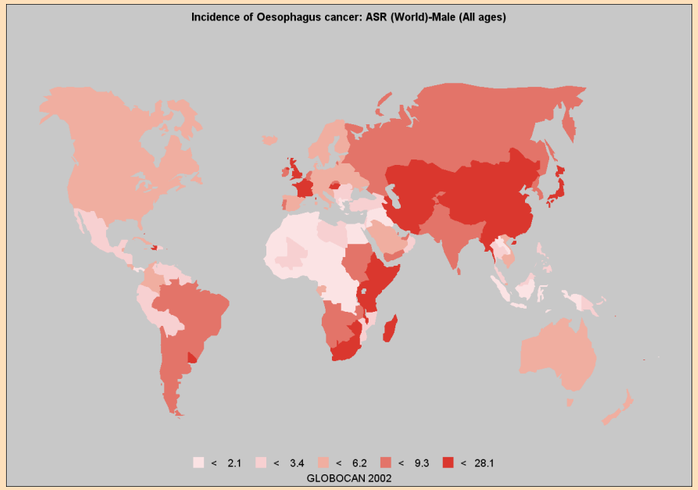
Hot tea consumption has also been suggested as a risk factor for esophageal cancer in Western populations. In a UK population-based case–control study on squamous cell cancer of the esophagus comprising 159 female case–control pairs, quantity of tea was identified as a risk factor for esophageal cancer along with a significant positive trend with temperature at which the tea was consumed (p=0.03) [8]. The increased risk for drinking tea at very hot temperatures was over threefold and, as the authors suggested, when coupled with smoking is likely to explain much of the increased incidence of esophageal cancer among UK women when compared to other European populations.

Other potential risk factors for squamous cell esophageal cancer include contamination of food products by fumonisin mycotoxins, which has been reported in studies from high-risk areas in China and Italy [9,10]. In the only prospective study of fumonisin exposure and esophageal cancer, which used sphingolipids as a biomarker of fumonison exposure in a high-risk population in Linxian, China, no relationship between fumonisis and esophageal cancer was observed [11]. Poor oral hygiene and tooth loss have also been reported to be associated with an increased risk of esophageal cancer, possibly related to alterations in oral bacterial flora and subsequent increases in the *in-vivo* production of carcinogens such as nitrosamines [12].

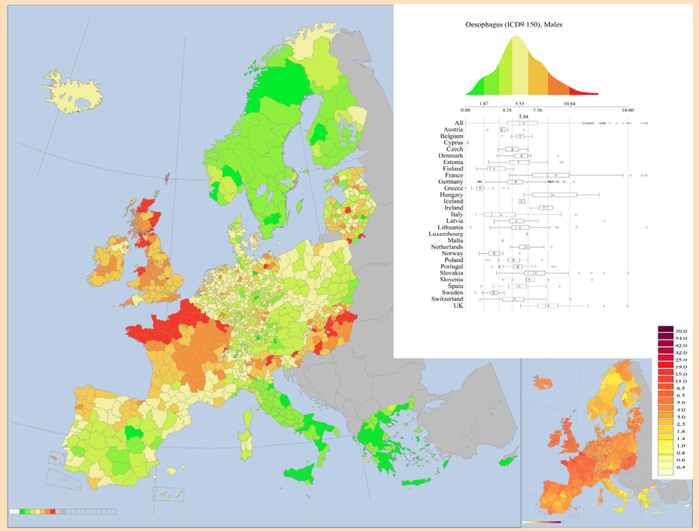
Regarding genetic susceptibility, esophageal cancer does not exhibit any strong familial component, and genetic studies of esophageal cancer have instead focused on genes such as cytochrome P 450 (CYP), gluthatione-S-tranferase (GST) and aldehyde dehydrogenase (ADH) 1C that metabolise suspected tobacco- and alcohol-derived carcinogens. No consistent findings have emerged, although most studies have been limited



World Map 5.2.1



World Map 5.2.2



European Map 5.2.1 *In males, the feature of the geographic pattern of esophageal cancer is the concentration of very high risk in northern France, extending up to the border with Belgium; there were also contiguous areas of above-average risk in the northeast of Italy, Slovenia and Hungary. Rates were also generally above average in the United Kingdom, particularly in parts of Scotland, and in Ireland.*
Lower rates were concentrated in Norway, Sweden and Finland, Greece and central and southern Italy. The geographical aldistribution was thus similar, but not identical, to that for oral cancer [Chapter 5.1] the main difference being above average mortality from esophageal cancer in the United Kingdom and Ireland [1].

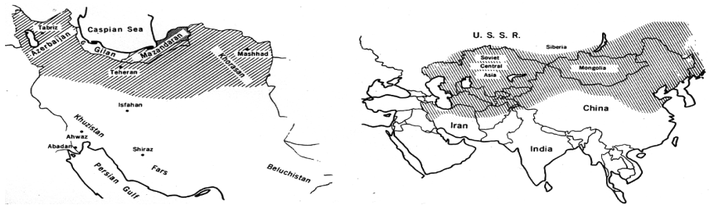


Fig. 5.2.3 *Iran and its position in the Central Asian Esophageal Cancer Belt*

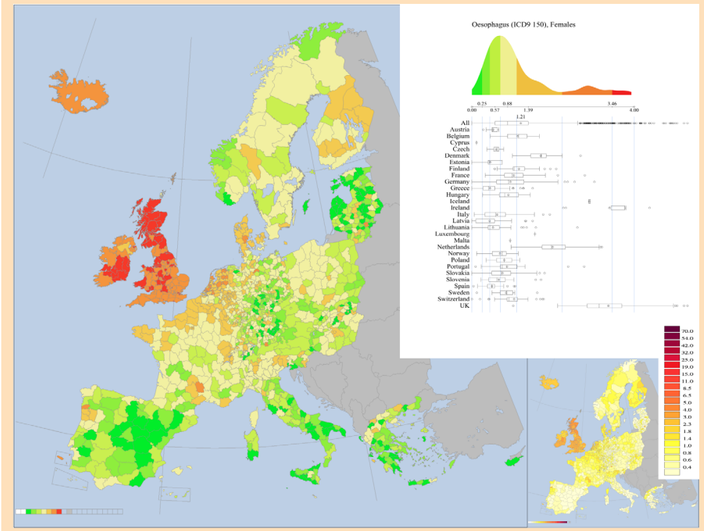
in size. Conversely, a strongly significant protective effect has been observed with ADHIB variants that encode for fast alcohol metabolism [13].

Increasing trends of esophageal adenocarcinoma have been reported, particularly in the USA and parts of Europe [14,15]. For example, incidence rates of esophageal adenocarcinoma in white males in the USA surpassed those of squamous cell cancer around 1990. The causes of this increasing trend include obesity, as well as an inverse association with *helicobactor* pylori [16,17].

Esophageal cancer in very high incidence regions

The geographical distribution of oesophageal cancer is characterised by very wide variations within relatively small areas. Although accurate cancer registry information is limited, very high rates (over 50/100 000) have been reported for both genders from northern Iran and the provinces of north central China, in certain areas of Kazakhstan and also among native Siberians [18,19]. These populations form a "Central Asian Esophageal Cancer Belt" (Figure 5.2.3), although whether these extremely high rates are due to a common risk factor is unclear. One possibility is that very high rates of esophageal cancer are linked to several factors including (i) a severely deficient in fruits and vegetables, (ii) a squamous injury from consumption of very hot beverages and (iii) intense carcinogen exposure from lifestyle factors including smoking or opium consumption. These hypotheses are however untested.

The earliest reports of the high incidence of cancer of the esophagus in northern parts of Iran go back to mid-1960s and early 1970s [20-24]. These reports emphasised the frequency of the disease in many young patients, a predominance of squamous cell cancers and a slightly higher female/male ratio. In order to investigate this finding in more detail a population based cancer registry was established in 1969 as a joint effort between Tehran University and the IARC, in the city of Babol,



European Map 5.2.2 *High rates of esophageal cancer among women were also apparent in the United Kingdom and Ireland. There was a belt of slightly above-average rates across northern France, Belgium, The Netherlands and Denmark, but no evidence of the excess risk in northeast Italy, Slovenia, Slovakia and Hungary that was seen in males [1].*
The geographical pattern observed in men can be related directly to the patterns of smoking and alcohol intake (in terms of ethanol) throughout Europe. It is much more difficult to ascribe the pattern of esophageal cancer observed in females to either these or other known risk factors. The similarity of the pattern in the ratios between the rates in men and women in each country with the corresponding pattern for oral cancer confirms that the risks arise from common etiological and/or cultural factors.

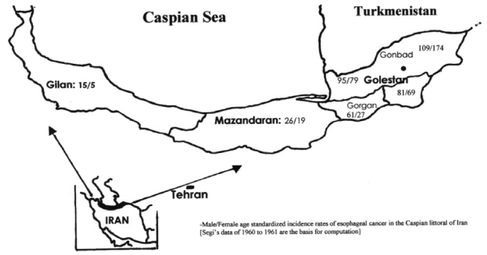


Fig. 5.2.4 *Age-standardised incidence rates /100 000 of esophageal cancer according to the data of the Caspian Littoral Cancer Registry, 1970*

Fig. 5.2.5 *A highly infiltrative adenocarcinoma in a Barrett oesophagus*

in Mazandaran province, on the eastern coast of the Caspian Littoral. This was subsequently extended to the western province of Gilan and the neighboring city of Ardabil in the southwest of the Caspian Sea in 1970 (Figure 5.2.4).

Initial results from this cancer registry emphasised the very high incidence of esophageal cancer in the eastern portion of Mazandaran province close to Turkmenistan (the Gonbad and Gorgan districts, now Golestan province), and particularly in the semi-desert plain settled mainly by people of Turkoman ethnicity, with incidence rates of 109/100 000 among men and 174/100 000 among women [21,22]. Sharp changes in the incidence of esophageal cancer were evident between regions only a few hundred kilometres apart. The incidence dropped to 17.2/100 000 for men and 5.5/100 000 for women in Gilan, 500

Registries			% by histological type - both sexes		
Africa	**Male**	**Female**	**SCC**	**Adeno**	**Other/unknown**
Zimbabwe, Harare	15.1	5.3	86.9	5.7	7.3
Uganda, Kyadondo	14.1	8.4	79.4	9.3	11.2
America, Central and South					
Brazil, Brasilia	13.1	3.9	67.1	15.7	17.2
Brazil, Sao Paolo	12.0	2.2	82.5	10.5	7.0
Brazil, Cuiaba	11.7	2.7	76.1	11.3	12.6
America, North					
USA, District of Columbia: Black	14.8	3.5	84.7	10.5	4.7
USA, South Carolina: Black	14.4	2.5	57.0	36.7	6.3
USA, Georgia: Black	11.1	3.1	89.3	7.0	3.7
Asia					
China, Jiashan	20.2	4.8	92.9	6.3	0.8
China, Zhongshan	16.5	1.9	73.5	3.0	23.6
Japan, Miyagi	15.4	2.2	91.3	3.0	5.8
Japan, Yamagata	13.0	1.6	90.1	5.6	4.3
Japan, Hiroshima	12.1	2.0	94.6	1.7	3.6
Europe					
France, Calvados	14.6	2.1	81.2	12.4	6.4
France, Somme	14.1	1.5	71.3	21.0	7.7
France, Manche	13.1	1.6	85.8	10.3	3.9
France, Loire-Atlantique	12.7	1.6	71.0	24.9	4.1
Scotland	11.7	4.7	42.6	51.2	6.2

Table 5.2.1 *Cancer registries with highest esophageal cancer rates, 1993-1997 – CI5 Vol IX*

kilometres to the west. Recent reports from the Ardibil cancer registry and from an esophageal cancer survey carried out in the eastern part of the Caspian littoral have confirmed these early findings [25,26].

Factor	Alteration
Tumour suppressor genes	
p53	60% mutation - high-grade intraepithelial neoplasia and carcinoma
APC	Late in intraepithelial neoplasia-carcinoma sequence
FHIT	Common, early abnormalities
CDKN2A (p16INK4A)	Hypermethylation common in intraepithelial neoplasia
Growth factor receptors	
CD95/APO/Fas	Shift to cytoplasm in carcinoma
EGFR	Expressed in 60% of carcinomas, gene amplification
c-erbB2	Late in dysplasia-carcinoma sequence, gene amplification
Cell adhesion	
E-cadherin	Loss of expression in intraepithelial and invasive carcinoma
Catenins	Similar loss of expression to E-cadherin
Proteases	
UPA	Prognostic factor in carcinoma
Proliferation	
Ki-67	Abnormal distribution in high-grade intraepithelial neoplasia
Membrane trafficking	
rab11	High expression in low-grade intraepithelial neoplasia

Table 5.2.2 *Genes and proteins involved in the development of adenocarcinoma from Barrett oesophagus*

REFERENCES

1. Boyle P, Smans M (2008). *IARC Scientific Publications, Number 156, Atlas of cancer mortality in the European Union and the European Economic Area 1993-1997*. Lyon, France: International Agency for Research on Cancer.

2. Castellsague X, Munoz N, De Stefani E, et al. (2000). Influence of mate drinking, hot beverages and diet on esophageal cancer risk in South America. *Int J Cancer* 88: 658-664.

3. Parkin DM, Whelan SL, Ferlay J, et al. (2002). *IARC scientific publications, Number 155, Cancer incidence in five continents, Volume VIII*. Lyon, France: International Agency for Research on Cancer.

4. Adami HO, Hunter DJ, Trichopoulos D (2002). *Textbook of cancer epidemiology*. Oxford: Oxford University Press.

5. World Cancer Research Fund / American Institute for Cancer Research (2007). *Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective*. Washington, DC: World Cancer Research Fund / American Institute for Cancer Research.

6. De Stefani E, Munoz N, Esteve J, et al. (1990). Mate drinking, alcohol, tobacco, diet, and esophageal cancer in Uruguay. *Cancer Res* 50: 426-431.

7. Sewram V, De Stefani E, Brennan P, et al. (2003). Mate consumption and the risk of squamous cell esophageal cancer in uruguay. *Cancer Epidemiol Biomarkers Prev* 12: 508-513.

8. Sharp L, Chilvers CE, Cheng KK, et al. (2001). Risk factors for squamous-cell carcinoma of the oesophagus in women: a case-control study. *Br J Cancer* 85: 1667-1670.

9. Li JY, Ershow AG, Chen ZJ, et al. (1989). A case-control study of cancer of the esophagus and gastric cardia in Linxian. *Int J Cancer* 43: 755-761.

10. Simonato L, Franceschi S, Zambon P (2000). A population at high risk for esophageal cancer in the north-east of Italy. *Mutat Res* 462: 355-363.

11. Abnet CC, Borkowf CB, Qiao YL, et al. (2001). Sphingolipids as biomarkers of fumonisin exposure and risk of esophageal squamous-cell carcinoma in china. *Cancer Causes Control* 12: 821-828.

12. Abnet CC, Qiao YL, Mark SD, et al. (2001). Prospective study of tooth loss and incident esophageal and gastric cancers in China. *Cancer Causes Control* 12: 847-854.

13. Hashibe M, Boffetta P, Zaridze D, et al. (2006). Evidence for an important role of alcohol- and aldehyde-metabolizing genes in cancers of the upper aerodigestive tract. *Cancer Epidemiol Biomarkers Prev* 15: 696-703.

14. Devesa SS, Blot WJ, Fraumeni JF (1998). Changing patterns in the incidence of esophageal and gastric carcinoma in the United States. *Cancer* 83: 2049-2053.

15. Wayman J, Forman D, Griffin SM (2001). Monitoring the changing pattern of esophago-gastric cancer: data from a UK regional cancer registry. *Cancer Causes Control* 12: 943-949.

16. Corley DA, Kubo A, Zhao W (2008). Abdominal obesity and the risk of esophageal and gastric cardia carcinomas. *Cancer Epidemiol Biomarkers Prev* 17: 352-358.

17. Rokkas T, Pistiolas D, Sechopoulos P, et al. (2007). Relationship between Helicobacter pylori infection and esophageal neoplasia: a meta-analysis. *Clin Gastroenterol Hepatol* 5: 1413-7, 1417.

18. Li L and Rao K (2000). A statistical analysis of registered cancer morbidity and mortality in 11 counties, China (1988-1992). *Bull Chinese Cancer* 9: 435-447.

19. Zaridze DG, Marochko A, Basieva T, et al. (1993). Cancer incidence in the native peoples of far eastern Siberia. *Int J Cancer* 54: 889-894.

20. Barekat AA, Saidi F, Dutz W (1971). Cancer survey in south Iran with special reference to gastrointestinal neoplasms. *Int J Cancer* 7: 353-363.

21. Habibi A (1965). Cancer in Iran. A survey of the most common cases. *J Natl Cancer Inst* 34: 553-569.

22. Habibi A (1970). [Survey on the most common cancers in Iran]. *Bull Cancer* 57: 133-150.

23. Habibi A (1970). Cancer in Iran. Statistical review on 28,000 cases. *Pathol Microbiol (Basel)* 35: 181-183.

24. Haghighi P and Nasr K (1971). Gastrointestinal cancer in Iran. *J Chronic Dis* 24: 625-633.

25. Sadjadi A, Malekzadeh R, Derakhshan MH, et al. (2003). Cancer occurrence in Ardabil: results of a population-based cancer registry from Iran. *Int J Cancer* 107: 113-118.

26. Saidi F, Sepehr A, Fahimi S, et al. (2000). Oesophageal cancer among the Turkomans of northeast Iran. *Br J Cancer* 83: 1249-1254.

5.3 Stomach Cancer

Summary

- In most countries, a steady decline in gastric cancer mortality rates has been observed in the last few decades
- The bacterium *Helicobacter pylori*, which establishes long-term infection of the stomach, is a major risk factor for gastric cancer, increasing the incidence rate by a factor of 6. It is estimated to be responsible for 63% of all cases of non-cardia gastric cancer worldwide
- Genetic variation between strains of *Helicobacter* pylori may play an important role in gastric cancer risk
- Epidemiological studies suggest a diet rich in fresh fruits and vegetables is protective against gastric cancer. However, intervention trials that supplement the diet with anti-oxidant vitamins have not been successful in reducing gastric cancer risk.

According to the most recent available estimates, gastric cancer is the fourth most common cancer worldwide, with 934 000 cases per year [2]. Survival from gastric cancer is poor since patients are often diagnosed with advanced disease. In the USA, for example, five-year survival is 24% [3].

Gastric cancer incidence shows wide geographical variation. World Maps 5.3.1 and 5.3.2 shows a map of the incidence rates of gastric cancer in males, standardised to the world population. Incidence rates in females follow a similar pattern, but are about 50% lower. This sex ratio cannot be entirely attributed to differences in the prevalence of known risk factors between the sexes, and a protective role of female hormones has been hypothesized [4].

The high-risk areas are in Japan, China, Eastern Europe and certain countries in Latin America. Low-risk populations are seen among whites in North America, India, the Philippines, most countries in Africa, some western European countries and Australia. There is a 15–20-fold variation in risk between the highest- and the lowest-risk populations. Substantial variations in gastric cancer incidence may also be found within countries; a good example is Italy, where there is threefold variation in risk within the country, with male incidence rates ranging between 10 and 30 per 100 000 [5].

Gastric cancer incidence rates in both sexes have been declining worldwide for several decades. The precise reasons for this decline are unknown. Figure 5.3.1 illustrates the decline of gastric cancer mortality rates in men in Northern Europe from 1950 to 2005. In 1950, all countries illustrated in Figure 5.3.1 were high-risk countries for gastric cancer, with standardised mortality rates in men over 30 per 100 000. Now, all have mortality rates under 10 per 100 000, with the exception of the Baltic states Latvia, Lithuania and Estonia. Even in these countries, mortality rates in both men and women are in decline.

When cancers of the gastric cardia, the proximal part of the stomach, are analysed separately, incidence rates show a strong increase in some industrialised countries [6]. The distinct time trend shown by cardia cancer is an indication that it has a different etiology. There has been a concomitant rise in the incidence of adenocarcinoma of the oesophagus, which suggests that gastric cardia shares the same risk factors as cancers that arise in the lowest part of the oesophagus, namely obesity, gastro-oesophageal reflux and its occasional sequel, Barrett's oesophagus.

Gastric carcinogenesis is a long-term process, taking several decades. The progression from normal tissue to cancer has intermediate stages of chronic gastritis, gastric atrophy, intestinal metaplasia and dysplasia [7]. These precursor lesions, which may be asymptomatic, can be diagnosed by taking gastric biopsies. Observational studies and randomised trials have also studied these precursor lesions in relation to risk factors for gastric cancer.

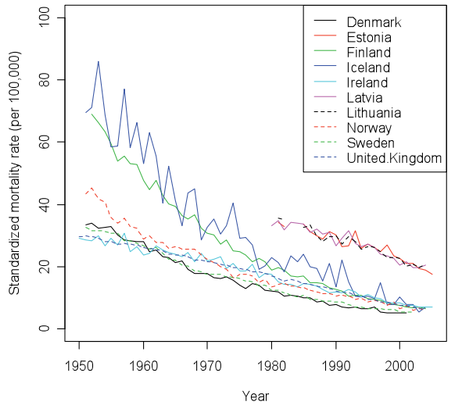


Fig. 5.3.1 *Mortality from gastric cancer in males in Northern Europe 1950–2005*

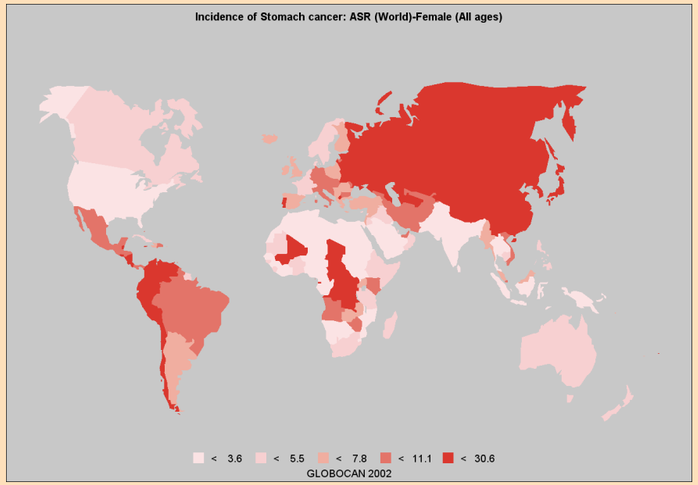
Risk factors for gastric cancer

Epidemiological evidence, mainly from case–control studies, suggests that a diet rich in fresh fruits and non-starchy vegetables is associated with a lower risk of gastric cancer. High salt intake has also been identified as a probable risk factor [8]. The hypothesis that fresh fruits and vegetables have a protective effect through the action of vitamins with anti-oxidant properties (e.g., vitamin C, beta-carotene and vitamin E) led to a number of intervention trials on gastric cancer or its precursor lesions using anti-oxidant vitamin supplementation [9].

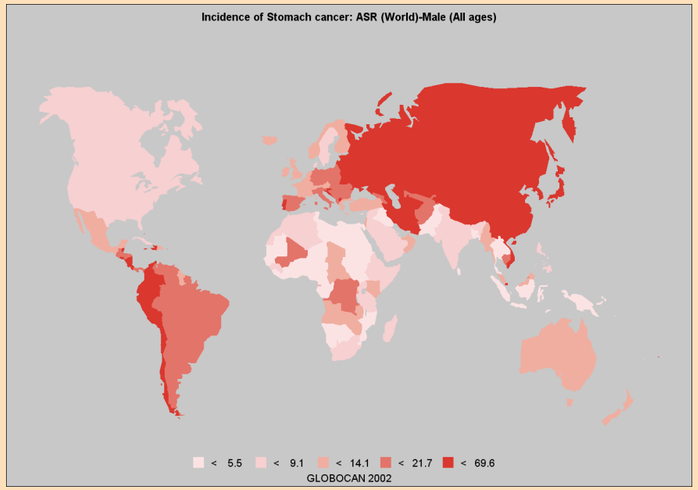
Helicobacter pylori (H. pylori) is a spiral gram-negative bacterium that colonises the stomach. It is one of the most common infections in humans with an estimated prevalence of 50% worldwide and 90% in developing countries. In high-prevalence populations, infection is rapidly acquired in childhood and persists throughout life. Prevalence of *H. pylori* infection is declining in many developed countries. It is believed that this is mainly a cohort effect, with the prevalence of infection declining in successive birth cohorts. Later acquisition of *H. pylori* may also contribute to low infection prevalence in children and young adults.

H. pylori was first isolated by Marshall and Warren (1984), who demonstrated its causal role in gastritis and peptic ulcer disease, and were awarded the 2005 Nobel prize for Medicine for their discovery. In 1994, an expert working group convened by IARC classified *H. pylori* as carcinogenic to humans [10] based on epidemiological evidence for its association with gastric cancer and gastric mucosa-associated lymphoid tissue (MALT) lymphoma. Since then, evidence has continued to accumulate for the causal role of *H. pylori* in gastric cancer.

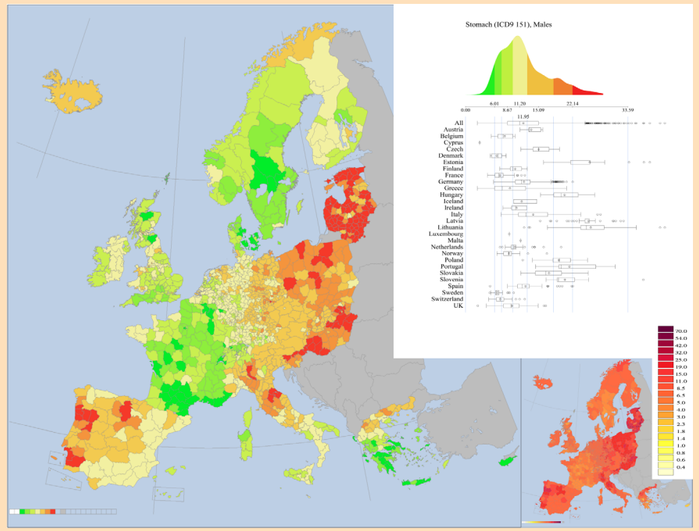
The strongest epidemiological evidence for the role of *H. pylori* in gastric cancer comes from a combined analysis of 10 prospective studies in which *H. pylori* antibodies were measured in stored blood samples, taken years before diagnosis of gastric cancer [11]. In this pooled



World Map 5.3.1

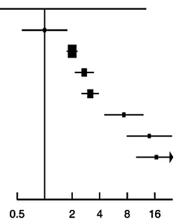


World Map 5.3.2



European Map 5.3.1 *There are very striking–and closely similar–geographic patterns for stomach cancer mortality in males and females. Moving broadly from southwest to northeast, there is a concentration of high rates in Portugal and much of the adjoining area of central and northern Spain. Rates were below average in the United Kingdom and Ireland, and in most of the mainland of western Europe; rates were also low in Scandinavia.*
Rates were above average in northern (but not southern) Greece, central and northern Italy, Austria, the east of Germany and the Czech Republic, and were highest across almost all of Slovenia, Slovakia, Hungary, Poland and the Baltic countries [1]

Diagnosis	cagA+ Hp+ /cagA- Hp+	OR[1] (95%CI)	FSE[2]	OR & 95% FCI[3]
Normal & superficial gastritis	16/48	1.00	0.291	
Chronic gastritis	346/532	2.00 (1.11-3.60)	0.071	
Chronic atrophic gastritis	124/144	2.71 (1.46-5.05)	0.123	
IM type I	162/166	3.16 (1.71-5.83)	0.111	
IM type II	53/24	7.35 (3.45-15.6)	0.250	
IM type III	61/15	14.0 (6.22-31.4)	0.291	
Dysplasia	90/18	16.7 (7.75-35.9)	0.260	



[1] *Odds ratio and 95% confidence interval adjusted for age and sex.*

[2] *Floating standard error on log scale.*

[3] *Odds ratio and 95% floating confidence interval adjusted for age and sex.*

Fig. 5.3.2 *The association between severity of precancerous lesions and H. pylori infection by cagA-genotype [16]*

analysis, *H. pylori* was not associated with gastric cardia cancer (relative risk=1.0, 95% CI 0.7–1.4). For non-cardia gastric cancers, however, the relative risk was 3.0 (95% CI 2.3–3.8). When analysis was restricted to blood samples taken more than 10 years before diagnosis, the relative risk was increased to 5.9 (95% CI 3.4–10.3).

The change in relative risk with time illustrates a hypothesis about the effect of progression to gastric cancer on *H. pylori* infection. The development of widespread gastric atrophy, a precursor lesion of gastric cancer, results in a reduction in bacterial load and consequent loss

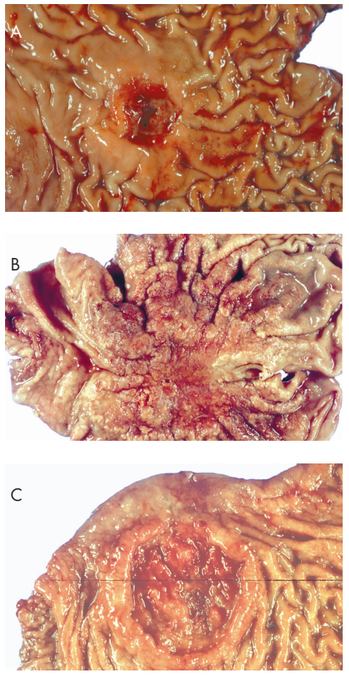
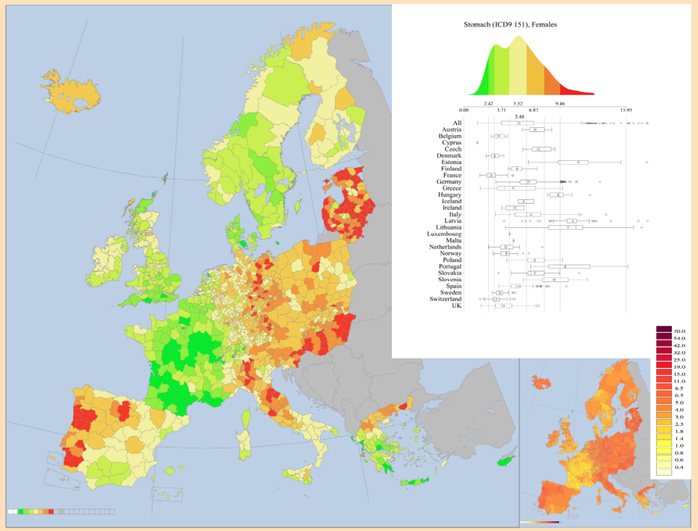


Fig. 5.2.3 *Advanced gastric carcinoma with varying degrees of infiltration*



European Map 5.3.2 *A clear message is the close similarity of the geographic patterns of stomach cancer observed in males and in females. This is present when considering the maps visually and is reinforced when statistical analyses are conducted [1]. There are traditional explanations put forward to explain some of the patterns apparent in the maps: the high rates in Portugal have been associated with the widespread practice of eating salted fish, and the high rates in Italy, Germany and Austria have been associated with cured meats. These hypotheses need to be re-assessed and tested as does the etiology underlying the regional variation in Greece.*
The important role of Helicobacter pylori in the etiology of stomach cancer provides an unusual opportunity for prevention via the development of an effective vaccine. Although the risk of stomach cancer is diminishing throughout Europe, pinpointing the risk factors responsible could help accelerate the decline of this form of cancer which has relatively poor survival (European average 22% in males and 26% in females at five years after diagnosis).

of antibody response. Therefore, measurements of *H. pylori* antibodies in gastric cancer cases are not considered reliable unless taken many years before diagnosis.

Based on the estimated relative risk of 5.9, the proportion of non-cardia gastric cancer attributable to *H. pylori* has been estimated to be 63% [12]. This aggregate measure of risk may conceal considerable variation between *H. pylori* strains. *H. pylori* is genetically highly diverse, and there is evidence that distinct genetic lineages of *H. pylori* differ in their pathogenicity. The most commonly studied pathogenicity genes are the cytotoxin-associated (*cagA*) gene and the vacuolating cytotoxin (*vacA*) gene. The *cagA* gene, which is not present in all strains, is considered to be a marker of a pathogenicity island of approximately 35 000 base pairs, encoding a type IV secretion system that transfers the CagA protein into the host cells [13]. Infection with *cagA*-positive strains increases the risk of atrophic gastritis and gastric cancer [14,15]. The *vacA* gene encodes a vacuolating cytotoxin that is excreted by *H. pylori* and damages epithelial cells. The *vacA* gene is present in all strains, but shows variation in *H. pylori* strains isolated from different populations worldwide. The *vacA* and *cagA* genotypes of *H. pylori* are strongly linked.

Figure 5.3.2 shows the results of a cross-sectional study on precancerous lesions of the stomach based on detection of *H. pylori* DNA from gastric biopsies [16]. Subjects in the study who were infected with *cagA*-positive *H. pylori* strains were at substantially increased risk of advanced precancerous lesions compared with uninfected subjects. Conversely, infection with *cagA*-negative *H. pylori* was not associated with any precursor lesion except chronic gastritis. These findings strongly implicate *cagA*-positive strains of *H. pylori* in gastric carcinogenesis.

Genetic susceptibility

The descriptive epidemiology of gastric cancer indicates that the risk is dominated by environmental causes. There may, however, still be a role for genetic factors. Individuals with blood group A have been known for decades to have an approximately 20% excess of gastric cancer compared with other blood groups. Germline mutations in a gene encoding the cell adhesion protein E-cadherin (CDH1) have also been found in familial diffuse gastric cancer [17].

One summary measure of the possible contribution of genetic risk factors to gastric cancer is the familial relative risk (FRR), the relative risk given gastric cancer in a first-degree relative. The FRR can be estimated from population-based studies that link cancer registries with a genealogical database. Three such studies have been conducted in Utah, USA [18], Sweden [19] and Iceland [20], giving FRR estimates of 2.09 (0.99–0.356), 1.31 (0.97–1.70), and 1.90 (1.74–2.05) respectively. Hence there is modest but consistent evidence for an increase in risk among relatives of gastric cancer cases. The impact of this familial aggregation in terms of attributable fraction is small however. In the Swedish study, the population attributable fraction of gastric cancer due to familial aggregation was estimated to be 0.45%. Moreover, the FRR is not

only a measure of the effect of shared genotype, but also includes the effect of shared environmental risk factors within the family. The studies in Sweden and Iceland found significantly elevated risk among spouses of gastric cancer patients.

Studies relating individual genes to gastric cancer risk have focused on candidate genes that may modulate the host response to infection with *H. pylori*. In particular, polymorphisms in interleukin-1B (IL-1B) and IL-1 receptor agonist (IL-1RN) genes have been extensively analysed, but results are not consistent between studies. Three independent meta-analyses have now been published, summarising the pooled results of studies on these polymorphisms, and all three reach slightly different conclusions [21-23]. This lack of agreement arises from the substantial heterogeneity between different studies conducted in different populations. A plausible explanation for this heterogeneity is that gastric cancer risk and susceptibility are determined by a combination of host genotype and virulent *H. pylori* strain genotype. Both factors must be measured to accurately quantify the risk.

Prevention of gastric cancer

The two major changes that could be made at a population level to reduce gastric cancer incidence are improvement in diet and reduction in the prevalence of *H. pylori*. These changes are already taking place in many populations, as a consequence of economic development, and may explain the decline observed in gastric cancer incidence. Active intervention in a population requires proof that the intervention is effective, and this can only come from randomised trials.

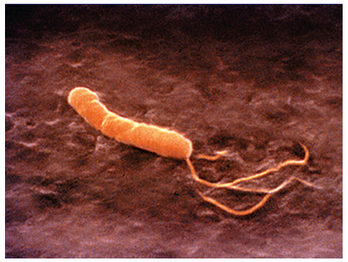


Fig. 5.3.4 *The Helicobacter pylori bacterium structure as revealed by scanning electron microscopy*

Several trials have been conducted using supplementation with selected vitamins as an intervention, and with gastric precancerous lesions or gastric cancer as an endpoint. The aim of vitamin supplementation in these trials was to simulate improved diet, assuming that the protective micronutrients in a healthy diet have been correctly identified. The results of these trials, however, have generally been disappointing, and it is unlikely that anti-oxidant vitamin supplementation is an effective tool for gastric cancer control [9]. Nevertheless, the negative results of randomised trials cannot be considered to contradict the epidemiological evidence for a protective effect of fresh fruits and vegetables, since the dose, duration and timing of anti-oxidant vitamin exposure in such trials are not directly comparable with a life-long healthy diet.

Several treatment regimens have been used to eradicate *H. pylori* infection, but triple therapy including bismuth salts, amoxicillin and clarithromycin is currently the regimen of choice. Randomised trials of anti-*H. pylori* treatment are reviewed by Correa [7], who concludes that curing *H. pylori* infection results in a modest retardation of the precancerous process, but does not prevent all cancers. The available trials of anti-*H. pylori* treatment are limited by the fact that they were conducted in adults in an advanced state of atrophy or intestinal metaplasia. It is possible that the impact on gastric cancer prevention may be magnified by eliminating *H. pylori* at an earlier stage of the precancerous process.

Conclusions

Geographical distribution and time trends suggest that the risk of gastric cancer is strongly determined by environmental factors. Etiological studies point to infection with *H. pylori* and poor diet as the main determinants of gastric cancer risk. Despite the long-term decline of gastric cancer incidence in many populations, there is considerable opportunity for active intervention to reduce the burden of gastric cancer, most notably the eradication of *H. pylori* in high-risk populations.

REFERENCES

1. Boyle P, Smans M (2008). *IARC Scientific Publications, Number 156, Atlas of cancer mortality in the European Union and the European Economic Area 1993-1997.* Lyon, France: International Agency for Research on Cancer.

2. Parkin DM, Bray F, Ferlay J, et al. (2005). Global cancer statistics, 2002. *CA Cancer J Clin* 55: 74-108.

3. Ries LA, Melbert D, Krapcho M, et al. (2007). *SEER Cancer Statistics Review, 1975-2004.* Bethesda, MD: National Cancer Institute.

4. Chandanos E and Lagergren J (2008). Oestrogen and the enigmatic male predominance of gastric cancer. *Eur J Cancer* 44: 2397-2403.

5. Curado MP, Edwards B, Shin HR, et al. *IARC scientific publications, Number 160, Cancer Incidence in Five Continents, Vol. IX.* Available from: http://www-dep.iarc.fr/ Date Accessed: October 12, 2008.

6. Devesa SS, Blot WJ, Fraumeni JF, Jr. (1998). Changing patterns in the incidence of esophageal and gastric carcinoma in the United States. *Cancer* 83: 2049-2053.

7. Correa P (2004). Is gastric cancer preventable? *Gut* 53: 1217-1219.

8. World Cancer Research Fund / American Institute for Cancer Research (2007). *Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective.* Washington, DC: AICR / World Cancer Research Fund

9. Plummer M, Vivas J, Lopez G, et al. (2007). Chemoprevention of precancerous gastric lesions with antioxidant vitamin supplementation: a randomized trial in a high-risk population. *J Natl Cancer Inst* 99: 137-146.

10. IARC (1994). IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 61, schistosomes, liver flukes and helicobacter pylori. Lyon, France: International Agency for Research on Cancer.

11. Helicobacter and Cancer Collaborative Group (2001). Gastric cancer and Helicobacter pylori: a combined analysis of 12 case control studies nested within prospective cohorts. *Gut* 49: 347-353.

12. Parkin DM (2006). The global health burden of infection-associated cancers in the year 2002. *Int J Cancer* 118: 3030-3044.

13. Hatakeyama M (2006). Helicobacter pylori CagA – a bacterial intruder conspiring gastric carcinogenesis. *Int J Cancer* 119: 1217-1223.

14. Blaser MJ, Perez-Perez GI, Kleanthous H, et al. (1995). Infection with Helicobacter pylori strains possessing cagA is associated with an increased risk of developing adenocarcinoma of the stomach. *Cancer Res* 55: 2111-2115.

15. Kuipers EJ, Perez-Perez GI, Meuwissen SG, et al. (1995). Helicobacter pylori and atrophic gastritis: importance of the cagA status. *J Natl Cancer Inst* 87: 1777-1780.

16. Plummer M, van Doorn LJ, Franceschi S, et al. (2007). Helicobacter pylori cytotoxin-associated genotype and gastric precancerous lesions. *J Natl Cancer Inst* 99: 1328-1334.

17. Guilford P, Hopkins J, Harraway J, et al. (1998). E-cadherin germline mutations in familial gastric cancer. *Nature* 392: 402-405.

18. Goldgar DE, Easton DF, Cannon-Albright LA, et al. (1994). Systematic population-based assessment of cancer risk in first-degree relatives of cancer probands. *J Natl Cancer Inst* 86: 1600-1608.

19. Hemminki K and Jiang Y (2002). Familial and second gastric carcinomas: a nationwide epidemiologic study from Sweden. *Cancer* 94: 1157-1165.

20. Amundadottir LT, Thorvaldsson S, Gudbjartsson DF, et al. (2004). Cancer as a complex phenotype: pattern of cancer distribution within and beyond the nuclear family. *PLoS Med* 1: e65.

21. Camargo MC, Mera R, Correa P, et al. (2006). Interleukin-1beta and interleukin-1 receptor antagonist gene polymorphisms and gastric cancer: a meta-analysis. *Cancer Epidemiol Biomarkers Prev* 15: 1674-1687.

22. Kamangar F, Cheng C, Abnet CC, et al. (2006). Interleukin-1B polymorphisms and gastric cancer risk–a meta-analysis. *Cancer Epidemiol Biomarkers Prev* 15: 1920-1928.

23. Wang P, Xia HH, Zhang JY, et al. (2007). Association of interleukin-1 gene polymorphisms with gastric cancer: a meta-analysis. *Int J Cancer* 120: 552-562.

5.4 Liver Cancer

Summary

> More than 80% of cases of hepatocellular carcinoma occur in Asia and Africa and irrespective of etiology, the incidence rate is more than twice as high in men as in women

> In Africa and Asia, hepatocellular carcinoma is most frequently caused by hepatitis B virus infection; concomitant dietary exposure to aflatoxins multiplies the risk. In Japan, this cancer is predominantly caused by hepatitis C virus infection

> In Western countries, liver cirrhosis due to chronic alcohol abuse is a major etiological factor. The spread of hepatitis C virus is a major challenge and is responsible for increasing rates of liver cancer in the USA and in parts of Europe

> Hepatocellular carcinoma is almost always lethal, survival from time of diagnosis often being less than six months; only 5–9% of patients survive five years or more

Hepatocellular carcinoma (HCC) arises from hepatocytes and accounts for about 80% of all primary cancers of the liver. Other tumour types include intrahepatic cholangiocarcinoma (tumours of that part of the bile duct epithelium located within the liver), hepatoblastoma (a malignant embryomal tumour of childhood) and angiosarcoma (arising from blood vessels) and are relatively rare compared to HCC. However, in some parts of the world such as eastern Thailand, cholangiocarcinoma occurs at a high rate as the result of infection of hepatic bile ducts by liver flukes (*Opistorchis viverrini*) due to the consumption of infected raw fish. The development of flukes in bile ducts induces a chronic inflammatory state that represents a major risk factor for the neoplastic transformation of bile duct epithelial cells.

Epidemiology

Liver cancer ranks third amongst the organ-specific causes of cancer-related deaths in men worldwide. Liver cancer accounts for approximately 6% of all new cancer cases diagnosed worldwide. Liver cancer is the fifth most common cancer among men worldwide, but is the eighth in women [2,3]. Globally, men are about three times as likely as women to be afflicted and the difference is higher in high-incidence than low-incidence areas. Liver cancer is a major health problem in low-resource countries, where more than 80% of the worldwide total occur (over 500 000 new annual cases). The highest incidence rates are recorded in China (55% of the world total), Japan, South East Asia and sub-Saharan Africa. In both high- and low-incidence areas, there is great variability in incidence among ethnic groups [4].

Age-specific rates of incidence show marked geographical variation. In the Gambia, age-specific rates peak in the 45–55 years age range, whereas in Europe and the USA, high risk is associated with older age.

Time trends in liver cancer are difficult to interpret due to changes in classification and variable inclusion of metastatic tumours. However, the incidence of hepatocellular carcinoma in Japan, the UK, Germany and the USA and several Nordic countries has demonstrated a sustained increasing trend over the past two decades and has become progressively associated with younger age groups [5]. Mortality rates have increased in several regions, including France. Some of these increases may be the result of improved detection, but the main causal factors are the spread of hepatitis C virus infection as well as the growing impact of non-alcoholic metabolic diseases.

Etiology

Hepatitis viral infections. Globally, the etiology of HCC is dominated by the interaction of viral and environmental risk factors. These factors and their overall impact are summarised in Table 5.4.1. The carcinogenic effect of chronic infection with hepatitis viruses B and C is well demonstrated by epidemiological and experimental evidence. Consistent epidemiological data have associated a significant risk of HCC with chronic HBV infection, which accordingly has been categorised as causing cancer in the context of IARC Monograph evaluations [6]. Worldwide, the proportion of HCC attributable to chronic hepatitis is about 54% for HBV and 31% for HCV. These figures should be considered as conservative estimates. Persistent, chronic HBV infection is usually defined by the release into the bloodstream of the surface antigen HBsAg for a period of at least 6 months post infection. There is evidence that HBV can also persist in an occult form, with no release of HBsAg but persistence of viral DNA. These occult infections may represent the terminal phase in the natural course of HBV persistent infection and they should be taken into account in estimates of the risk of HCC attributable to HBV. Furthermore, co-infections with HBV and HCV may occur, with a cumulative effect on the risk of HCC that varies from additive to multiplicative. Thus, overall, the burden of liver cancer attributable to hepatitis viral infections is likely to be close to 90%.

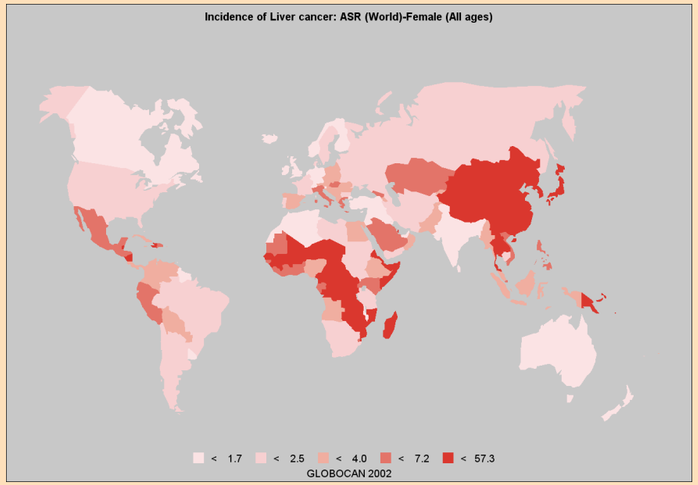
It should be noted that the impact of hepatitis virus infections shows substantial geographic variation, in both the population prevalence of persistent infection and the specific genetic characteristic of the viruses involved. In many low-resource tropical countries, chronic HBV carriage is high in the general population (10–15%), and it can be estimated that over two thirds of liver cancer cases in low-resource countries are attributable to this virus [7]. HBV is particularly implicated in hepatocellular carcinoma in Africa and Asia, and HCV in Japan and the USA. However, the relationship between chronic carrier prevalence and incidence of HCC is a complex one, and striking discrepancies exist in some populations and geographic areas. Inuits (Canada, Greenland) and Maoris (New Zealand) have among the highest population rates of HBV carriage in the world but they show relatively modest incidences of HCC. HBV exists in 8 distinct genotypes (defined by groups of viruses that have 8% or more differences in their DNA sequence, Figure 5.4.1), which differ by their infectivity, transmission mechanisms, pathogenicity, rate at which they persist, and risk of chronic liver disease and HCC. For example, Genotype F, which is found among the native population of Alaska, carries a risk of HCC several fold higher than most other genotypes.

There are an estimated 400 million HBV chronic carriers worldwide. Of those carriers, at least 50% will remain asymptomatic with progressive disappearance of HBsAg. Of the remainder, many will develop chronic liver disease of variable severity. A common, severe condition is liver cirrhosis. In western countries, about 70–90% of hepatocellular carcinomas develop in patients with macronodular cirrhosis. In eastern Asia and West Africa, the proportion of patients with pre-existing liver cirrhosis at the time of HCC diagnosis appears to be much lower, perhaps in the range of 25–50%. However, there is a lack of detailed prospective studies on precursor liver conditions in these areas. Therefore, cirrhosis is not an obligatory pre-cancer step to HCC.

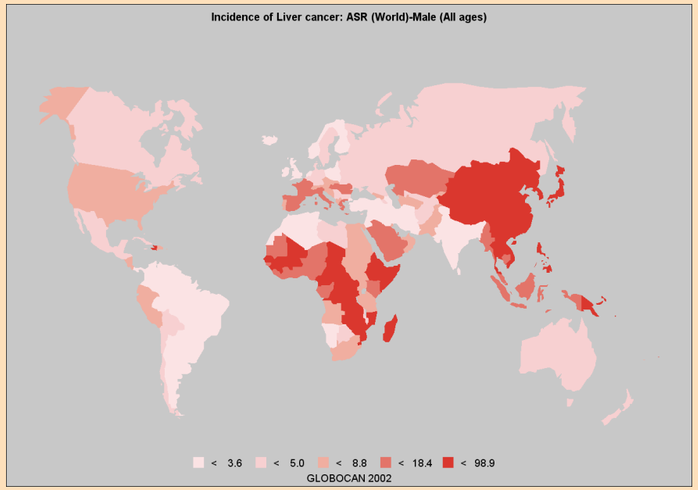
Significant differences related to the population rate of chronic carriage and the viral genotype also exist for HCV. In several countries, for example in Egypt, there is evidence that the extremely high population prevalence of chronic carriage (21%) results from the dissemination of the virus through the use of inadequately sterilised needles during medical interventions such as mass vaccination programmes.

Dietary and environmental carcinogenesis

In low-resource tropical countries, dietary exposure to aflatoxins, a class of mycotoxins produced by moulds of the genus Aspergillus, is a significant risk factor that operates synergistically with both HBV and HCV chronic infection. Aflatoxins contaminate many traditional crops such as groundnuts (peanuts), grains or



World Map 5.4.1



World Map 5.4.2

maize. Furthermore they develop under poorly ventilated storage conditions in hot and humid climates. Aflatoxin B1 (produced by Aspergillus flavus) is a significant contaminant of staples throughout sub-Saharan Africa and Southeast Asia, as well as in many parts of Latin America. The toxin is metabolised in the liver to produce an epoxide that covalently binds on the N7 position of Guanines, in particular at the third base of codon 249 in TP53. Processing of this adduct leads to the formation of promutagenic DNA lesions which, if not repaired, lead to the formation of stable mutations during transcription or replication (R249S, AGG to AGT, arginine to serine). Subjects with several "at-risk' polymorphisms in genes encoding aflatoxin metabolising and detoxifying enzymes, as well enzymes involved in DNA adduct repair, have a significantly higher risk of HCC in combination with aflatoxin exposure. The reasons why the R249S occurs almost exclusively in a context of joint exposure to HBV and aflatoxin B1 are unknown. Presence of HBV may play a role in site-specific DNA damage by aflatoxin or in affecting the efficiency of repair at that defined position. Alternatively, the R249S mutant may have special functional properties that cause efficient hepatocyte transformation.

In high-resource countries, the main known risk factors are smoking and, significantly, chronic alcohol abuse [8]. Alcohol is primarily responsible for metabolic liver injury that leads to the development of liver cirrhosis, which is a common precursor of HCC. Iron overload caused by untreated haemochromatosis or by excess exposure to iron in some African populations may provoke in some patient series a risk of death of as much as 45% from hepatocellular carcinoma [9]. Hepatic iron overload in these conditions often results in fibrosis and cirrhosis, suggesting that free iron-induced chronic necroinflammatory hepatic disease plays a role in hepatocarcinogenesis.

Metabolic syndrome. Non-alcoholic fatty liver disease (NAFLD) is a rapidly increasing metabolic syndrome that is a risk factor for HCC, and may be considered a precursor disease [10]. This syndrome is characterised by lipid accumulation within hepatocytes leading to hepatic steatosis, non-alcoholic steatohepatitis (NASH), fibrosis and cirrhosis. In the USA, the estimated prevalence of NAFLD in the general population ranges from 3–24%, with highest estimates in the 6–14% range. NAFLD is extremely common among patients undergoing bariatric surgery, ranging from 84–96%. NAFLD is strongly associated with caloric overconsumption, physical inactivity, hypertension, obesity, insulin resistance including diabetes and with other features of the metabolic syndrome, such as high serum triglyceride and low HDL levels. The metabolic syndrome appears to be more common in men, and increases with increasing age and after menopause. An AST/ALT ratio greater than 1 in the serum may also indicate more severe disease. Other metabolic disorders that may carry an increased risk of hepatocellular carcinoma or other liver cancers include tyrosinaemia, alpha-1-trypsin deficiency, hypercitrullinaemia, porphyria cutanea tarda and glycogen storage disease.

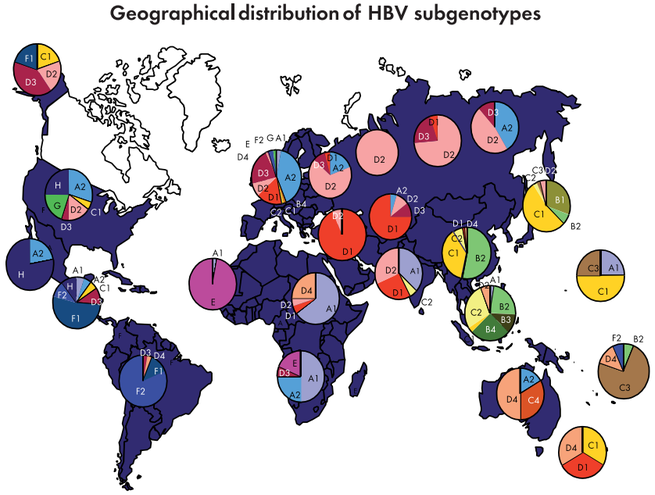


Fig. 5.4.1 *Geographical distribution of HBV subgenotypes*
Figure provided by Heléne Norder - Swedish Institute for Infectious Disease Control

Pathology and genetics

Hepatocellular carcinoma is a malignant epithelial tumour derived from hepatocytes, and thus resembles normal liver both structurally and cytologically. Small early-stage hepatocellular carcinomas (<2 cm) are generally well-differentiated histologically and arranged in a thin trabecular pattern without a capsule (Figure 5.4.2) [9]. Tumour cells grow in cords of variable thickness that are separated by sinusoid-like blood spaces. Hepatocellular carcinoma is believed to progress from adenomatous hyperplasia (or dysplastic nodules) through atypical hyperplasia to early hepatocellular carcinoma. Trabeculae become thicker with de-differentiation. Larger cancer nodules may consist of more than two types of tissue of different histological grade [11]. Invasion into the blood vessels, especially the portal vein, is a characteristic of hepatocellular carcinoma. The malignant cells produce alpha-fetoprotein which may be detected in the serum of many patients.

Genetic change in hepatocellular carcinoma may be directly related to relevant environmental factors. In areas with high exposure to aflatoxin B1, mutation of the third nucleotide in codon 249 of TP53 is frequent, compatible with miscoding due to the binding of aflatoxin (adduct formation) to relevant nucleotides in DNA. There is evidence that mutation of p53 is an early event in hepatocellular carcinomas in high-incidence areas. In high-resource countries, TP53 mutations occur at many different positions in the coding sequence and are thought to represent late events. Recent studies on biomarkers of HCC have identified broad molecular categories of cancers, based on genetic changes and viral infection status [11]. The first category contains tumours that are genetically unstable, often contain TP53 mutations, mutations in AXIN1 and multiple loss of alleles at different loci. These tumours are often associated with persistent HBV infection. The second category includes tumours that are genetically more stable, contain mutations in CNNB1 encoding beta-catenin, and often develop in the absence of HBV infection. Whether these two broad categories correspond to cancers with different biological and clinical characteristics remains to be demonstrated.

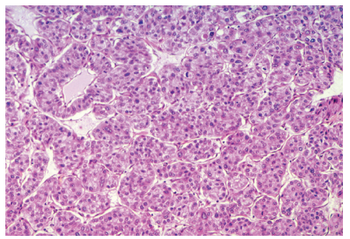
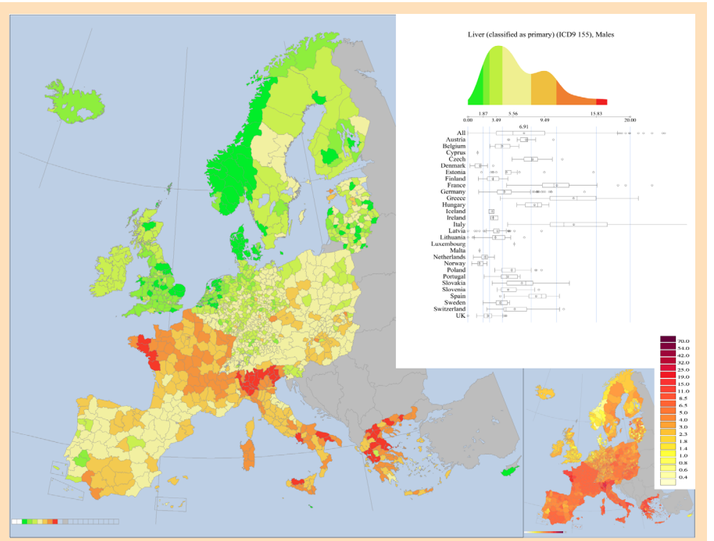


Fig. 5.4.2 *Histological appearance of hepatocellular carcinoma: a well-differentiated, trabecular carcinoma containing numerous sinusoid-like capillary vessels*



European Map 5.4.2 *In men, higher-than-average rates were found in most of France, Italy and Greece and in southern Spain. In women, the higher rates were also found in most of Italy and Greece and in Spain—but not in France; there were also higher rates in the neighbouring countries of Hungary, Slovakia, the Czech Republic and Poland in central Europe, and in parts of Sweden but not elsewhere in Scandinavia. In both sexes, the lowest rates were to be found in the United Kingdom, Ireland, Belgium, The Netherlands, Denmark, Finland and Norway.*
The patterns apparent in the maps are compatible with an alcohol and hepatitis etiology in males, with high rates in France (alcohol) and Greece, Italy and (southern) Spain (hepatitis). In females, where alcohol consumption levels are much lower, the geographic pattern is compatible with a hepatitis etiology. Hepatitis B, and particularly hepatitis C, should be regarded as public health priorities in southern Europe. The difficulties in separating the diagnosis of metastases from primary liver cancer in many countries must, however, be borne in mind [1].

The contribution of hepatitis viruses to the mechanisms of carcinogenesis is still a matter of debate. With HBV, at least three overlapping mechanisms may be involved. First, persistent HBV infection induces oxidative stress damage as well as endoplasmic reticulum stress due to accumulation of HBsAg in the reticulum. These stresses cause widespread cell destruction and stimulate compensatory cell proliferation, resulting in a deregulated, inflammatory context which is one of the hallmarks of cirrhosis. In this modified environment, transformed cells would have survival advantage due to their capacity to proliferate and to escape apoptosis, and may thus be selected to form rapidly expanding lesions. Second, HBV DNA integrates into the genome of the host cell and may act as an insertional mutagen to activate or repress the transcription of genes in the vicinity of the integration point. There is however no consensus integration region in the genome of hepatocytes. Third, the virus encodes several proteins that have a significant impact on the host cell's signalling pathways. HBx, the protein encoded by the X gene of the viral genome, is a multi-factorial protein that acts as a transcriptional regulator, interferes with several signalling pathways and may promote degradation of several intracellular proteins. These biochemical effects may contribute to tumour initiation or to the maintenance of the transformed phenotype.

HBV virus persistence contributes to a chronic inflammatory state that may predispose to cancer. There is also evidence that viral antigens may interfere with the pathways of apoptosis in hepatocytes, thus providing a survival advantage. In the case of HCV, the mechanisms involved are much less well understood.

The role of NAFLD as a precursor disease may also be linked to overproduction of reactive oxygen species overload and chronic inflammation resulting from the intracellular accumulation of lipids as well as from mitochondrial leakage during hyperactive oxygen-dependent energy metabolism.

Intrahepatic cholangiocarcinoma comprises cells resembling those of bile ducts, which is the site parasitized by liver flukes [12] . Most intrahepatic cholangiocarcinomas are adenocarcinomas showing tubular and/or papillary structures with a variable fibrous stroma. Mutations of the KRAS and TP53 genes are the most common genetic abnormalities identified.

Major Etiologic Factors	Incidence Data	Mortality Data
Hepatitis B infection (>50%) Hepatitis C infection (>25%) Alcohol consumption Aflatoxin B1 Tobacco smoking Obesity/diabetes/fatty liver/ Iron overload	551 000 cases/year worldwide 5th most common cancer 83% of all cases in developing countries 54% of the total cases in China	529 000 deaths/year worldwide 3rd most frequent cause of cancer death 8.8% of total cancer deaths

Table 5.4.1. *Liver cancer: Etiologic factors, incidence and mortality*
From Kirk, Bah and Montesano [7].

T = primary tumour	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma in situ
T1	Tumour invades submucosa
T2	Tumour invades muscularis propria
T3	Tumour invades through muscularis propria into subserosa or into non-
	peritonealised pericolic or perirectal tissues
T4	Tumour directly invades other organs or structures and/or
	perforates visceral peritoneum
N = regional lymph nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1 to 3 regional lymph nodes
N2	Metastasis in 4 or more regional lymph nodes
M = distant metastasis	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Table 5.4.2 *TNM classification of cancer of the colon and rectum*

Detection

Screening for HCC in those patients at highest risk for progression has the potential to significantly reduce morbidity and mortality [13]. Elevated AFP levels are an aid to diagnosis but this biomarker lacks specificity for application in a screening context. Other plasma biomarkers have been proposed but none of them has been fully validated in prospective studies.

Recent observations indicate that free DNA originating from tumour cells is detectable in the plasma of liver cancer patients at an early stage. Detection of relevant genetic changes in the plasma (such as TP53 mutation at codon 249 in the inhabitants of high incidence areas and aberrant methylation of CDKN2A in most parts of the world) may soon become useful aids in screening tests for hepatocellular carcinoma. In a series of patients from the Gambia, the combination of high mutant TP53 plasma DNA levels (over 10 000 DNA copies per ml) with HBV chronic infection carries a risk of HCC increased by over 65-fold as compared to low TP53 plasma DNA levels [14]. The availability of simple, genetic or proteomic plasma-based tests would be an important contribution to screening programmes.

Clinical manifestations

Common symptoms of hepatocellular carcinoma are abdominal pain, weight loss, fatigue, abdominal swelling and anorexia. Most patients, particularly in sub-Saharan Africa, present with hepatomegaly; other common signs are ascites and jaundice. Hepatocellular carcinoma that infiltrates a cirrhotic liver often compromises the already impaired hepatic function and thus causes death before becoming very large, as is the case in most patients in Japan and the USA. Intrahepatic cholangiocarcinoma is characterised by general malaise, mild abdominal pain and weight loss, and by jaundice and cholangitis at later stages. The majority of cases can be diagnosed by computed tomography (CT) (Figure 5.4.3) and ultrasonography. A definitive diagnosis may depend on histological analysis via fine needle biopsy. Endoscopic retrograde, transhepatic or magnetic resonance cholangiography can identify the level of biliary obstruction in the case of intrahepatic cholangiocarcinoma.

Management

The treatment of primary and malignant liver tumours depends on the extent of the disease and the underlying liver function [15]. The most frequently used staging system is that in which the patient is evaluated according to the adverse criteria of ascites, serum albumin and bilirubin concentration and tumour size. The TNM system is less useful as it does not take into account underlying liver disease. Liver cancer follows a rapid, progressive course: only about 8% of patients survive at least five years in the USA, and the percentage is much lower in low-resource countries. In the absence of extrahepatic disease, resection with negative pathologic margins is the mainstay of treatment for malignant liver neoplasms. In patients in whom a small liver remnant is anticipated, portal vein embolisation is used to increase the size of the future liver remnant [16]. The fact that most hepatocellular carcinomas occur in a cirrhotic liver excludes many patients from consideration for surgical resection, due to the risk of liver failure. Other techniques used alone or as an adjuvant to resection include radiofrequency ablation and cryoablation. Liver transplantation is currently used as a curative therapeutic approach in such patients. In Europe and in the USA, the use of this procedure has declined due to a number of factors, including the frequency of death from tumour recurrence, especially in the transplanted liver, and organ shortages. This procedure is however becoming widespread in the management of liver cancer in China and in several other countries of Southeast Asia. In some countries, there is a justified fear that the rapidly expanding demand of transplantable organs may fuel uncontrolled commerce in organs.

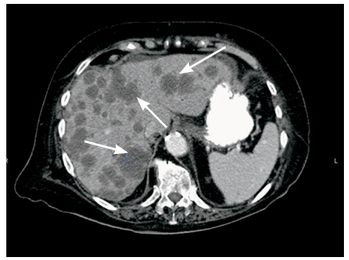


Fig. 5.4.3 *CT image of a multifocal hepatocellular carcinoma (arrows)*

Hepatocellular carcinoma is largely radiotherapy resistant [11]. Non-surgical treatments include hepatic artery infusion of drugs or thrombotic agents (via implanted infusion port or pump), chemoembolisation and percutaneous alcohol or acetic acid injection, although side-effects are many and benefit to the unresectable patient is doubtful [17,18]. Recent results suggest that a chemotherapy regimen combining cisplatin, doxorubicin, interferon and 5-fluorouracil may elicit a response, although previously no agent, either singly or in combination, has been found to improve survival. Hormone therapy is also disappointing, although results with octreotide are more hopeful than with tamoxifen. Metastatic hepatocellular cancer commonly spreads to the lungs and bones. Response to chemotherapy and local regional therapy is poor [18,19]. The liver is also a frequent site of metastases from cancers at other sites, of which the most common is colorectal cancer.

Prevention

The poor prognosis and lack of effective therapies for hepatocellular cancer indicate that the development of prevention programmes is of critical importance. Since the early 1980s, safe and affordable HBV vaccines have been available. Their introduction in mass vaccination programmes has demonstrated that these vaccines are efficient for reducing the rate of HBV infection and, significantly, of acquisition of carrier status. In Taiwan, where infection occurs mostly in adolescents and liver cancer in young adults, a sharp and significant drop in the incidence of HCC has been observed in young, vaccinated adults in the years following the introduction of the vaccine [20]. However, due to the long-term impact of chronic carriage, a full evaluation of long-term vaccine protection is not yet available. In high incidence areas, several randomised or semi-randomised trials are currently in progress to evaluate the protective efficacy of newborn HBV vaccination against persistent infection, chronic liver disease and, ultimately, cancer. Two population-based trials were started in the mid-1980s and will reach their evaluation phase around 2015, when the target population will be around 40 years of age. The largest trial, in The Gambia, West Africa, is a joint endeavour of IARC, the Medical Research Council of the UK and the government of the Republic of The Gambia. The trial was developed in the period of introduction of HBV vaccine in the Expanded Programme of Immunization in The Gambia, from 1986 to 1990 [21]. During that period, 125 000 newborns were recruited, half of whom received HBV vaccine before 1 year of age in addition to other Expanded Programme of Immunisation (EPI) vaccines. Since 1990, all newborns have been vaccinated, and the two arms of the 1986–1990 cohort are being followed-up for the evaluation of vaccine efficacy against infection and carriage, as well as for the assessment of liver cancer incidence through a National Cancer Registry. Recent cross-sectional studies within the vaccination cohort showed sustained, excellent protection of adolescents against chronic carriage. This trial provides a model for introduction of HBV vaccine in other African countries. Current projections support the view that complete coverage of the continent with the current, low-cost vaccine could reduce HCC incidence by over 60% within the next 50 years.

The lack of an equivalent vaccine-based preventive strategy is a major challenge in the control of HCV infection. Current prevention

measures focus on the absolute requirement for using disposable or adequately sterilised material in medical and public health interventions in low-resource countries and on the screening of blood and organ donors for the risk of HCV infection.

There is evidence that regulation against the distribution of aflatoxin-contaminated foodstuffs effectively decreases levels of aflatoxin exposure in the population [22] Such measures remain very difficult to implement in low-resource countries, where aflatoxin-contaminated crops represent an important part of the rural income as well as a major component of the diet that cannot be easily replaced by other foodstuffs. In such a context, it is however possible to implement relatively simple, commonsense measures to triage contaminated crops, and store them in conditions that will limit the proliferation of the moulds. A pilot, community-based intervention in Guinea has shown that such measures could significantly reduce individual exposure to aflatoxin, as measured by the levels of aflatoxin biomarkers in blood and urine.

Other risk factors are amenable to prevention, such as alcohol drinking, tobacco smoking or exposure to excess environmental iron. One of the biggest challenges in high-resource countries is to develop public health policies that will be effective in curbing the increase in the incidence of NAFLD.

REFERENCES

1. Boyle P, Smans M (2008). *IARC Scientific Publications, Number 156, Atlas of cancer mortality in the European Union and the European Economic Area 1993-1997*. Lyon, France: International Agency for Research on Cancer.

2. Parkin DM, Bray F, Ferlay J, et al. (2005). Global cancer statistics, 2002. *CA Cancer J Clin* 55: 74-108.

3. Parkin DM (2006). The global health burden of infection-associated cancers in the year 2002. *Int J Cancer* 118: 3030-3044.

4. Flores YN, Yee HF, Jr., Leng M, et al. (2008). Risk factors for chronic liver disease in Blacks, Mexican Americans, and Whites in the United States: results from NHANES IV, 1999-2004. *Am J Gastroenterol* 103: 2231-2238.

5. Bosetti C, Levi F, Boffetta P, et al. (2008). Trends in mortality from hepatocellular carcinoma in Europe, 1980-2004. *Hepatology* 48: 137-145.

6. IARC (1994). *IARC monographs on the evaluation of carcinogenic risks to humans, Volume 59, Hepatitis viruses*. Lyon, France: International Agency for Research on Cancer.

7. Kirk GD, Bah E, Montesano R (2006). Molecular epidemiology of human liver cancer: insights into etiology, pathogenesis and prevention from The Gambia, West Africa. *Carcinogenesis* 27: 2070-2082.

8. Marrero JA, Fontana RJ, Fu S, et al. (2005). Alcohol, tobacco and obesity are synergistic risk factors for hepatocellular carcinoma. *J Hepatol* 42: 218-224.

9. Kew MC and Asare GA (2007). Dietary iron overload in the African and hepatocellular carcinoma. *Liver Int* 27: 735-741.

10. Qureshi K and Abrams GA (2007). Metabolic liver disease of obesity and role of adipose tissue in the pathogenesis of nonalcoholic fatty liver disease. *World J Gastroenterol* 13: 3540-3553.

11. Zucman-Rossi J and Laurent-Puig P (2007). Genetic diversity of hepatocellular carcinomas and its potential impact on targeted therapies. *Pharmacogenomics* 8: 997-1003.

12. Sripa B, Kaewkes S, Sithithaworn P, et al. (2007). Liver fluke induces cholangiocarcinoma. *PLoS Med* 4: e201.

13. McMahon BJ (2008). Natural history of chronic hepatitis B - clinical implications. *Medscape J Med* 10: 91.

14. Lleonart ME, Kirk GD, Villar S, et al. (2005). Quantitative analysis of plasma TP53 249Ser-mutated DNA by electrospray ionization mass spectrometry. *Cancer Epidemiol Biomarkers Prev* 14: 2956-2962.

15. Lau WY and Lai EC (2008). Hepatocellular carcinoma: current management and recent advances. *Hepatobiliary Pancreat Dis Int* 7: 237-257.

16. Capussotti L, Muratore A, Baracchi F, et al. (2008). Portal vein ligation as an efficient method of increasing the future liver remnant volume in the surgical treatment of colorectal metastases. *Arch Surg* 143: 978-982.

17. Nagai H and Sumino Y (2008). Therapeutic strategy of advanced hepatocellular carcinoma by using combined intra-arterial chemotherapy. *Recent Patents Anticancer Drug Discov* 3: 220-226.

18. Schwartz JD and Beutler AS (2004). Therapy for unresectable hepatocellular carcinoma: review of the randomized clinical trials-II: systemic and local non-embolization-based therapies in unresectable and advanced hepatocellular carcinoma. *Anticancer Drugs* 15: 439-452.

19. Lin DY, Lin SM, Liaw YF (1997). Non-surgical treatment of hepatocellular carcinoma. *J Gastroenterol Hepatol* 12: S319-S328.

20. Huang K and Lin S (2000). Nationwide vaccination: a success story in Taiwan. *Vaccine* 18: S35-S38.

21. Viviani S, Carrieri P, Bah E, et al. (2008). 20 Years into the Gambia Hepatitis Intervention Study: Assessment of initial hypotheses and prospects for evaluation of protective effectiveness against liver cancer. *Cancer Epidemiol Biomarkers Prev* 17: 3216-3223.

22. Turner PC, Sylla A, Gong YY, et al. (2005). Reduction in exposure to carcinogenic aflatoxins by postharvest intervention measures in west Africa: a community-based intervention study. *Lancet* 365: 1950-1956.

5.5 Pancreas Cancer

Summary

- Pancreatic cancer is the 13th most common cancer worldwide, with over 232 000 new cases diagnosed each year. In general, the highest incidence rates occur in more developed countries
- About 20% of pancreatic cancer is attributable to tobacco smoking
- Familial clustering of pancreatic cancer and pancreatic cancer related to rare genetic syndromes, including hereditary pancreatitis, occurs in 5–10% of cases of pancreas cancer
- No population-based screening or early diagnostic testing procedures are currently available, although there are efforts underway to address these deficiencies
- The five-year survival rate is <5%, the lowest survival rate of the major cancers
- Mutations in *KRAS, TP53, p16/CDKN2A,* and *SMAD/DPC4* are implicated in over 50% of pancreatic tumours. Ductal pancreatic adenocarcinomas appear to progress from pancreatic intraepithelial neoplasia, PanIN, to pancreatic adenocarcinoma. Stromal elements and a strong desmoplastic response appear to play a role in the growth and aggressiveness of pancreas tumours
- Treatment and management for pancreas cancer patients have seen few recent improvements. Management for most patients still focuses on palliation. Surgical resection is still performed in fewer than 15% of all cases. Combined modalities involving both standard and new treatments may improve the management and survival of pancreas cancer in the coming years

Pancreas cancer is one of the most aggressive human tumours. At diagnosis, fewer than 10% of cases present with disease locally confined to the pancreas. The majority of pancreas tumours (95%) occur in the exocrine portion of the pancreas with the remainder occurring in the endocrine portion or arising from the islets of Langerhans. Most pancreatic tumours of the exocrine pancreas are classified as ductal adenocarcinomas. Tumours of the body or tail of the pancreas occur with a 30-40% frequency, while the remainder occur in the head of the pancreas. About 80% of pancreas tumours occurring in the body or tail are more advanced (stage IV), while about 33% of those in the head are diagnosed at stage IV. Consequently, survival and prognosis vary by the initial site of the tumour within the pancreas.

Epidemiology

Pancreas cancer is the 13th most common cancer worldwide, with over 232 000 new cases occurring each year. The overall 5-year survival rate for pancreas cancer is the lowest of all the major cancers at 3% to 5% (Figure 5.5.1). In the minority of pancreas cancer patients for whom surgery is an option, the 5-year survival rate is between 10 and 15%. In the USA, pancreas cancer is now the fourth leading cause of cancer death for men and women, and in the year 2008, it is estimated that there will be 37 680 new cases of pancreas cancer and 34 290 deaths [2]. Reasons for the poor survival in pancreas cancer include the typically insidious and aggressive nature of these tumours, late diagnosis, low rates of resection, and lack of effective therapies.

Pancreas cancer incidence and mortality rates vary around the world. Incidence and mortality are generally higher in the Americas, Europe, Australia and Japan. More specifically, worldwide rates are highest for African American men, New Zealand Maoris (particularly women), Korean Americans, female native Hawaiians, and the male population in Kazakhstan. Worldwide incidence and mortality rates are lowest in India, Africa (although quality data are generally lacking), Southeast Asia, and parts of the Middle East. Rates in Latin America are generally intermediate between the higher rates in North America and the lower rates in India [3].

Etiology

Advancing age is one of the strongest and most consistent predictors of pancreas cancer risk. Pancreas cancer is very rare under the age of 30 years, with the majority of cases occurring after the age of 65 years. Incidence rates are about 25–50% higher in men than in women until later in life, when incidence rates become nearly equivalent (Figure 5.5.2). These observations, along with data from animal studies, suggest that hormonal factors could play a role in the development of pancreas cancer. So far, the epidemiological studies that have addressed reproductive factors and hormone use in relation to pancreas cancer have yielded inconclusive results.

The most important (and avoidable) environmental risk factor for pancreas cancer is tobacco smoking. Most studies to evaluate smoking and pancreas cancer report relative risks around

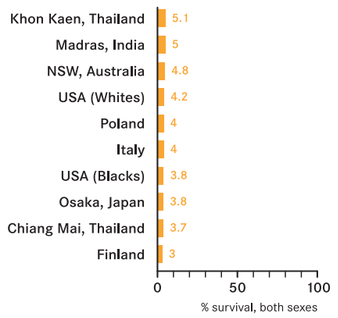
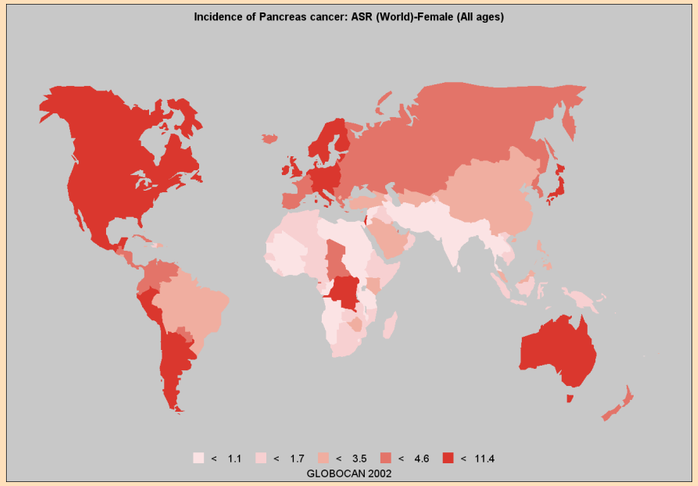


Fig. 5.5.1 *Five-year relative survival rates for both sexes combined by region [USA (blacks), USA (whites); India (Madras/Chennai), Finland, Italy, Poland, Thailand, Australia, Japan]*

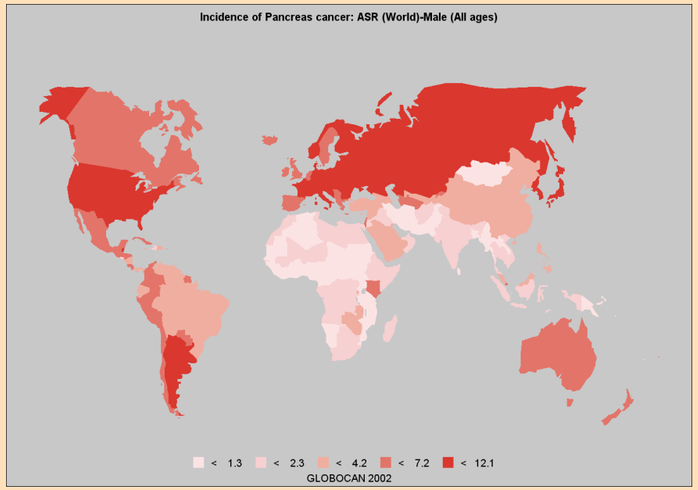
two-fold [3]. It is estimated that 20–29% of all pancreas cancers are attributable to smoking [4,5]. Despite the overwhelming evidence that smoking is a cause of pancreas cancer, the biological mechanism underlying pancreatic carcinogenesis remains elusive. Quitting smoking can reduce the risk of pancreas cancer by up to 50% after two years of not smoking, and after about 10 years of not smoking may decrease risks to those seen in never-smokers [4].

Various dietary factors have been associated with increased and decreased risks for pancreas cancer. Diets high in red meats and fat and high in calories appear to increase the risk of pancreas cancer, while diets high in fruits, vegetables and fibre appear to decrease risk. Further, the method of cooking, in particular methods that increase heterocyclic amines in cooked meats such as high temperature broiling, grilling and barbequing, may also increase the risk of pancreas cancer [6]. Moderate consumption of coffee and alcohol do not appear to increase risk; however, very heavy alcohol drinking and alcohol bingeing may increase risk. Obesity appears to be related to a higher risk for pancreas cancer [7]. Higher levels of physical activity, possibly related to higher energy expenditure, appear to be associated with a decreased risk for pancreas cancer [8].

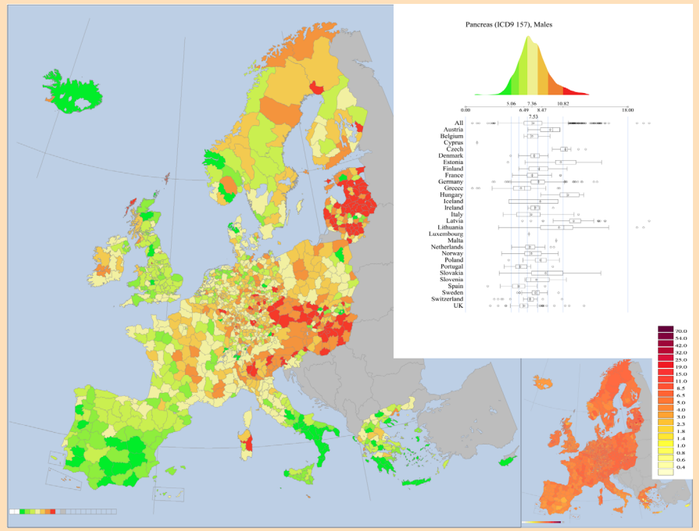
Long standing diabetes is associated with about a two-fold increased risk for pancreas cancer. Chronic inflammatory pancreatitis, in particular hereditary pancreatitis, although rare, is associated with a high risk (greater than 10-fold and higher) for developing pancreas cancer. The biological mechanisms underlying the increased risks for pancreas cancer associated with diabetes and pancreatitis are currently unknown. A recent analysis of pre-diagnostic plasma C-peptide showed a positive association with subsequent risk of pancreas cancer, suggesting that underlying insulin resistance and hyperinsulinemia may play a role in pancreatic carcinogenesis [9]. The relation between a history of allergies and pancreas cancer risk has been evaluated in a number of studies. A



World Map 5.5.1



World Map 5.5.2



European Map 5.5.1 *In men, there were several distinct aggregations of regions with high rates of pancreas cancer. One extended over northern Sweden and Norway; a second covered all three Baltic Countries; and a third extended from northern Italy into eastern Austria, the Czech Republic, Slovakia and Hungary. There is marked contrast between the high rates in the north of Italy and the very low rates in the south of the country; and there were low rates in Portugal, Spain and most of Greece and the United Kingdom [1].*

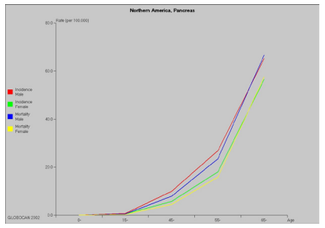


Fig. 5.5.2 *Age-specific incidence and mortality of pancreas cancer in men and women (in North America). The small differences between incidence and mortality reflect the poor prognosis for this disease. Men are somewhat more frequently affected than women*

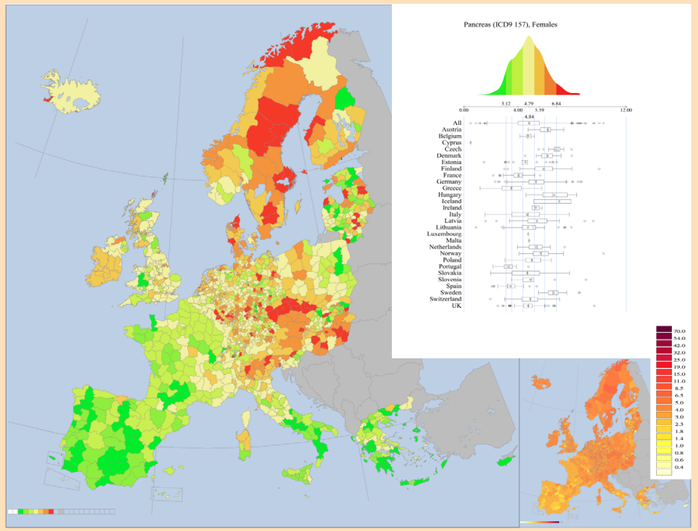
recent review and meta-analysis suggested that having a history of allergies, in particular those related to atopy, is associated with a lower risk of pancreas cancer [10]. There is some evidence that *H pylori* infection may contribute to pancreas cancer incidence, but studies to date have involved too few cases to adequately address this topic. The use of aspirin has been inconsistently associated with pancreas cancer, with some studies showing inverse associations and others showing little or no association. To date, the possibility that aspirin and other non-steroidal anti-inflammatory drugs lower pancreas cancer risk is inconclusive.

Many studies have evaluated occupations and workplace exposures in relation to risk of pancreas cancer. In general, there does not appear to be any single occupation or workplace exposure that explains much of the disease. The few consistent occupations that have been associated with pancreas cancer have been those associated with exposure to chlorinated hydrocarbons, pesticides, solvents, metals, polycyclic aromatic hydrocarbons and nitrosamines, and some occupations involved in the pulp and paper industry.

Detection

There is currently no early diagnostic test or population-based screening procedure for pancreas cancer detection and screening. Patients usually report symptoms that lead to a physical examination and several tests on urine, blood, and stool. Laboratory tests which may indicate the presence of pancreas cancer include elevated bilirubin levels and increased levels of liver enzymes. Based on the physical examination and laboratory tests, the physician may request imaging studies of the pancreas, the best being multiphase spiral or helical computerised tomography (CT), although transabdominal or endoscopic ultrasonography (EU) and magnetic resonance imaging (MRI) may also be used. Endoscopic retrograde cholangiopancreatography (ERCP) has risks associated with the procedure (pancreatitis, perforation and bleeding) and is now largely reserved for therapeutic purposes for stent placement to relieve obstruction.

If an imaging study identifies a possible mass or tumour in the pancreas, a biopsy may be taken to determine definitively the presence of pancreas cancer and to provide staging information. There are two ways that a biopsy may be performed to diagnose pancreas cancer (or to determine resectability), including EU-guided fine-needle aspiration and brush biopsy performed in conjunction with ERCP. Pancreas cancer may also be diagnosed (or resectability determined) with biopsy material taken during surgery on the pancreas such as laparoscopy and laparotomy.



European Map 5.5.2 *In women, the broad pattern was similar, but there were some noticeable differences, with high rates over most of the Nordic Countries, particularly Sweden, and in Austria, the Czech Republic and Hungary, but only average rates in the three Baltic Countries. As in males, there were low rates throughout Spain, Portugal, southern Italy and much of Greece [1].*

Pathology and genetics

There is growing evidence that the molecular pathogenesis of pancreas cancer progresses from early stage neoplasia, or PanIN, to malignant ductal pancreatic cancer (Figure 5.5.3). The first stage of neoplasia, flat hyperplasia, involves the columnarisation of the ductal epithelium. This may then advance to papillary hyperplasia, the presence of crowded mucosa with a folded structure, which may possess varying degrees of cellular and nuclear abnormalities. True carcinoma of the pancreas is characterised by invasion of the ductal walls of the lumen and a strong desmoplastic (inflammatory) response. The molecular pathways and genes involved in pancreas cancer progression are being actively pursued by the scientific community [11].

Hereditary conditions. From 5 to 10% of pancreas cancer cases exhibit some degree of familial clustering. There are a number of hereditary syndromes that have been associated with an increased lifetime risk of pancreas cancer (Table 5.5.1). Over 20 genes have been implicated in the molecular pathogenesis of pancreas cancer (Table 5.5.2). Somatic alterations involving four genes have been implicated in over 50% of pancreas tumours, including *KRAS* oncogene (>90%) and *p16/CDKN2A* (>40%), *TP53* (>50%) and *DPC4/SMAD4* (>35%) tumour suppressor genes [12] (Table 5.5.2). The genetic progression of pancreas cancer from normal epithelium to invasive carcinoma is generally associated with the accumulation of genetic alterations starting with *KRAS* mutations and telomere shortening followed by *p16/CDKN2A* loss and finally mutations in *TP53*, *DPC4/SMAD4*, and *BRCA2* (Figure 5.5.3) [11]. Other genes known to be involved in pancreas cancer development, albeit less frequently than the genes listed above, include *BRCA1*, *MKK4*, *PRSS1*, *LKB1/STK11*, *MSH2*, *MLH1*, *FANC-C* and *FANC-G*. Germ-line mutations in *BRCA2* represent the most common inherited predisposition to pancreas cancer described so far. In one study, 7% of sporadic cases of pancreas cancer (those with no apparent family history of pancreatic cancer) were found to harbour inherited mutations in *BRCA2* [13]. In addition to the above-mentioned genetic alterations, a number of growth factors are over-expressed in pancreas tumours, including EGF, TGF-alpha, TGF-beta, alphaFGF, and their receptors [12,14].

Molecular epidemiology

The discipline of molecular epidemiology is a relatively new field of study. Despite this, there are a small but increasing number of published reports addressing common, inherited genetic variation and environmental exposures such as tobacco smoking in relation to the risk of sporadic pancreas cancer. Early evidence suggests that DNA repair and carcinogen metabolism gene variation, in combination with heavy smoking, may help to define susceptible subgroups at greater risk for pancreas cancer [15,16]. Additional studies and pooled analyses involving thousands of cases may help to define combinations of genes and exposures that increase the risk of developing pancreas cancer. Such information may lead to improved screening and detection as well as treatment and management of sporadic forms of pancreas cancer.

Management

Pancreas cancer is often referred to as a "silent" disease because the tumour can grow for years before there are any notable signs or symptoms. Typical symptoms of pancreas cancer include jaundice, generalised itching, pain in the abdomen or back, nausea, loss of appetite, unexplained weight loss and general weakness. These symptoms are often ignored by many

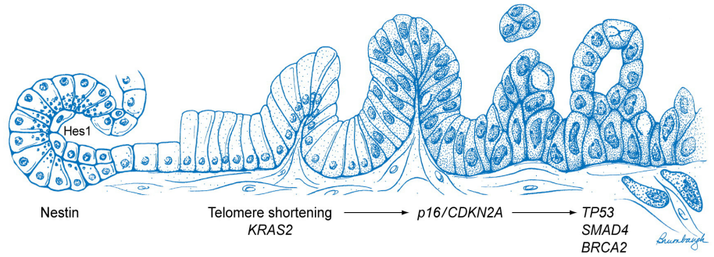


Fig. 5.5.3 *Genetic progression model of pancreatic adenocarcinoma (Pancreatic Cancer. Ann. Rev. of Pathol. Mech. Dis. Vol.3:157-188, 2008)*

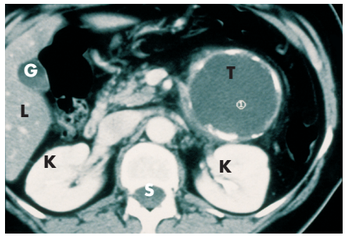


Fig. 5.5.4 *A CT image of a mucinous cystic neoplasm in the pancreas. The thick wall shows focal calcification. T = tumour, K = kidney, L = liver, S = spinal cord, G = gallbladder*

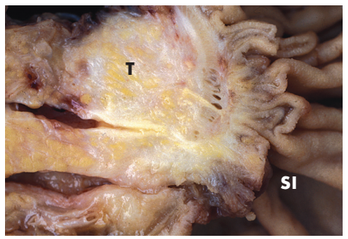


Fig. 5.5.5 *Surgical specimen of a pancreatic ductal adenocarcinoma (T) in the head of the pancreas. SI = small intestine*

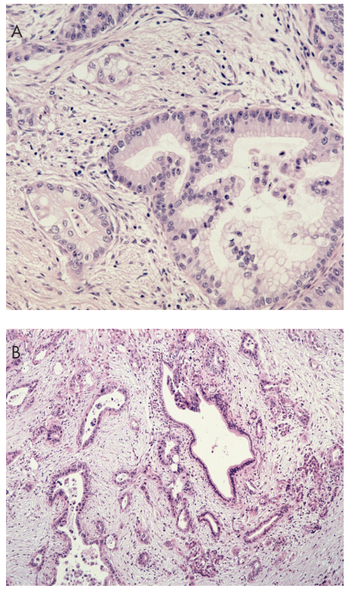


Fig. 5.5.6 *Ductal adenocarcinoma. A: Well differentiated tumour with desmoplasia and irregular gland formation. B: Well differentiated neoplasm involving a normal duct (right part).*

patients early on and can be mistakenly attributed to other general health problems. Tumours in the head of the pancreas are more likely to cause jaundice, whereas advanced tumours and tumours in the body of the pancreas are more likely to cause pain.

Surgery remains the best chance for a cure, but only a minority of patients receive any form of surgery (less than 15% of cases, usually tumours in the head of the pancreas). Pancreaticoduodenectomy (the "Whipple procedure") involves resection of the entire duodenum with a short section of the jejunum, the pancreatic head, and the gallbladder, excision of the common bile duct, and distal gastrectomy followed by reconstruction. Unfortunately, complications are common, morbidity is high and patient recovery is slow. The outcome in specialist centres is considerably better [17]. In total pancreatectomy, the entire pancreas as well as the duodenum, common bile duct, gallbladder, spleen and local lymph nodes are removed. The serum biomarker CA19-9 is elevated in pancreatic cancer and can be used to monitor curative resection. Symptoms and obstruction in non-resectable tumours can also be relieved by bypass surgery. In terms of chemotherapy, single-agent gemcitabine is still the current standard of treatment for most pancreas cancer. Combinations of radiation plus 5-flourouracil or gemcitabine are in use to control local spread. A number of clinical investigations of combined therapies and multimodality approaches are currently underway in the USA and other countries [18,19]. Progress has been very slow and at times disappointing, but it is hoped that with continued understanding of the molecular pathogenesis of pancreas cancer along with clinical trials of new therapeutic approaches [11] the outlook for pancreas cancer patients will improve in the coming years.

Hereditary condition	Gene (chromosome)	Lifetime risk of pancreas cancer
Hereditary pancreatitis	*PRSS1* (7q35)	25–40%
Familial atypical multiple mole melanoma (FAMMM)	*p16/CDKN2A* (9p21)	10–17%
Familial breast cancer	*BRCA2* (13q12) *BRCA1* (17q21)	5% 1%
Fanconi anaemia syndrome (young-age-onset pancreatic cancer)	*FANCC* (9q22) *FANCG* (9p13)	Unknown
Ataxia telangiectasia (heterozygotes)	*ATM, ATB*, others (11q22-q23)	Unknown
Peutz-Jeghers syndrome	*STK11/LKB1* (19p13)	30-60%
Hereditary non-polyposis colorectal cancer (HNPCC)	*MSH2* (2p15) *MLH1* (3p25) *PMS2* (7p1) *MSH6* (2p16)	<5%
Cystic fibrosis (heterozygotes)	*CFTR* (7q31)	Unknown; rare
Familial pancreatic cancer (3 or more first-degree relatives with pancreatic cancer)	Unknown	16%

Table 5.5.1 *Table of hereditary syndromes with lifetime risk of pancreatic cancer*

Gene	Chromosome	Mechanism of alteration	% of cancers
Oncogenes			
KRAS2	12p	Point mutation	>90
CMYC	8q	Amplification	20-30
MYB, AKT2, AIB1, EGFR	6q, 19q, 20q, 7p	Amplification	10-20
ERBB2 (Her/2-neu)	17q	Overexpression	70
BRAF	7q	Point mutation	Rare
Tumour suppressor genes			
P16/CDKN2A	9p	Homozygous deletion Loss of heterozygosity and intragenic mutation Promoter hypermethylation	40 40 15
TP53	17p	Loss of heterozygosity and intragenic mutation	50-75
DPC4/SMAD4	18q	Homozygous deletion Loss of heterozygosity and intragenic mutation	35 20
BRCA2	13q	Inherited mutation and Loss of heterozygosity	5-10
LKB1/STK11	19p	Loss of heterozygosity and intragenic mutation Homozygous deletion	5-10
ACVR1B	12q	Homozygous deletion	5-10
TGFBR1, TGFBR2	9q, 3p	Homozygous deletion	5
BRCA1	17p	Inherited mutation	<5
MKK4	17p	Homozygous deletion, Loss of heterozygosity and intragenic mutation	<5
RNASEL	1q	Inherited mutation	1-3
DNA mismatch repair			
MSH2, MLH1	2p, 3p	Inherited mutation Methylation?	<5

Table 5.5.2 *Genes modified in pancreas cancer*

REFERENCES

1. Boyle P, Smans M (2008). *IARC Scientific Publications, Number 156, Atlas of cancer mortality in the European Union and the European Economic Area 1993-1997*. Lyon, France: International Agency for Research on Cancer.

2. Jemal A, Siegel R, Ward E, et al. (2008). Cancer Statistics, *CA Cancer J Clin* 58: 71-96.

3. Anderson KE, Mack TM, Silverman DT (2006). Cancer of the pancreas. In: Schottenfeld D, Fraumeni Jr JF, eds., *Cancer Epidemiology and Prevention*. New York: Oxford University Press. 721-762.

4. Fuchs CS, Colditz GA, Stampfer MJ, et al. (1996). A prospective study of cigarette smoking and the risk of pancreatic cancer. *Arch Intern Med* 156: 2255-2260.

5. Iodice S, Gandini S, Maisonneuve P et al. (2008). Tobacco and the risk of pancreatic cancer: a review and meta-analysis. *Langebecks Arch Surg* 393: 535-54

6. Stolzenberg-Solomon RZ, Cross AJ, Silverman DT, et al. (2007). Meat and Meat-Mutagen Intake and Pancreatic Cancer Risk in the NIH-AARP Cohort. *Cancer Epidemiol Biomarkers Prev* 16: 2664-2675.

7. Larsson SC, Orsini N, Wolk A (2007). Body mass index and pancreatic cancer risk: A meta-analysis of prospective studies. *Int J Cancer* 120: 1993-1998.

8. Michaud DS, Giovannucci E, Willett WC, et al. (2001). Physical Activity, Obesity, Height, and the Risk of Pancreatic Cancer. *JAMA* 286: 921-929.

9. Michaud DS, Wolpin B, Giovannucci E, et al. (2007). Prediagnostic Plasma C-Peptide and Pancreatic Cancer Risk in Men and Women. *Cancer Epidemiol Biomarkers Prev* 16: 2101-2109.

10. Gandini S, Lowenfels AB, Jaffee EM, et al. (2005). Allergies and the Risk of Pancreatic Cancer: A Meta-analysis with Review of Epidemiology and Biological Mechanisms. *Cancer Epidemiol Biomarkers Prev* 14: 1908-1916.

11. Maitra A and Hruban RH (2008). Pancreatic Cancer. *Annu Rev Pathol* 3: 157-188.

12. Bardeesy N and DePinho RA (2002). Pancreatic cancer biology and genetics. *Nat Rev Cancer* 2: 897-909.

13. Goggins M, Schutte M, Lu J, et al. (1996). Germline BRCA2 Gene Mutations in Patients with Apparently Sporadic Pancreatic Carcinomas. *Cancer Res* 56: 5360-5364.

14. Sakorafas GH, Tsiotou AG, Tsiotos GG (2000). Molecular biology of pancreatic cancer; oncogenes, tumour suppressor genes, growth factors, and their receptors from a clinical perspective. *Cancer Treatment Reviews* 26: 29-52.

15. Duell EJ, Holly EA, Bracci PM, et al. (2002). A Population-based Study of the Arg399Gln Polymorphism in X-Ray Repair Cross- Complementing Group 1 (XRCC1) and Risk of Pancreatic Adenocarcinoma. *Cancer Res* 62: 4630-4636.

16. Jiao L, Hassan MM, Bondy ML, et al. (2007). The XPD Asp312Asn and Lys751Gln polymorphisms, corresponding haplotype, and pancreatic cancer risk. *Cancer Letters* 245: 61-68.

17. Winter JM, Cameron JL, Campbell KA, et al. (2006). 1423 Pancreaticoduodenectomies for Pancreatic Cancer: A Single-Institution Experience. *Journal of Gastrointestinal Surgery* 10: 1199-1211.

18. Saif MW (2007). Pancreatic cancer: is this bleak landscape finally changing? *JOP J Pancreas* 8: 365-373.

19. Yang GY, Wagner TD, Fuss M, et al. (2005). Multimodality Approaches for Pancreatic Cancer. *CA Cancer J Clin* 55: 352-367.

WEBSITES

NCI Pancreatic Cancer Homepage:

http://www.cancer.gov/cancer_information/cancer_type/pancreatic

The John Hopkins Medical Institution, Pancreatic Cancer Homepage:

http://www.path.jhu.edu/pancreas/

CANCER INSTITUTE PROFILE: Oncology Institute of Southern Switzerland (IOSI)

The Oncology Institute of Southern Switzerland (IOSI) is a multisite oncology institute that comprises all the facilities related to cancer treatment at different public hospitals. Among them, the Ospedale San Giovanni in Bellinzona harbours the most important assets: the radiotherapy centre, the PET-scan, the haematology division and the inpatient ward for palliative treatment, as well as 30 beds for chemo-radiotherapy and for aggressive chemotherapy treatment, including autologous bone marrow transplantation.

The institute sees 2500 new patients a year, representing a comprehensive care centre that also includes a cancer register, a central library and facilities for clinical and translational research. Three of Europe's major cancer research structures have their operational offices at IOSI: IELSG (International Extranodal Lymphoma Study Group), IBCSG (International Breast Cancer Study Group), and SENDO-SAKK (coordinating Phase I trials).

website: www.iosi.ch

Oncology Institute of Southern Switzerland
Ospedale San Giovanni
CH-6500 Bellinzona, Switzerland

CANCER INSTITUTE PROFILE: National Colorectal Cancer Roundtable

The (USA) National Colorectal Cancer Roundtable, cofounded by the American Cancer Society and the US Centers for Disease Control and Prevention, is a national coalition of public, private and voluntary organisations, and invited individual experts dedicated to reducing the incidence of and mortality from colorectal cancer through coordinated leadership, strategic planning and advocacy. The Roundtable works as a catalyst to stimulate key member organisations to act earlier, act more effectively, and act collaboratively in the area of colorectal cancer.

The Roundtable taps into the expertise of its members to create tools, conduct studies, develop consensus and support projects that can advance the community's overall work in this area. Many of these projects, such as the creation of the Blue Star symbol, the development of a colorectal cancer Clinician's Guide and Toolbox, and the development of a study to measure how increasing screening rates impacts downstream costs, fill a key need among collaborating partners. Such initiatives create a multiplier effect in the community's work against this disease.

website: www.nccrt.org

5.6 Gallbladder Cancer

Summary

> Gallbladder cancer incidence is higher in women than in men in most areas of the world. The highest incidence areas are Chile, India and some other countries of Latin America, Asia and central Europe

> Incidence and mortality have been declining in most areas of the world over the last few decades, mainly due to the increasing frequency of cholecystectomy

> Gallbladder anomalies and cholelithiasis are the major risk factor for GC

> Other risk factors are obesity and selected aspects of diet, linked to gallstones

The biliary tract consists of an interconnected system of intra- and extrahepatic ducts that transport bile secreted from the liver to the digestive tract. The gallbladder, lying just under the liver, is an important organ of the biliary system, receiving, storing and then releasing the bile through bile ducts into the duodenum to help in the digestion of fat. Gallbladder cancer (GC) is the most common type of cancer of the biliary tract [2]. GC is a relatively rare neoplasm, and despite being a non-sex-related cancer, is more frequent among women than among men in most populations. Detection of GC is difficult because symptoms and signs of GC are not specific and often appear late in the clinical course of the disease. For this reason, diagnosis is generally made when the cancer is already in advanced stages, and prognosis for survival is less than 5 years in 90% of cases [3].

Descriptive epidemiology

Gallbladder cancer incidence is characterised by worldwide variation (Figure 5.6.1), being low in several European countries and the USA, relatively high in selected central European countries, and very high in some countries of Latin America and Asia. GC has been shown to be the most common cause of cancer death among women in some areas of Chile[4].

According to incidence rates recorded by cancer registries in the mid-1990s, the highest incidence rate worldwide occurs in women from Delhi, India (21.5/100 000), followed by South Karachi, Pakistan (13.8/100 000) and Quito, Ecuador (12.9/100 000). Cancer registries reporting high GC incidence rates were in East Asia (Korea and Japan), Eastern Europe (including Slovakia, Poland and the Czech Republic) and South America (Colombia). In Western Europe, elevated incidence rates were shown in Granada, Spain. Although systematically lower than in women, high incidence rates among men (ranging between 4.4 and 8.0/100 000) were found in some areas of Asia and Eastern Europe [4]. Most registries from Northern Europe indicate low incidence rates (below 3/100 000 women and 1.5/100 000 men), with the partial exception of Sweden.

The female to male (F/M) incidence ratio of GC incidence rates varied greatly; it was >5 in several high-risk areas (e.g. Pakistan, India, Colombia and Spain) as well as in a few selected low-risk areas (e.g. Denmark), but was typically between 2 and 3 in the majority of countries. F/M ratio was close to 1 in Korea, Japan and some parts of China [4].

Incidence rates of GC in various ethnic groups from selected cancer registries in the USA confirmed the worldwide pattern (Figure 5.6.2), as GC was substantially more frequent among Hispanic than non-Hispanic white women, and remarkably elevated among Korean and Chinese men. Very high incidence was also among Native Americans in New Mexico. Also the F/M ratio was high among Hispanic whites, and close to 1 among Koreans, Filipinos, Japanese and Chinese [4].

Risk factors

The number of epidemiological which studies published on risk factors for GC has been limited because of 1) the rarity of GC in countries where most medical research is funded and performed, 2) the difficulties of histological identification of GC, 3) the lack of relevant animal models and tumour cell lines for GC, and 4) the lack of comprehensive national or international registries for information on GC cases [2]. Risk factors for GC include genetic predisposition, geographic variation and ethnicity, female gender, chronic inflammation, congenital abnormalities, low socio-economic status, low frequency of cholecystectomy for gallbladder diseases and exposure to certain chemicals.

Selected major risk factors for GC are reported in Table 5.6.1. History of gallstones and cholecystitis are considered the major risk factors for GC. Several cohort and case–control studies found strong associations between history of benign gallbladder diseases (mainly gallstones) and GC risk. Relative risks (RRs) from case-control studies varied greatly, and this variation probably results from differences in study design and methods and definitions used to collect information on gallstones. The summary RR for history of gallstones was 4.9 [95% CI 3.3–7.4], and was 2.2 (95% CI 1.2–4.2) among cohort studies and 7.1 (95% CI 4.5–11.2) among case–control studies [4].

Cholesterol and mixed gallstones (containing >50% of cholesterol) account for 80% of all gallstones, and pigment stones (composed largely of calcium bilirubinate) account for the remaining fraction. The aetiology of cholesterol gallstones is thought to involve the interaction of genetic factors (e.g. modification of MDR3 and CYP7A1 genes, and numerous lithogenic genes) and several environmental factors (age, female gender, obesity, multiple pregnancies, family history of gallstones and low levels of physical activity) [2].

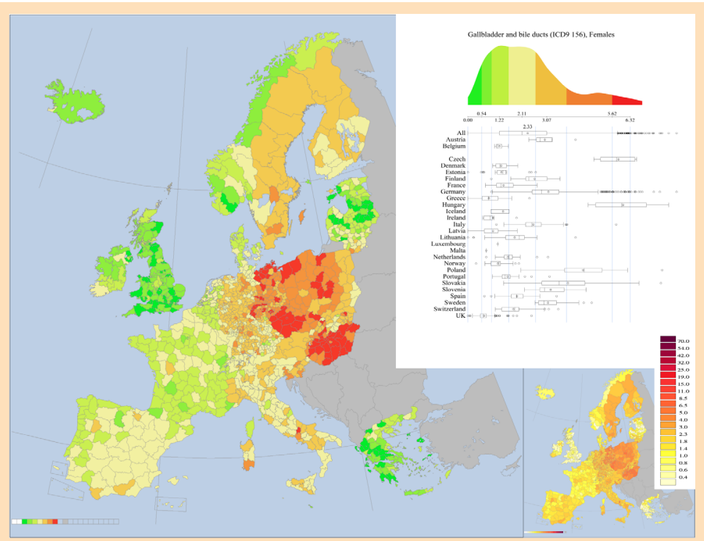
The worldwide distribution of gallstone prevalence shows a strong geographic and ethnic variation, and a positive correlation with the incidence rates of GC. High gallstone prevalence (≥50%) among women was found among American Indians in the USA, and among Mapuche Indians in Chile, both populations presenting very high GC incidence rates. Other areas with high or intermediate prevalence of gallstones were identified in South America, and in Eastern and Western Europe. Very little is known about some regions of the world, such as India, where a high incidence of symptomatic gallstones has been observed, but results from ultrasound-based studies are not available. Low-risk areas for gallstones (i.e. where prevalence is <10% among women) included African countries, but also Thailand, China, Korea and Japan which reported high GC incidence rates [4].

Only a small proportion (1–3%) of patients with gallstones develop GC; thus other risk factors are thought to play a role [5].

Obesity and overweight are major risk factors for gallstones, and large cohort studies show that the association of GC with obesity is one of the strongest seen for any cancer site (Table 5.6.2). Compared with individuals of 'normal weight', the summary RR of GC for those who were overweight was 1.2 (95% CI 1.0–1.3) and for those who were obese the OR was 1.7 (95% CI 1.5–1.9). The association with obesity was stronger for women than for men [4,6]. The influence of obesity, however, like the influence of belonging to certain ethnic groups, seemed to be at least in part mediated by an increased predisposition to develop gallstones.

The overall increased frequency of GC in women suggests a possible role for hormonal factors, especially in the formation of cholesterol gallstones. High parity and high number of pregnancies, again recognised risk factors for gallstones, have been related to increased GC risk. Among parous women, older age at first birth or pregnancy has been associated with reduced risk of GC. Oral contraceptive use was not materially related to GC risk; neither were duration of use and time since first and last use. Inconsistent results were obtained for the association of GC risk with menopausal status and HRT use. Thus, the precise role of female hormones remains unresolved, but it is unlikely that they play a major role [4,7].

Chronic infection of the gallbladder may contribute to the onset of GC, *per se* or via gallstone formation. Most available evidence implicates *(S.)-typhi* and *paratyphi* and *Helicobacter* species [5]. Eleven epidemiological studies concerning the relation between *Salmonella (S.) typhi* and *paratyphi* and GC have been published. The summary RR for typhoid infection was 4.8 (95% CI 1.4–17.3), and rose to 10.2 (95% CI 2.0–50.9) after exclusion of studies based on self-reported diagnosis of infection. The summary RR for case-control studies was 2.6 (95% CI 1.1–6.1), which rose to 5.2 (95% CI 2.1–12.7) after exclusion of studies based on self-reported diagnosis of infection [4]. All epidemiological studies on *S. typhi* and *paratyphi* and GC based on biological markers, such as serum Vi antigen or the presence of the bacteria in bile specimens, found a significant positive association between *S. typhi* and *paratyphi*



European Map 5.6.1 *The distribution of gallbladder and bile duct cancer mortality in women in Europe was quite unlike that for any other form of malignant disease, with generally lower than average rates in the west of Europe, including Iceland, Norway, the United Kingdom and Ireland, Denmark, The Netherlands, Belgium, France, Spain and Portugal. Rates were above average in a band across most of the centre of Europe, extending from Italy in the south through Germany to Sweden in the north. The high rates also extended eastwards into eastern Austria, the Czech Republic, Hungary and parts of Slovakia in both males and females, and into Poland for females [1].*

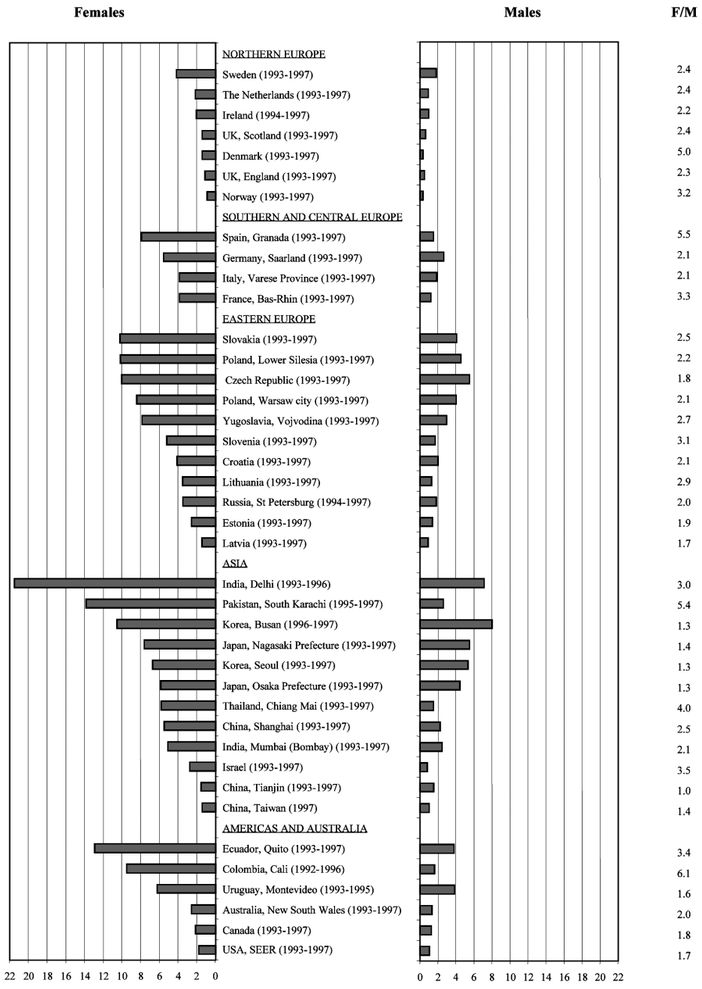


Fig. 5.6.1 *Age-standardised incidence rates* per 100 000 (world population) and female/male ratio for gallbladder cancer in 40 selected areas*
**Truncated for individuals aged 35–74*

carrier status and GC risk. Also *Helicobacter bilis* and *pylori* have been identified in bile specimens and associated with risk of biliary tract cancer (RR 4.3; 95% CI 2.1–8.8) [4].

Most studies of infection and GC to date have had limited power (no more than 15 exposed cases), have lacked well-matched controls (with or without gallstones), and have been hampered by a lack of standardised and non-invasive methods for the detection of these infectious agents.

With respect to dietary factors, in the multinational collaborative study from the Surveillance of Environmental Aspects Related to Cancer in Humans (SEARCH) Programme of the International Agency for Research on Cancer (IARC), which included 169 cases and 1515 controls [8], the strongest direct associations with GC risk were for total carbohydrate intake (RR 11.3 for the highest quartile versus the lowest quartile) and total energy intake (RR 2.0), with inverse associations for dietary intake of fibre, vitamin B6, E and C (RRs ranging from 0.4–0.5). However, apart from obesity, there is no nutritional or dietary factor consistently related to GC risk.

Conclusions and perspectives

It has been proposed that there are two main pathways to GC [2]. The predominant pathway involves gallstones and resultant cholecystitis, and affects women to a greater extent than men. The other pathway involves an anomalous pancreatobiliary duct junction (APBDJ), a congenital malformation of the biliary tract that is more prevalent in Japan, Korea, and possibly China than in Western countries. With APBDJ, the pancreatic and common bile ducts join together before reaching the duodenal wall, allowing reflux of secretions of the exocrine pancreas into the gallbladder. APBDJ appears to be associated with papillary carcinoma of the gallbladder, which is less invasive and fatal than other carcinomas of the gallbladder [2].

Author, Year (Country)		RR (95% CI)	Adjustment
History of benign gallbladder diseases[1]			
Cohort studies[2]			
Maringhini, 1987 [Ann Intern Med 107: 30-35] (USA)		2.8 (0.9-6.6)	Age and sex
	Men	8.3 (1.0-30.0)[3]	Age and sex
	Women	2.0 (0.4-5.7)[3]	Age and sex
Chow, 1999 [Br J Cancer 79: 640-644] (Denmark)		3.6 (2.6-4.9)	Age and sex
Yagyu, 2004 [Cancer Sci 95: 674-678] (Japan)	Men	1.2 (0.3-4.7)	Age
	Women	1.1 (0.4-2.9)	Age
Case-control studies[4]			
Lowenfels, 1985 [J Natl Cancer Inst 75: 77-80] (USA)	Non-Indians	4.4 (2.6-7.3)	Age, sex, centre, alcohol, smoking, education and response status
	Indians	20.9 (8.1-54.0)	Age, sex, centre, alcohol, smoking, education and response status
Nervi, 1988 [Int J Cancer 41: 657-660] (Chile)		7.0 (5.9-8.3)	Age, sex, country
WHO, 1989[5] [Int J Epidemiol 18: 309-314]		2.3 (1.2-4.4)	None reported
Kato, 1989 (Japan) [Jpn J Cancer Res 80: 932-938]		34.4 (4.51-266.0)	None reported
Zatonski, 1997[6] [J Natl Cancer Inst 89: 1132-1138]		4.4 (2.6-7.5)	Age and sex
Okamoto, 1999 (Japan) [Am J Gastroenterol 94: 446-450]		10.8 (4.1-28.4)[7]	
Khan, 1999 (USA) [Am J Gastroenterol 94: 149-152]		26.6 (7.0-101.4)	Sex, age, ethnicity, smoking and socioeconomic status
	Women	28.9 (4.7-173.0)[3]	Age, ethnicity, socioeconomic status, hysterectomy, menopause, parity, diabetes and smoking
Family history of benign gallbladder diseases			
Case-control studies[8]			
Kato, 1989 (Japan) [Jpn J Cancer Res 80: 932-938]		3.0 (1.3-6.5)	None reported
Strom, 1995 (Bolivia, Mexico) [Cancer 76: 1747-1756]		3.6 (1.3-11.4)	Age, sex and hospital
Family history of gallbladder cancer[9]			
Cohort studies[10]			
Goldgar, 1994 (USA) [J Natl Cancer Inst 86: 1600-1608]	First-degree relatives	2.1 (0.2-6.1)	Age at diagnosis
Hemminki, 2003 (Sweden) [Gut 52: 592-596]	Parents	5.1 (2.4-9.3)	Age, sex, region, period and socioeconomic status
	Offspring	4.1 (2.0-7.6)[3]	Age, sex, region, period and socioeconomic status
Case-control studies			
Fernandez, 1994 (Italy) [Cancer Epidemiol Biomarkers Prev 3: 209-212]	First degree relatives	13.9 (1.2-163.9)	Age, sex, residence and education

Table 5.6.1 *Relative risks (RR) with corresponding 95% confidence intervals (CI) of gallbladder cancer for the history of selected diseases*
[1] Summary RR for all studies was 4.9 (95% CI: 3.3–7.4) and heterogeneity test between studies was χ_6^2 = 57.361, p < 0.001. [2] Summary RR for cohort studies was 2.2 (95% CI: 1.2–4.2) and heterogeneity test between studies was χ_3^2 = 6.918, p 5 0.075. [3] Not included in the summary estimates.[4]Summary RR for case-control studies was 7.1 (95% CI: 4.5–11.2) and heterogeneity test between studies was χ_2^2 = 28.540, p < 0.001. [5]Chile, China, Colombia, Israel, Kenya, Mexico.[6]Australia, Canada, Netherlands, Poland.[7]Estimated from available data.[8]Summary RR for case-control studies was 3.2 (95% CI: 1.7–6.1) and heterogeneity test between studies was χ_1^2 = 0.007, p = 0.791.[9]Summary RR for all studies was 4.8 (95% CI: 2.6–8.9) and heterogeneity test between studies was χ_2^2 = 1.647, p 5 0.439. [10]Summary RR for cohort studies was 4.5 (95% CI: 2.4–8.5) and heterogeneity test between studies was χ_2^2 = 0.895, p = 0.344.
Taken from Randi et al, 2006

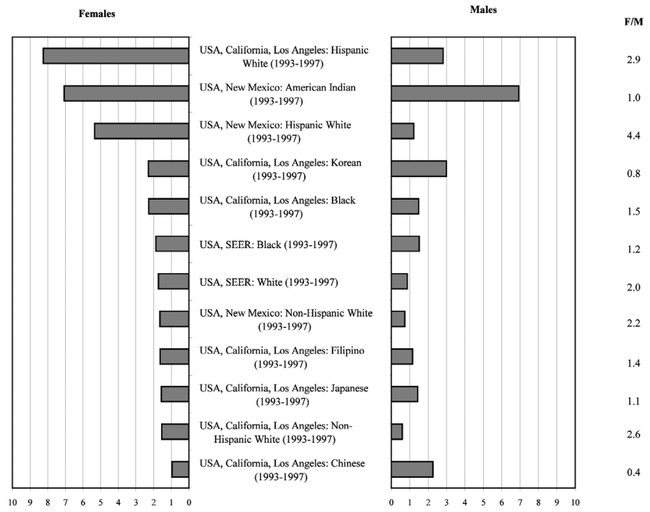


Fig. 5.6.2 *Age-standardised incidence rates* per 100 000 (world standard population) and female-to-male (F/M) ratio for gallbladder cancer in selected ethnic groups of the USA*
**Truncated for individuals aged 35–74.*

Gallbladder cancer is a highly lethal and aggressive disease with a poor prognosis, but radical surgery can be curative when appropriate clinical assessments are performed preoperatively. Behavioural interventions meant to prevent overweight and obesity are difficult to implement, but have the added benefit of preventing diabetes mellitus, cardiovascular diseases and some cancers in addition to GC. If the etiologic roles of *S. typhi* and *paratyphi*, *Helicobacter* species or other agents were better demonstrated, the benefits of prevention and treatment of these infections could be substantial. Diagnosis of gallstones and removal of the gallbladder represent the keystone to GC prevention in the majority of the populations at high risk.

Fig. 5.6.3 *Gallbladder carcinoma with a white, irregular cut surface next to a large gall stone*

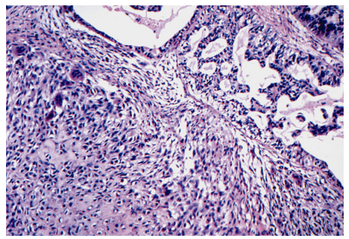


Fig. 5.6.4 *Carcinosarcoma of gallbladder. The tumour shows malignant glandular elements and a sarcomatous component with osteoid formation*

Author, Year (Country)	Reference category	Highest category		RR (95% CI)	Adjustment
Cohort studies					
Moller, 1994 [Eur J Cancer 30A: 344-350] (Denmark)	Non obese	Obese	Men	0.5 (0.1-1.8)	None reported
	Non obese	Obese	Women	1.4 (0.9-2.1)	None reported
Wolk et al, 2001 [Cancer Causes Control 12; 13-21] (Sweden)	Non obese	Obese	Men	0.9 (0.1-3.4)	Age and calendar year
	Non obese	Obese	Women	1.7 (1.1-2.5)	Age and calendar year
Calle et al, 2003 [N Engl J Med 348: 1625-1638] (US)	18.5-24.9	30.0-34.9	Men	1.8 (1.1-2.9)	Age, race, education and many (8) lifestyle variables
	18.5-24.9	30.0-34.9	Women	2.1 (1.6-2.9)	Age, race, education and many (8) lifestyle variables
Samanic et al, 2004 [Cancer Causes Control 17: 901-909] (US)	Non obese	Obese	White men	1.7 (1.1-2.6)	Age and calendar year
	Non obese	Obese	Black men	0.9 (0.2-3.9)	Age and calendar year
Kuriyama et al, 2005 [Int J Cancer 113: 148-157] (Japan)	18.5-24.9	25.0-27.4	Men	0.5 (0.1-3.9)	Age and many (11) lifestyle and reproductive variables
	18.5-24.9	≥30	Women	4.5 (1.4-14.2)	Age and many (11) lifestyle and reproductive variables
Oh et al, 2005 [J Clin Oncol 23: 4742-4754] (Korea)	18.5-22.9	≥27	Men	1.3 (0.7-2.2)	Age, area of residence, smoking, physical activity, alcohol
England et al, 2006 [Cancer Causes and control 16: 987-996] (Norway)	18.5-24.9	>30	Men	1.4 (1.0-1.9)	Age and birth cohort
	18.5-24.9	>30	Women	1.9 (1.6-2.2)	Age and birth cohort
Samanic et al, 2006 [Cancer causes and control 17: 901-909] (Sweden)	18.5-24.9	>30	Men	1.4 (0.7-2.7)	Age and smoking
Case-control studies					
Moerman, 1994 [Int J Cancer 57: 146-153] (Netherlands)	<27	≥27	Women	1.4 (0.7-2.6)*	Subjects frequently matched for age and sex
Strom, 1995 [Cancer 76: 1747-1756] (Bolivia, Mexico)	<24	>28	BMI average	1.6 (0.4-6.1)	Age and sex
	<25	>29	BMI maximum	2.6 (0.5-18.6)	Age and sex
Zatonski, 1997 [J Natl Cancer Inst 89: 1132-1138] (†)	I quartile	IV quartile	Men	1.0 (0.3-2.8)	Age, centre, alcohol, smoking, education and response status
	I quartile	IV quartile	Women	2.1 (1.2-3.8)	Age, centre, alcohol, smoking, education and response status
Serra, 2002 (Chile)	< 24.9	> 30		0.9 (0.4-1.8)	Age, sex, gallstone disease

Table 5.6.2 *Relative risks (RR) with corresponding 95% confidence intervals (CI) of gallbladder cancer for highest vs lowest category of body mass index (BMI)*
**Estimated from available data 1Australia, Canada, Netherlands, Poland*
Updated from Randi et al, 2006

REFERENCES

1. Boyle P, Smans M (2008). *IARC Scientific Publications, Number 156, Atlas of cancer mortality in the European Union and the European Economic Area 1993-1997*. Lyon, France: International Agency for Research on Cancer.

2. Wistuba II and Gazdar AF (2004). Gallbladder cancer: lessons from a rare tumour. *Nat Rev Cancer* 4: 695-706.

3. Lazcano-Ponce EC, Miquel JF, Munoz N, et al. (2001). Epidemiology and molecular pathology of gallbladder cancer. *CA Cancer J Clin* 51: 349-364.

4. Randi G, Franceschi S, La Vecchia C (2006). Gallbladder cancer worldwide: geographical distribution and risk factors. *Int J Cancer* 118: 1591-1602.

5. Misra S, Chaturvedi A, Misra NC, et al. (2003). Carcinoma of the gallbladder. *Lancet Oncol* 4: 167-176.

6. Larsson SC and Wolk A (2007). Obesity and the risk of gallbladder cancer: a meta-analysis. *Br J Cancer* 96: 1457-1461.

7. Randi G, Malvezzi M, Levi F, et al. *Epidemiology of biliary tract cancers: an update. In Press.*

8. Zatonski WA, Lowenfels AB, Boyle P, et al. (1997). Epidemiologic aspects of gallbladder cancer: a case-control study of the SEARCH Program of the International Agency for Research on Cancer. *J Natl Cancer Inst* 89: 1132-1138.

CANCER INSTITUTE PROFILE:
The University of Texas M. D. Anderson Cancer Center

The University of Texas M. D. Anderson Cancer Center was created by the Texas Legislature in 1941 and named one of the first three Comprehensive cancer centres by the National Cancer Act of 1971. It was ranked in 2007 by *U.S. News & World Report* as the top American hospital for cancer care. M. D. Anderson, which receives more research grants from the US National Cancer Institute than any other institution, spent in excess of US $465 million on research last year. Almost 84 000 patients were served in Houston-based facilities that include 512 inpatient beds and ambulatory units where more than 922 000 outpatient visits and treatments were provided. A record 12 000 patients participated in therapeutic clinical trials in 2007. M. D. Anderson awards bachelor's degrees in seven allied health disciplines and jointly confers master's and Ph.D. degrees in biomedical sciences. It also operates a two-unit Science Park in central Texas, has affiliations with caregivers as far away as Madrid, Spain, and has sister institution agreements in Asia, Europe, and Central and South America.

Website: www.mdanderson.org

5.7 Colorectal Cancer

Summary

> Colon and rectal cancers account for approximately 9.4% of total worldwide cancer cases, equivalent to about 1 million new cases, with a similar number of cases in men and women for colon cancer and a male predominance for rectal cancer

> Worldwide, there is at least a 25-fold variation in occurrence of colorectal cancer, with high incidence rates in affluent societies (accounting for 65% of all new cases)

> Differences in diet and lifestyle, particularly alcohol intake and physical inactivity, are believed to account for a large proportion of this variation

> Familial clustering has a genetic basis, usually through familial adenomatosis polyposis (FAP) and hereditary non-polyposis colon cancer (HNPCC)

> Randomised trials have demonstrated the efficacy of faecal occult blood testing in reducing mortality from colorectal cancer. Trials of sigmoidoscopy are approaching completion. Colonoscopy is the most reliable means for early detection and prevention of colorectal cancer by removal of adenomatous polyps

> Improved treatment has resulted in a five-year survival rate of about 50%, although this rate varies considerably worldwide based on available treatment options and between developed and developing areas

Incidence of colorectal cancer ranks fourth in men (after lung, prostate and stomach) and third in women, after breast and cervix uteri, with over 1 million new cases occurring every year worldwide [1]. The majority of cancers occurring in the colon and rectum are adenocarcinomas, which account for more than 90% of all large bowel tumours.

Colorectal cancer incidence shows wide geographical variation, with higher rates observed in New Zealand, Australia, North America, Europe and more recently Japan, and lower rates reported in Asia and Africa. Overall, similar patterns are observed in the two sexes, although colon and rectal cancer rates are 20% and up to 50% higher, respectively, in men than women. Incidence rates of colorectal cancer are increasing in countries where overall risk was formerly low (especially in Japan, but also elsewhere in Asia), while in high-risk countries, rates are either gradually increasing, stabilising (Northern and Western Europe) or declining with time (North America) [1].

Five-year survival estimates (in men) have been reported to be 65% in North America and 54% in Western Europe, 34% in Eastern Europe, and 30% in India. Globally, mortality is approximately one half that of incidence (about 529 000 deaths in 2002 in men and women combined). In terms of prevalence, colorectal cancer is the second most common cancer worldwide next to breast cancer [1]. The ratio of colon to rectal cancer incidence is about 2:1 or more, with higher values in North America and Australia/New Zealand, whereas in lower-risk countries the incidence is similar between the two anatomical sites. Overall, higher colon to rectal cancer ratios are observed in women.

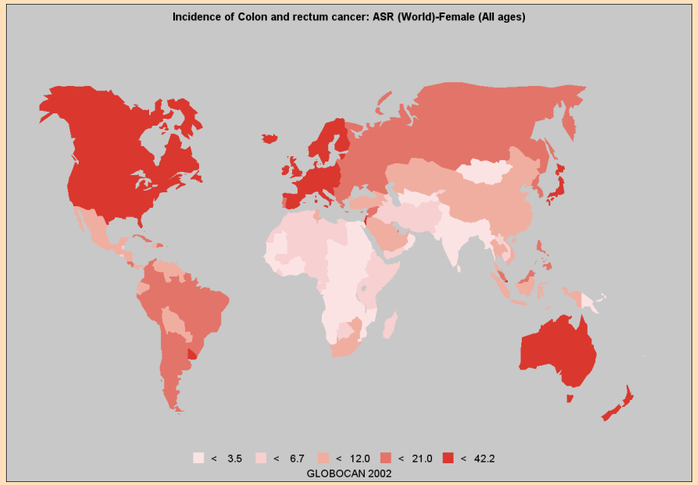
Colorectal cancer incidence presents a large economic burden worldwide, indicating a high benefit-cost ratio for research investment and the development of appropriate prevention and screening strategies.

Etiology and prevention

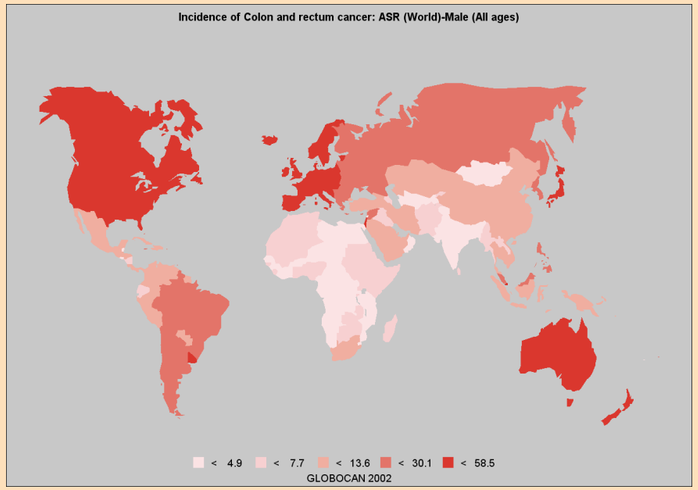
Initially, colorectal cancer was thought to arise primarily via a multistep process highlighted by changes in cell proliferation patterns with loss of growth control leading to sequential development of pre-malignant lesions (adenoma-carcinoma sequence) and involving several genetic changes (Figure 5.7.1). However, the underlying genetics and molecular mechanisms of colorectal cancer development are being continually refined. Recent studies of the genomes of a small series of colorectal tumours suggest that although a large number of genes are mutated, only a small proportion are responsible for driving tumour progression and growth [4]. It has been suggested that most colorectal tumours develop via three somewhat distinct pathways (suppressor, mutator and methylator), each of which appears to be associated with various genetic changes [5]. Some recent evidence is also suggestive of different etiologies for cancers based on their anatomical location in the colorectum [6]. The majority (~75%) of colorectal cancers are sporadic, arising from somatic mutations and clonal evolution at the tumour site. The remainder of cases are comprised of hereditary syndromes (familial adenomatous polyposis [FAP; 1%] and hereditary nonpolyposis colorectal cancer [HNPCC; 4–7%]), family/personal history of the disease or adenomatous polyps (15–20%), or other high-risk conditions (inflammatory bowel diseases, previous diagnoses for cancers of the ovary, endometrium, breast, bile duct, pancreas, stomach; 1%). HNPCC cancers do not usually develop via the adenoma-carcinoma sequence and are highlighted by mutations in mismatch repair genes and microsatellite instability. Genetic predisposition and age are the main non-modifiable risk factors for this disease.

Evidence from migrant studies has shown that populations moving from low- to high-risk areas rapidly reach the higher level of risk of the adopted country, indicating that lifestyle and dietary factors likely play an important role in colorectal cancer aetiology. Indeed, of all common cancers, a dietary influence on colorectal cancer risk is the most plausible because the colorectal mucosa is in direct and constant contact with food components and is also exposed to diet-induced metabolic and physiologic changes. However, the complexities of various dietary patterns, macro/micro-nutrient composition of foods, multiple potential interactions between nutrients, hormonal effects, gene-diet interactions and methodological issues make the study of the diet-colorectal cancer connection inherently difficult. Nonetheless, numerous dietary risk factors have been identified from experimental platforms as well as retrospective and prospective epidemiological studies. The weight of the existing evidence suggests that higher intake of total energy [7], red/processed meats [8,9] and alcohol [10] are all associated with increased risk of colorectal cancer whereas higher intake of fruits and vegetables may only moderately reduce the risk [11,12]. A colorectal cancer preventive role of dietary or cereal fibre is debatable [13], despite recent findings suggesting a negative association with high intakes [14]. Higher intake of calcium and Vitamin D has been reported to be colorectal cancer protective, but except for modest findings for calcium supplementation in some intervention studies of adenoma recurrence [15,16], evidence is still lacking for any firm conclusions. Much further research is required to elucidate the role of other compounds, foods, food components or their derivatives that may have effects that are colorectal cancer protective (folate, antioxidants, vitamins C/E, magnesium, selenium, phytochemicals, phytoestrogens, butyrate, resistant starches, tea/coffee, fish, whole grains, low glycemic index foods) or promotive (insulin, dietary carcinogens, secondary bile acids, iron, heterocyclic amines, refined sugars, high glycemic index foods). In addition, there are many complex interactions between environmental, dietary and genetic factors that may well modify colorectal cancer risk.

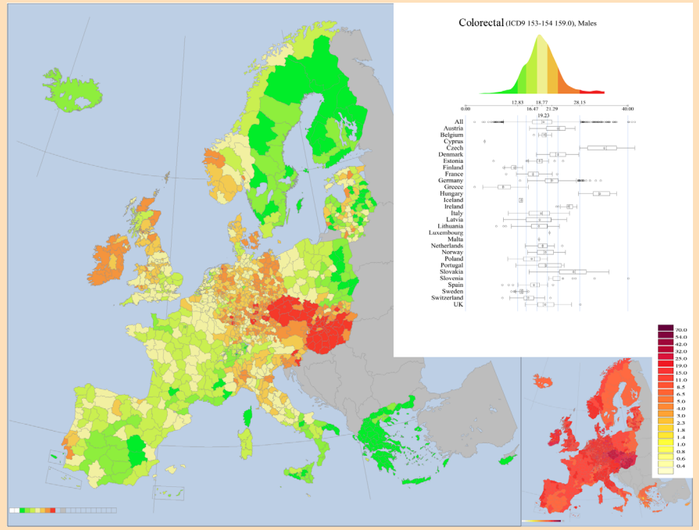
Among lifestyle factors, obesity has been suggested to be associated with an increased risk of colorectal cancer, although effects may vary by anatomical site and gender [17,18]. Physical inactivity has also been associated with an increased risk, although primarily for colon and less clearly for rectal cancer[20,21]. Thus, regular physical activity and avoidance of calorie over-consumption may represent two of the most effective ways of preventing this



World Map 5.7.1



World Map 5.7.2



European Map 5.7.1 *It is apparent from the maps that the pattern of geographical distribution in both men and women is substantially the same, with a broad band of high rates running east-west across the middle of Europe. Higher-than-average rates were found in Ireland and the northern parts of the United Kingdom, Denmark, southern parts of Norway, Germany and eastern Austria. Rates were also above average in parts of northern Italy and southern Portugal–more markedly in males than in females.*

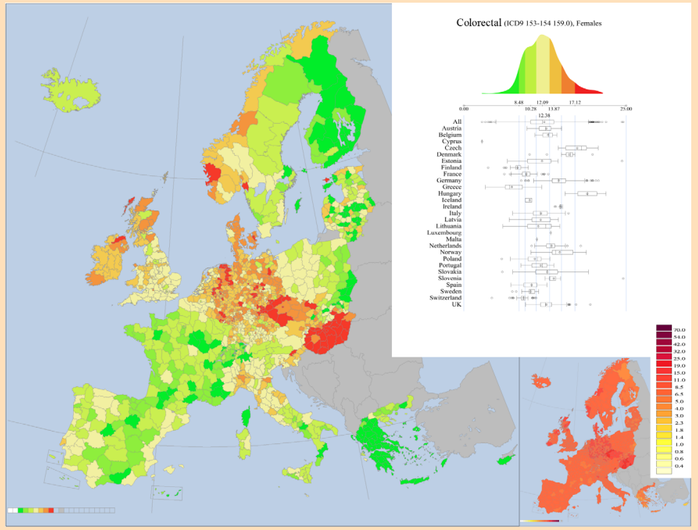
disease. Cigarette smoking is another major modifiable lifestyle factor that recent studies suggest is involved in the colorectal carcinogenesis process [22], although an induction period of four decades has been suggested [23].

Evidence from observational studies indicates that long term use of non-steroidal anti-inflammatory drugs (NSAIDS), particularly aspirin, may reduce the risk of colorectal cancer [24-27]. Although randomised controlled trials on the risk of colorectal adenoma indicate that these medications may have anti-cancer effects [28-32], results from trials actually focusing on colorectal cancer risk have been inconsistent. Trials providing lower-dose aspirin failed to show a protective effect [33-35], while those providing higher doses show a protection against colorectal cancer after at least 5 years of treatment, with a latency period of about 10 years [24]. Nevertheless, recommendations to general populations on NSAID or aspirin use for cancer prevention are premature given that use of these medications is accompanied by many side effects and may increase the risk of other serious medical conditions, necessitating close medical supervision. Thus, their use as chemopreventive agents may only be practical in those at very high risk of developing colorectal cancer (e.g. FAP patients). In women, use of hormone replacement therapy (HRT) has been associated with a reduced risk of colorectal cancer but also with concomitant increases in the risk of breast cancer, and possibly coronary heart disease and thromboembolic events, making its use in any colorectal cancer prevention strategy impractical. Removal of adenomatous polyps has also been found to reduce disease risk, but in practice it is only applicable to those undergoing invasive screening.

As with many cancers, early detection of precancerous lesions and rapid, effective treatment of early colorectal tumours appear to be key points of screening and treatment strategies, not only for those at high risk of the disease, but also for general populations at large. Nonetheless, the primarily sporadic nature of the disease indicates that a reduction in colorectal cancer incidence worldwide can best be achieved by effective primary prevention and changes in modifiable risk factors.

Conclusions

The worldwide variations in colorectal cancer risk suggest a large contribution of dietary and lifestyle factors to the etiology of the disease. Most colorectal cancers are sporadic adenocarcinomas arising via a multistep process that involves identifiable pre-cancerous lesions. Although it is understood that regular screening and removal of adenomatous polyps are effective prevention strategies, they are expensive and necessitate close medical supervision. The most important lifestyle changes for disease prevention appear to be weight reduction, physical activity and smoking cessation. The weight of the current literature suggests that a diet low in alcohol, red/processed meats, and refined carbohydrates, and higher in fruits, vegetables, whole grains and dietary fibre may assist in colorectal cancer prevention. Although NSAIDS and HRT have been shown to decrease colorectal cancer risk, their association with increased risk of other disease states makes their use as chemopreventive agents impractical, except in those at very high risk. Future research should focus on elucidating the role of complex gene-diet interactions, and identifying protective dietary and lifestyle patterns.



European Map 5.7.2 *The highest rates in men and women were in the Czech Republic, Slovakia, Slovenia and Hungary. Low rates were found in Finland, Sweden and Poland, and in much of southern Europe: Greece and southern Italy, France, Switzerland and Spain [Boyle and Smans, 2008].*

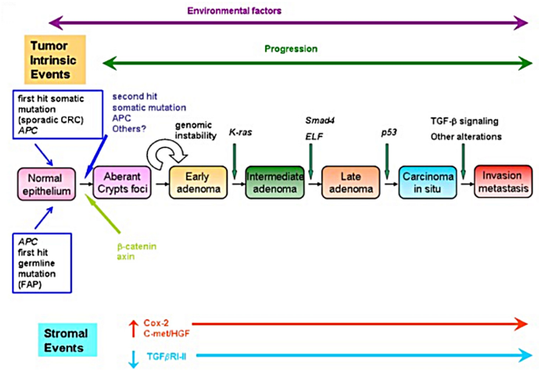


Fig. 5.7.1 *A schematic diagram of pathways that control colorectal tumourigenesis. Adapted from Misbra et al; Oncogene (2005) 24, 5775-5789*

REFERENCES

1. Parkin DM, Bray F, Ferlay J, et al. (2005). Global cancer statistics, 2002. *CA Cancer J Clin* 55: 74-108.

2. Ferlay J, Bray F, Pisani P, et al., eds. (2004). GLOBOCAN 2002: Cancer incidence, Mortality and Prevalence Worldwide. *IARC CancerBase* No. 5 Version 2.0. Lyon, France: International Agency for Research on Cancer. Available from: http://www-dep.iarc.fr/ Date Accessed: November 14, 2008.

3. Boyle P, Smans M (2008). IARC Scientific Publications, Number 159, Atlas of cancer mortality in the European Union and the European Economic Area 1993-1997. Lyon, France: International Agency for Research on Cancer.

4. Wood LD, Parsons DW, Jones S, et al. (2007). The genomic landscapes of human breast and colorectal cancers. *Science* 318: 1108-1113.

5. Worthley DL, Whitehall VL, Spring KJ, et al. (2007). Colorectal carcinogenesis: road maps to cancer. *World J Gastroenterol* 13: 3784-3791.

6. Smith D, Ballal M, Hodder R, et al. (2006). The adenoma carcinoma sequence: an indoctrinated model for tumorigenesis, but is it always a clinical reality? *Colorectal Dis* 8: 296-301.

7. Giovannucci E and Goldin B (1997). The role of fat, fatty acids, and total energy intake in the etiology of human colon cancer. *Am J Clin Nutr* 66: 1564S-1571S.

8. Larsson SC and Wolk A (2006). Meat consumption and risk of colorectal cancer: a meta-analysis of prospective studies. *Int J Cancer* 119: 2657-2664.

9. Norat T, Bingham S, Ferrari P, et al. (2005). Meat, fish, and colorectal cancer risk: the European Prospective Investigation into cancer and nutrition. *J Natl Cancer Inst* 97: 906-916.

10. Moskal A, Norat T, Ferrari P, et al. (2007). Alcohol intake and colorectal cancer risk: a dose-response meta-analysis of published cohort studies. *Int J Cancer* 120: 664-671.

11. Riboli E and Norat T (2003). Epidemiologic evidence of the protective effect of fruit and vegetables on cancer risk. *Am J Clin Nutr* 78: 559S-569S.

12. Koushik A, Hunter DJ, Spiegelman D, et al. (2007). Fruits, vegetables, and colon cancer risk in a pooled analysis of 14 cohort studies. *J Natl Cancer Inst* 99: 1471-1483.

13. Obrador A (2006). Fibre and colorectal cancer: a controversial question. *Br J Nutr* 96: S46-S48.

14. Bingham SA, Day NE, Luben R, et al. (2003). Dietary fibre in food and protection against colorectal cancer in the European prospective investigation into cancer and nutrition (EPIC): an observational study. *Lancet* 361: 1496-1501.

15. Baron JA, Beach M, Mandel JS, et al. (1999). Calcium supplements for the prevention of colorectal adenomas. Calcium Polyp Prevention Study Group. *N Engl J Med* 340: 101-107.

16. Baron JA, Beach M, Mandel JS, et al. (1999). Calcium supplements and colorectal adenomas. Polyp Prevention Study Group. *Ann N Y Acad Sci* 889: 138-145.

17. Larsson SC and Wolk A (2007). Obesity and colon and rectal cancer risk: a meta-analysis of prospective studies. *Am J Clin Nutr* 86: 556-565.

18. Dai Z, Xu YC, Niu L (2007). Obesity and colorectal cancer risk: a meta-analysis of cohort studies. *World J Gastroenterol* 13: 4199-4206.

19. Moghaddam AA, Woodward M, Huxley R (2007). Obesity and risk of colorectal cancer: A meta-analysis of 31 studies with 70,000 events. *Cancer Epidemiol Biomarkers Prev* 16: 2533-2547.

20. Friedenreich C, Norat T, Steindorf K, et al. (2006). Physical activity and risk of colon and rectal cancers: the European prospective investigation into cancer and nutrition. *Cancer Epidemiol Biomarkers Prev* 15: 2398-2407.

21. Samad AK, Taylor RS, Marshall T, et al. (2005). A meta-analysis of the association of physical activity with reduced risk of colorectal cancer. *Colorectal Dis* 7: 204-213.

22. Luchtenborg M, White KK, Wilkens L, et al. (2007). Smoking and colorectal cancer: different effects by type of cigarettes? *Cancer Epidemiol Biomarkers Prev* 16: 1341-1347.

23. Giovannucci E and Martinez ME (1996). Tobacco, colorectal cancer, and adenomas: a review of the evidence. *J Natl Cancer Inst* 88: 1717-1730.

24. Flossmann E and Rothwell PM (2007). Effect of aspirin on long-term risk of colorectal cancer: consistent evidence from randomised and observational studies. *Lancet* 369: 1603-1613.

25. Chan AT, Giovannucci EL, Meyerhardt JA, et al. (2005). Long-term use of aspirin and nonsteroidal anti-inflammatory drugs and risk of colorectal cancer. *JAMA* 294: 914-923.

26. Larsson SC, Giovannucci E, Wolk A (2006). Long-term aspirin use and colorectal cancer risk: a cohort study in Sweden. *Br J Cancer* 95: 1277-1279.

27. Jacobs EJ, Thun MJ, Bain EB, et al. (2007). A large cohort study of long-term daily use of adult-strength aspirin and cancer incidence. *J Natl Cancer Inst* 99: 608-615.

28. Baron JA, Cole BF, Sandler RS, et al. (2003). A randomized trial of aspirin to prevent colorectal adenomas. *N Engl J Med* 348: 891-899.

29 Baron JA, Sandler RS, Bresalier RS, et al. (2006). A randomized trial of rofecoxib for the chemoprevention of colorectal adenomas. *Gastroenterology* 131: 1674-1682.

30. Benamouzig R, Deyra J, Martin A, et al. (2003). Daily soluble aspirin and prevention of colorectal adenoma recurrence: one-year results of the APACC trial. *Gastroenterology* 125: 328-336.

31. Bertagnolli MM, Eagle CJ, Zauber AG, et al. (2006). Celecoxib for the prevention of sporadic colorectal adenomas. *N Engl J Med* 355: 873-884.

32. Sandler RS, Halabi S, Baron JA, et al. (2003). A randomized trial of aspirin to prevent colorectal adenomas in patients with previous colorectal cancer. *N Engl J Med* 348: 883-890.

33. Cook NR, Lee IM, Gaziano JM, et al. (2005). Low-dose aspirin in the primary prevention of cancer: the Women's Health Study: a randomized controlled trial. *JAMA* 294: 47-55.

34. Gann PH, Manson JE, Glynn RJ, et al. (1993). Low-dose aspirin and incidence of colorectal tumors in a randomized trial. *J Natl Cancer Inst* 85: 1220-1224.

35. Sturmer T, Glynn RJ, Lee IM, et al. (1998). Aspirin use and colorectal cancer: post-trial follow-up data from the Physicians' Health Study. *Ann Intern Med* 128: 713-720.

CANCER INSTITUTE PROFILE: Children's Cancer Research Institute (CCRI)

The Children's Cancer Research Institute (CCRI), in Vienna, Austria, conducts specialised research into the causes and improved treatment of malignant childhood diseases. It is supported by the St. Anna Kinderkrebsforschung, which was founded as a charity-based non-profit association in 1986 by a parents' initiative. The CCRI is closely associated with the St. Anna Kinderspital, the major children's hospital in Austria, which has a strong focus on oncology. The CCRI currently houses 9 research groups and a documentation department. Major areas of research comprise the study of functional consequences of genetic aberrations in childhood cancer, engineering of the immune system to fight the tumour and to improve haematopoietic stem cell transplantation, improved diagnosis and individualisation of therapy. In addition, the CCRI supports a number of clinical trials in paediatric cancer patients. The CCRI is involved in several European research projects and closely collaborates with the major paediatric research and treatment centres in Europe and the USA to advance scientific knowledge and improve outcomes in children with cancer.

website: www.ccri.at

5.8 Nasopharyngeal Carcinoma

Summary

> Nasopharyngeal carcinoma (NPC) is a significant health problem in southern and eastern Asia

> Preserved foods and EBV are key exposure factors involved in NPC etiology

> Genetic susceptibility is certainly a risk factor, but which genes are involved remains unclear

Nasopharyngeal carcinoma (NPC) is a malignant tumour arising in the epithelial lining of the nasopharynx. NPC presents most commonly among people of 40-55 years of age, but presentation in adolescence has also been observed. There is a gender bias, NPC being approximately 2-3 times more common in males than females. Treatment of this malignancy usually involves radiotherapy, either alone or in conjunction with chemotherapy, with a 5-year survival rate of approximately 60-65% and a slightly better prognosis in women than men [1]. WHO criteria classifies NPC into general histological subtypes: keratinizing squamous-cell carcinoma (WHO-I) and non-keratinising squamous-cell carcinoma. Non-keratinising squamous-cell carcinoma was previously subdivided into differentiated (WHO-II) and non-differentiated forms (WHO-III) but it has more recently suggested to be merged into a single broader category to account for overlap between the two [2]. A quite rare form, basaloid squamous-cell carcinoma, is also recognized [2]. Keratinizing squamous-cell carcinoma histology tends to be more common in Caucasian (non-endemic) populations [2], while non-keratinising squamous-cell carcinoma tends to be more prominent in Asian (endemic) populations [3].

Etiology

NPC incidence has an extremely heterogeneous geographical and ethnic distribution which is currently not explained. In high-resource nations NPC is generally a rare malignancy (incidence 3 <1/100 000/year). By contrast, relatively high rates are recorded across Asia where age-standardised incidence rates reach 20/100 000 among men [2,5-8] (Figure 5.8.1). Regions of Southern China contain the most clearly described high-risk areas, although similar high rates are reported across most of Southeast Asia. Moderately high rates have also been reported in Northern Africa and among natives of the Arctic region [4,7]. The Malaysian region of Sarawak has one of the highest incidences of NPC, where age-standardised rates of NPC were 13.5 and 6.5 among men and women, respectively. Rates among Chinese and Malays in Sarawak were similar to rates observed in these ethnic groups in Singapore. However, the Malaysian Bidayuh ethnic subgroup population appeared to have an exceptionally high incidence, reaching 31.5/100 000 and 11.8/100 000 among men and women respectively. These incidence levels represent the highest reported rates in any population, being approximately 50% higher than in Hong Kong (summarised in Figure 5.8.1), which has the next highest reported incidence rate [4]. The reason for this high risk in this particular ethnic subset is unclear, and other studies from other regions show relatively little difference between ethnic subgroups [8].

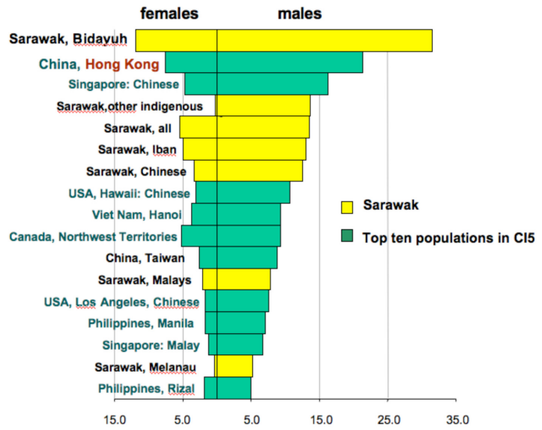


Fig. 5.8.1 *Age-standardised incidence rates of NPC across various populations in number of new cases per 100 000 population per year.[4]*

NPC risk exposures

Epstein-Barr Virus (EBV). From research dating to the 1960s, EBV has been consistently implicated in NPC susceptibility [9]. Titres of EBV antibodies have been found to be higher in NPC cases compared to control individuals [1,5]. The full-length EBV genome is found in the nuclei of almost all malignant NPC cells. The tight correlation between EBV and NPC has meant that there have been efforts to use EBV, or indicators of EBV-related activation, as early NPC detection tools [8,10]. The carcinogenic mechanisms underlying EBV infection and NPC susceptibility remain unclear. Infection with EBV is relatively ubiquitous in most populations, yet NPC incidence has an extremely heterogeneous geographical and ethnic distribution. It is therefore unlikely that EBV infection itself is a single cause of NPC. An underlying etiological model may be that some EBV strains may escape immune surveillance, with genetic susceptibility and other environmental factors playing an important role in this process.

Preserved foods. The consumption of foods preserved using high amounts of salt or other preservatives has also been consistently linked with NPC risk [6]. Epidemiological studies have consistently noted that consumption of fish

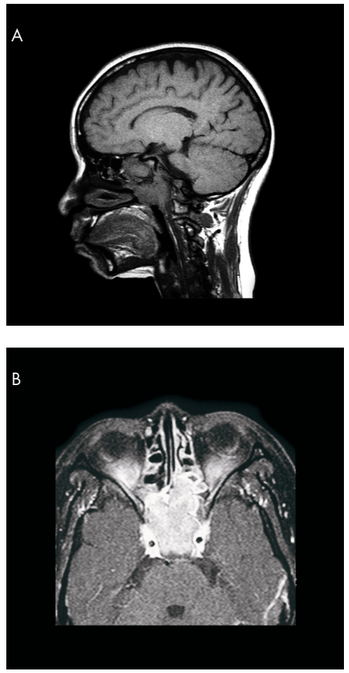
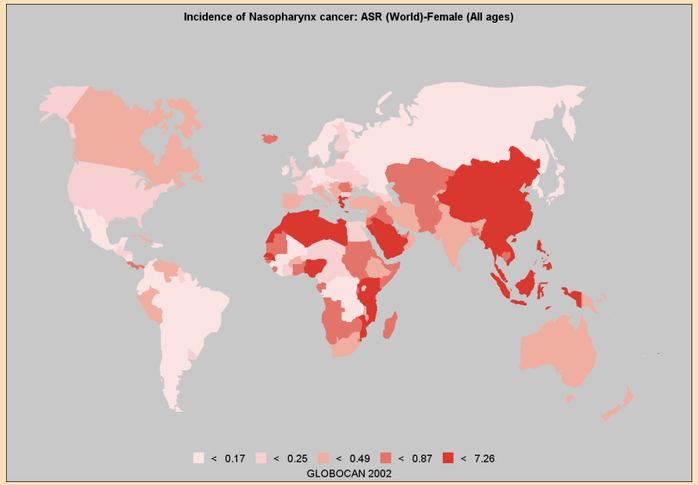
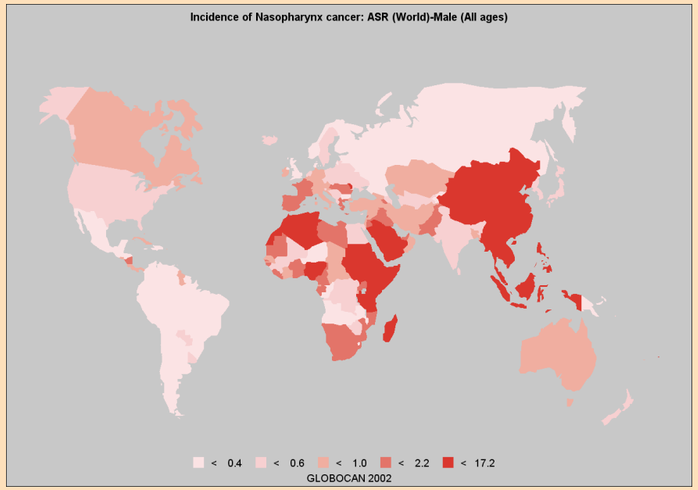


Fig. 5.8.2 *A and B: Magnetic resonance imaging of nasopharyngeal carcinoma*



World Map 5.8.1



World Map 5.8.2

preserved using high levels of salt conferred a 2-3-fold increase in NPC risk. This risk appears to be most apparent when such foods are consumed at early ages [1]. Although the evidence is somewhat less consistent, similar risks have been associated with other preservation processes [11]. The majority of the high-risk regions appear to use such preservation practices, notably in Southern China and South East-Asia (salted fish), and similarly in other at-risk populations such as North Africa (*quaddid*, rancid butter). Early-age exposure may have particular relevance to these populations as use of such foodstuffs as weaning foods is relatively common in many of the high-risk NPC populations.

The evidence that high-salt preservation techniques are implicated in NPC is also supported by experiments in animal models, with diets high in salted fish leading to occurrence of NPC in rats [12,13]. The carcinogenic mechanism is thought to be related to the food preservation process not being completely efficient, thus leading to a partial putrefaction of the food material. This partial putrefaction results in high levels of N-nitrosamines (N-nitrodimethlyamine (NDMA), N-nitropyrrolidine (NPYR) and N-nitrosopiperidine (NPIP)), which have been postulated to be carcinogens [14].

Tobacco, alcohol and other exposures. There is sufficient evidence to suggest that tobacco exposure increases risk of NPC, [15] with most studies reporting a 2-6 fold increase in risk for those exposed. Whether consumption of alcohol is involved in NPC risk is less clear [9], with some studies suggesting an increased risk, but most studies finding no association. Although again their role has not yet been clearly elucidated, occupations that result in exposure to chemicals and solvents, smoke fumes or wood dust have been suggested to play a role in NPC risk, particularly in Causasian populations [8].

Genetic susceptibility to NPC

Genetics appear to play an important role in susceptibility to NPC. Familial clustering appears common among NPC patients, with >5% of NPC cases reported to have a similarly affected first-degree relative [16]. The familial relative risk has been estimated to be in the region of 8-10 fold, [17] indicating that NPC has one of the most important genetic relative risks of all types of cancer [18]. Conclusions from migrant studies are also consistent with genetic risk, with second-and third-generation migrants from endemic regions maintaining an increased risk of developing NPC in low-risk areas [1].

Genes implicated in NPC susceptibility. The identity of the genes involved in susceptibility to NPC is far from clear. The most consistent line of evidence for genetic risk factors for NPC is the HLA Class I region, with increased risks being observed for both HLA-A and B variants in a number of studies [19,20]. Involvement of the HLA region and immunological response would also be consistent with the involvement of EBV in NPC susceptibility.

Family-based linkage analysis has also provided evidence of two other susceptibility loci. A family study based on 20 multicase families from Guangzhou, southern China has also been conducted, [21] showing LOD scores of up to 3.67 for the region 4p15.1-q12, suggesting the potential for a major susceptibility locus in this region. A subsequent study was based on 18 multiple-case families from Hunan Province, southern China, including 46 affected and 96 unaffected individuals, who were genotyped for 5 polymorphic markers in the region 4p15-q12, as well as for 8 markers on chromosome 3q and 7 markers on the short arm of chromosome 9q [22]. In contrast to the initial study by Feng et al. [21], no evidence for linkage was identified for polymorphic markers on chromosome 4. An NPC susceptibility locus was identified on 3p21 with a maximum LOD score of 4.18.

While some NPC susceptibility genes have been suggested under the linkage peaks on chromosomes 3, 4 and 6 [23-25], there have been no conclusive candidates, and considerable effort in this area is clearly required. Additional candidate genes deduced from the proposed function of the gene (e.g. *NAT2* or *CYP2A6*) have been examined, but again without conclusive evidence [8].

Conclusions

In the high-prevalence regions such as Southeast Asia and southern China, NPC makes a considerable contribution to the overall burden of cancer morbidity and mortality. Exposure to EBV and consumption of partially putrefied foods appear to play key roles in NPC development, but each of these alone does not appear predominant in causing NPC susceptibility. How these factors interact with other unknown NPC risk factors (in particular genetic factors) remains unclear. Recent technological advances in genetic research, in combination with large, well-designed epidemiological studies, offer the possibility of elucidating the factors that lead to this multifactorial disease.

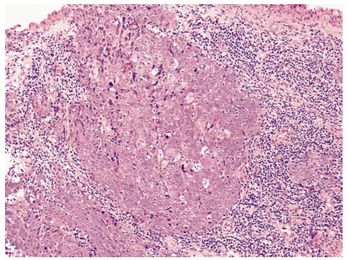


Fig. 5.8.3 *Nasopharyngeal nonkeratinizing carcinoma. Tumour islands are obvious in the lymphoid stroma*

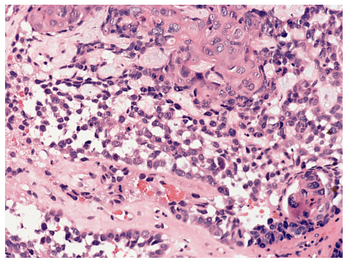


Fig. 5.8.4 *Basaloid squamous-cell carcinoma of the nasopharynx. The basaloid tumour cells show a festooning growth pattern, and are interspersed by tumour cells with squamous differentiation*

REFERENCES

1. Parkin DM, Whelan SL, Ferlay J, et al. (2002). *IARC scientific publications, Number 155, Cancer incidence in five continents, Volume VIII*. Lyon, France: International Agency for Research on Cancer.

2. Barnes L, Eveson JW, Reichart P, et al. (2005). *World Health Organization classification of tumours. Pathology and genetics of tumours of the head and neck*. Lyon: International Agency of Research on Cancer.

3. Ou SH, Zell JA, Ziogas A, et al. (2007). Epidemiology of nasopharyngeal carcinoma in the United States: improved survival of Chinese patients within the keratinizing squamous-cell carcinoma histology. *Ann Oncol* 18: 29-35.

4. Devi BC, Pisani P, Tang TS, et al. (2004). High incidence of nasopharyngeal carcinoma in native people of Sarawak, Borneo Island. *Cancer Epidemiol Biomarkers Prev* 13: 482-486.

5. Spano JP, Busson P, Atlan D, et al. (2003). Nasopharyngeal carcinomas: an update. *Eur J Cancer* 39: 2121-2135.

6. Yu MC and Henderson BE (1987). Intake of Cantonese-style salted fish as a cause of nasopharyngeal carcinoma. *IARC Sci Publ* 84: 547-549.

7. Yu MC (1991). Nasopharyngeal carcinoma: epidemiology and dietary factors. *IARC Sci Publ* 105: 39-47.

8. Chang ET and Adami HO (2006). The enigmatic epidemiology of nasopharyngeal carcinoma. *Cancer Epidemiol Biomarkers Prev* 15: 1765-1777.

9. IARC (1997). *IARC monographs on the evaluation of carcinogenic risks to humans, Volume 70, Epstein-Barr virus and Kaposi's sarcoma herpesvirus/human herpesvirus 8*. Lyon, France: International Agency for Research on Cancer.

10. Zong YS, Sham JS, Ng MH, et al. (1992). Immunoglobulin A against viral capsid antigen of Epstein-Barr virus and indirect mirror examination of the nasopharynx in the detection of asymptomatic nasopharyngeal carcinoma. *Cancer* 69: 3-7.

11. Feng BJ, Jalbout M, Ayoub WB, et al. (2007). Dietary risk factors for nasopharyngeal carcinoma in Maghrebian countries. *Int J Cancer* 121: 1550-1555.

12. Huang DP, Ho JH, Saw D, et al. (1978). Carcinoma of the nasal and paranasal regions in rats fed Cantonese salted marine fish. *IARC Sci Publ* 20: 315-328.

13. Yu MC, Nichols PW, Zou XN, et al. (1989). Induction of malignant nasal cavity tumours in Wistar rats fed Chinese salted fish. *Br J Cancer* 60: 198-201.

14. IARC (1993). *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 56, Some naturally occurring substances, food items and constituents, heterocyclic aromatic amines and mycotoxins*. Lyon, France: International Agency for Research on Cancer.

15. IARC (2004). *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 83, Tobacco smoke and involuntary smoking*. Lyon, France: International Agency for Research on Cancer.

16. Yu MC, Garabrant DH, Huang TB, et al. (1990). Occupational and other non-dietary risk factors for nasopharyngeal carcinoma in Guangzhou, China. *Int J Cancer* 45: 1033-1039.

17. Ung A, Chen CJ, Levine PH, et al. (1999). Familial and sporadic cases of nasopharyngeal carcinoma in Taiwan. *Anticancer Res* 19: 661-665.

18. Goldgar DE, Easton DF, Cannon-Albright LA, et al. (1994). Systematic population-based assessment of cancer risk in first-degree relatives of cancer probands. *J Natl Cancer Inst* 86: 1600-1608.

19. Hildesheim A, Apple RJ, Chen CJ, et al. (2002). Association of HLA class I and II alleles and extended haplotypes with nasopharyngeal carcinoma in Taiwan. *J Natl Cancer Inst* 94: 1780-1789.

20. Hu SP, Day NE, Li DR, et al. (2005). Further evidence for an HLA-related recessive mutation in nasopharyngeal carcinoma among the Chinese. *Br J Cancer* 92: 967-970.

21. Feng BJ, Huang W, Shugart YY, et al. (2002). Genome-wide scan for familial nasopharyngeal carcinoma reveals evidence of linkage to chromosome 4. *Nat Genet* 31: 395-399.

22. Xiong W, Zeng ZY, Xia JH, et al. (2004). A susceptibility locus at chromosome 3p21 linked to familial nasopharyngeal carcinoma. *Cancer Res* 64: 1972-1974.

23. Duh FM, Fivash M, Moody M, et al. (2004). Characterization of a new SNP c767A/T (Arg222Trp) in the candidate TSG FUS2 on human chromosome 3p21.3: prevalence in Asian populations and analysis of association with nasopharyngeal cancer. *Mol Cell Probes* 18: 39-44.

24. Seng TJ, Low JS, Li H, et al. (2007). The major 8p22 tumor suppressor DLC1 is frequently silenced by methylation in both endemic and sporadic nasopharyngeal, esophageal, and cervical carcinomas, and inhibits tumor cell colony formation. *Oncogene* 26: 934-944.

25. Yau WL, Lung HL, Zabarovsky ER, et al. (2006). Functional studies of the chromosome 3p21.3 candidate tumor suppressor gene BLU/ZMYND10 in nasopharyngeal carcinoma. *Int J Cancer* 119: 2821-2826.

5.9 Kaposi Sarcoma

Summary

> Kaposi sarcoma is an AIDS-defining malignancy, and it has become one of the commonest cancers in both men and women in Sub-Saharan Africa

> Kaposi's sarcoma-associated herpesvirus (KSHV), the eighth human herpesvirus to be identified (also called HHV-8) is the causative agent of Kaposi's sarcoma

> Different subtypes of KSHV are related to geographical localisation, ethnicity and prevalence of HIV

> The widespread use of combined antiretroviral treatment has led to a marked decrease in the incidence of KS in the developed world whereas it remains extremely common among AIDS patients in Sub-Saharan Africa

Kaposi sarcoma (KS) is a tumour that develops from lymphatic endothelial cells. The clinical hallmarks of KS are red-purple nodular lesions on skin or visceral surfaces associated with prominent angiogenesis [1].

KS is classified in four different clinico-epidemiological forms: a) classic KS, usually affecting elderly men from the Mediterranean region; b) endemic KS, found mainly in Equatorial Africa; c) iatrogenic KS, found in patients submitted to immunosuppressive therapy and d) epidemic KS, affecting patients with Acquired Immunodeficiency Syndrome (AIDS-KS) [2]. Kaposi's sarcoma-associated herpesvirus (KSHV) is now recognised to be the cause of all forms of KS. KSHV is also the causative agent of primary effusion lymphoma (PEL) and HIV-associated multicentric Castleman's disease, a B-cell lymphoproliferative disorder [1].

Epidemiology of Kaposi sarcoma

Kaposi sarcoma (KS) was first described in 1872 by Moritz Kaposi, a Hungarian dermatologist, who reported five elderly men of Mediterranean origin with indolent multi-focal vascular tumours designated "idiopathic multiple pigmented sarcoma of the skin" (classic KS). Subsequently, a form affecting the skin of the lower limbs of young men was described in the 1920s in Sub-Saharan Africa (endemic KS). KS remained a rare cancer for many years until the 1980s, when an increase in the incidence of an aggressive form of KS was associated with the advent of AIDS (epidemic KS). The observation that homosexual and bisexual men were at higher risk of KS than any other HIV transmission group triggered suspicions that specific sexual practices would increase the risk of KS, leading to the search and discovery of Kaposi's sarcoma-associated herpesvirus (KSHV), the infectious agent causative of KS.

The worldwide epidemiology of KS has changed dramatically since the advent of AIDS. Before the spread of HIV (years 1968–1970), KS represented approximately 7% of all cancers registered in males in Sub-Saharan Africa, whereas in the years 1989–1991, KS accounted for 50% of the total number of cancers affecting males [2]. All of the highest-risk areas for KS are in Sub-Saharan Africa (Figure 5.9.1). Elsewhere, KS incidence rates are lowest in England (ASR of 0.014) and highest in Sardinia, Italy (ASR of 1.6 per 100 000) in both men and women [2].

In the early phase of the HIV epidemic, KS was the cancer type most frequently diagnosed among AIDS patients. Since the introduction of highly active antiretroviral therapy (HAART) for HIV in the developed world, the incidence of KS has declined sharply, with incidence rates coming second to non-Hodgkin lymphomas between years 1996–2002 [3]. However, it has become the commonest cancer diagnosed in the general male population in some areas of Sub-Saharan Africa (ASR of 30 per 100 000 in Central Africa), whereas among women it is now surpassed only by cervical cancer [4].

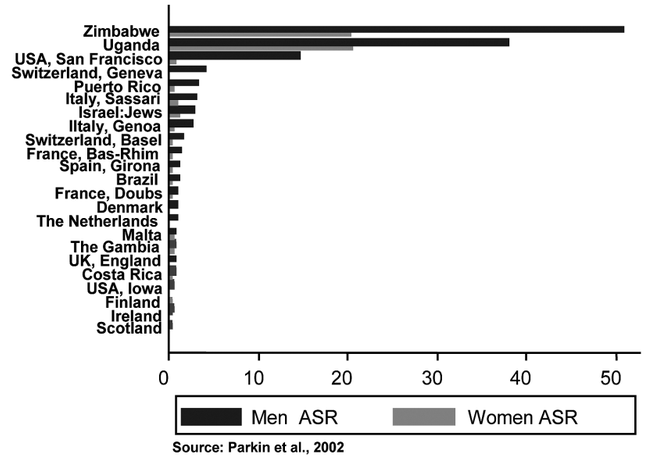


Fig. 5.9.1 *Kaposi sarcoma age-standardised (world) incidence (ASR) per 100.000 among males in selected countries*

Epidemiological studies have shown that the risk of KS is a thousandfold greater in patients with AIDS than in the general population and men are at higher risk of developing KS than women. Male to female ratios of 2–3:1 are found in classic KS [2]. In epidemic KS, the KS incidence was much higher in men (ASR of 8.0 per 100 000) than women (ASR of 0.09 per 100 000) in the USA during years 1979-1998 [5], whereas in Africa, the male to female ratio has declined from 10:1 in the pre-AIDS era to 3:1 after the spread of HIV [2]. The risk of KS is significantly higher in homosexual and bisexual men than among other HIV transmission groups, and women who report having had sex with bisexual men are 4 times more likely to have KS in comparison with women reporting sexual partners from other HIV transmission groups [6].

The age distribution of KS has been changed by the AIDS epidemic. While classic KS used to be diagnosed mainly in elderly men, the incidence of the associated KS is now highest in the late thirties [2]. No strong risk factors other than age, gender and immunosupression have been so far identified in HIV-seronegative populations in various case–control studies.

AIDS-defining KS is strongly associated with a decrease in CD4+ T-cell count and is seldom seen with CD4+ T-cell count above 300/µl. Immune deficiency is also associated with the development of KS in solid-organ transplant recipients (iatrogenic KS). People living with HIV however, have shown a much greater risk of developing KS than iatrogenically immunosuppressed patients, probably on account of differences in KSHV prevalences [7]. Indeed, the incidence of KS among iatrogenically immunosuppressed patients is higher in geographic areas where the prevalence of KSHV infection is also high, such as in the Mediterranean basin, e.g. Italy [8] than in Northern Europe or the United States. Unexplained low incidences of KS are reported in a few populations where the prevalence of KSHV infection is notably high, such as among Brazilian Amerindians [9]. Such discrepancies between the prevalence of KSHV and KS incidence point to either severe underreporting of KS in some countries or unknown protector factors in the development of KS [9].

Etiology of Kaposi sarcoma

As early as 1972, herpesvirus-like particles were first identified in cell lines prepared from endemic KS tumour tissue, suggesting that a herpesvirus could play a role in the pathogenesis of KS [1].

It was not until 1993 when "herpesvirus-like" DNA sequences were identified in 25/26 (92.7%) AIDS-KS biopsies by using advanced techniques of molecular biology for DNA amplification. The sequences found were homologues to the gammaherpesvirus herpesvirus saimiri and Epstein-Barr virus. After comparisons of viral genomes, Kaposi sarcoma-associated herpesvirus (KSHV), the first human gamma-2 herpesvirus to be identified, was classified as belonging to the Rhadinovirus genus, sub-family gammaherpesvirus [10]. The authors that discovered the virus named it Kaposi sarcoma-associated herpesvirus (KSHV), but the designation human herpesvirus eight (HHV-8) is also used.

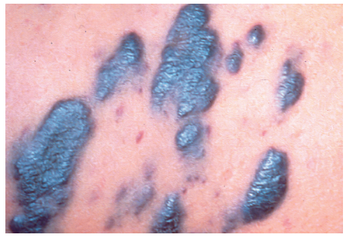
Subsequently, several studies described the presence of KSHV DNA in tumour tissue biopsies of classic, endemic, iatrogenic and epidemic types of KS [10].

Diagnostic tests to detect infection with Kaposi sarcoma-associated herpesvirus (KSHV)

Polymerase Chain Reaction (PCR). KSHV/DNA can be detected by PCR in tumour tissue samples obtained from the large majority of patients with classic, endemic, iatrogenic or epidemic KS (AIDS-KS). Less frequently, KSHV DNA can be amplified from blood cells obtained from patients with any type of KS, with successful detection in up to 50% in some cases series [2].

KSHV DNA detection from blood of general populations is difficult. The virus is more often detected in blood donors using second-round PCR or quantitative real-time PCR, with prevalence of detection ranging between 0% in USA to 20% in Sub-Saharan Africa [2] among blood donors.

Serological diagnosis. As with any other herpesvirus, KSHV genome encodes for viral proteins involved in latent and lytic viral life cycles. Serological assays using KSHV latent and lytic cycle-associated viral antigens have been developed to detect KSHV infection [11]. The viral antigen expressed during the latent phase of infection is termed latency-associated nuclear antigen (LANA). Immunofluorescence-based assays (IFA) can identify nuclear (IFA-LANA) or cytoplasmic (IFA-lytic assay) punctuate staining under the fluorescence microscope [12]. Since the identification of a handful of KSHV antigens that are able to initiate antibody response, serological assays have been produced using these antigens, with IFA or enzyme-linked immunosorb-



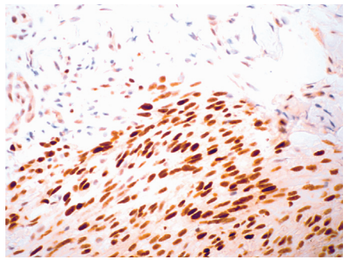


Fig. 5.9.2 *Kaposi sarcoma of the skin in a patient with AIDS. The biopsy (below) reveals the presence of human herpes virus 8 (HHV-8) in tumour cell nuclei, demonstrated by immunohistochemistry (brown colour). Affected individuals are uniformly co-infected with HIV and HHV-8*

ent (ELISA) based-assays being the most widely used diagnostic tests to detect KSHV infection.

A gold standard serological assay for KSHV infection does not yet exist; therefore some discrepancies between studies may be attributable to the use of different testing methods [2].

Epidemiology of Kaposi's sarcoma-associated Herpevirus (KSHV) infection

KSHV serosurveys have shown that the seroprevalence of KSHV infection amongst HIV-seronegative populations varies geographically, being as high as 50% in Uganda and only 0.2–5% in Asia, USA and United Kingdom (Table 5.9.1). Risk factors associated with KSHV seropositivity have not been clearly defined in the general population (Table 5.9.1). The strong association with anal intercourse among men who have sex with men suggested that KSHV would be a sexually transmitted agent, but sexual transmission has not been consistently confirmed among heterosexuals. Sexual behaviour has been associated with KSHV infection among men (OR=2.8; 95% CI 1.3–5.7) but not women in the USA [13]. Consistent increases in KSHV seroprevalence with increasing age have only been found in areas where infection with KSHV is endemic such as Sub-Saharan Africa. The risk of KSHV infection is also higher among children living with a sibling infected with KSHV in French Guiana (OR=3.8 95% CI 1.1–16.5), indicating that the KSHV transmission can occur horizontally, probably through saliva. Vertical transmission of KSHV has not been demonstrated in HIV-seronegative populations, but reactivation of KSHV during pregnancy in HIV-infected women suggests the possibility of vertical transmission in this population [14].

Molecular epidemiology

KSHV is an ancient virus that probably started spreading 100 000 years through human migrations between continents. Molecular studies based on a genetically variable genomic region of KSHV DNA (namely, ORF K1), have identified 5 main subtypes of KSHV (designated A, B, C, D and E) that are not associated with severity of disease, but have preferential geographical distributions [15]. Thus, subtypes A and C are found in Europe, the USA and Asia; strains B and A5 are found mainly in Africa and French Guyana. Subtype D, first reported in Taiwan and in some Pacific islands, has also been described in Australia, while the most recently reported subtype E has been found among South American Amerindian populations from the Amazon and French Guyana [9]. In addition to clustering by geographical localisation, KSHV strains have also been associated with ethnic background, with KSHV subtypes B and variant A5 being detected mainly in people of African descent and subtypes A and C, being usually found in Caucasian populations. The rarer subtypes D and E have only being described in Amerindians and Indigenous people from the Pacific Islands [9,15].

Management of Kaposi sarcoma

No cure exists for KS and the treatment is mostly palliative. In AIDS patients, the control of HIV replication and the consequent increase in CD4+ T-cell counts lead to marked regression of KS mucocutaneous lesions following initiation of HAART.

The use of HAART alone is an option for treatment of KS among HIV-infected patients [16]. The dissemination to internal organs and the obstruction of lymphatic systems are rare in AIDS patients receiving HAART, but the severest clinical pictures are often seen in Sub-Saharan Africa, where HAART is not available and life expectancy following the diagnosis of KS is less than one year.

Gatrointestinal and pulmonary symptoms warrant endoscopic examination to search for visceral KS lesions. Like AIDS patients, organ-transplanted recipients also experience improvement of their KS lesions after the cessation of the immune suppressive treatment.

The clinical presentation of classic KS is less severe, and local treatment can often be employed to treat the characteristic indolent lesions.

The use of systemic cancer chemotherapy is indicated when mucocutaneous lesions are disseminated or visceral organs are affected. Chemotherapy agents used in the management of KS include adryamycin, bleomycin, vinblastine, vincristine, doxorrubicin and etoposide. The use of liposomal anthracyclines and taxanes are considered the best option for disseminated KS. Other options include radiotherapy, cryotherapy and intra-lesional chemotherapy for local treatment of isolated cutaneous lesions for cosmetic and palliative reasons [16].

Region/Country	Population (N)	KSHV infection (% positive)*	Risk factors associated with KSHV seropositivity
Latin America			
Jamaica	Blood donors (n=1,010)	2.7%	Older age > 26 (Ptrend=0.001) [17]
French Guiana	Rural community	13.2%	Age > 39 y (Ptrend<0.001), KSHV infected sibling (OR=3.84 [95% CI: 1.6-9.5) [18]
Brazil, Sao Paulo	Blood donors (N=400)	4%	Female gender (OR=3.86 [95% CI: 1.1-16.6]) [19]
North America			
USA (San Francisco)	Blood donors (N=122)	0	Not analysed [20]
USA	General population (n=13,894)	1.6% 1.5%	Hepatitis B (OR=3.1 [95% CI: 1.6-5.8]) Sexual behaviour for men (OR=2.3 [95% CI: 1.4-3.8]) [13]
Europe			
Italy North			Not analysed [21]
Po valley	B. donors (N=139)	13%	
Milan & Trieste	B. donors (N=265)	3%	
Italy South			
Calabria	B. donors (N=38)	4%	
Sicily	Bl. donors (N=60)	20%	
United Kingdom	Blood donors (N=174)	5%	Not analysed [22]
Asia			
India	N=108	4.0%	Not analysed [23]
Thailand	N=75	4.0%	
Malaysia	N=159	4.4%	
Sri Lanka	N=80	3.8%	
Africa			
Tanzania	Blood donors (N=174)	2.9% 22%	Not analysed Not analysed [24]
Uganda (Kampala)	HIV-seronegative cancer patients from a case-control study (N=607)	50%	Older age (Ptrend<0.001), Ever married (OR=2.1 [95% CI: 1.1-4.1]) [25]
South Africa	HIV-seronegative cancer patients (N=2,191)	39%	Older age among men (OR=2.1 [95% CI: 1.2-3.8]) Older age among women (OR=3.8 [95% CI: 1.6-9.3]) [26]

Table 5.9.1 *Worldwide seroprevalence of KSHV infection in cross-sectional studies of HIV-seronegative individuals. N, number of HIV-seronegative individuals tested for KSHV; OR, odds ratio; CI, confidence interval; *Serological asssays detect anti-KSHV antibodies either to lytic of LANA KSHV antigens.*

REFERENCES

1. Boshoff C and Weiss RA (2001). Epidemiology and pathogenesis of Kaposi's sarcoma-associated herpesvirus. *Philos Trans R Soc Lond B Biol Sci* 356: 517-534.

2. IARC (1997). Kaposi`s sarcoma herpesvirus/human herpesvirus 8. In: *IARC monographs of the evaluation of carcinogenic risks to humans, Volume 70, Epstein-Barr virus and kaposi´s sarcoma herpesvirus/human herpes virus 8* Lyon, France: International Agency for Research on Cancer 375-492.

3. Biggar RJ, Chaturvedi AK, Goedert JJ, et al. (2007). AIDS-related cancer and severity of immunosuppression in persons with AIDS. *J Natl Cancer Inst* 99: 962-972.

4. Parkin DM, Whelan SL, Ferlay J, et al. (2002). *IARC Scientific Publications, Number 155, Cancer incidence in five continents, Volume VIII*. Lyon, France: International Agency for Research on Cancer.

5. Eltom MA, Jemal A, Mbulaiteye SM, et al. (2002). Trends in Kaposi's sarcoma and non-Hodgkin's lymphoma incidence in the United States from 1973 through 1998. *J Natl Cancer Inst* 94: 1204-1210.

6. Beral V, Peterman TA, Berkelman RL, et al. (1990). Kaposi's sarcoma among persons with AIDS: a sexually transmitted infection? *Lancet* 335: 123-128.

7. Grulich AE, van Leeuwen MT, Falster MO, et al. (2007). Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis. *Lancet* 370: 59-67.

8. Serraino D, Angeletti C, Carrieri MP, et al. (2005). Kaposi's sarcoma in transplant and HIV-infected patients: an epidemiologic study in Italy and France. *Transplantation* 80: 1699-1704.

9. de Souza VA, Sumita LM, Nascimento MC, et al. (2007). Human herpesvirus-8 infection and oral shedding in amerindian and non-amerindian populations in the brazilian Amazon region. *J Infect Dis* 196: 844-852.

10. Moore PS and Chang Y (2003). Kaposi's sarcoma-associated herpesvirus immunoevasion and tumorigenesis: two sides of the same coin? *Annu Rev Microbiol* 57: 609-639.

11. Nascimento MC, de Souza VA, Sumita LM, et al. (2007). Comparative study of Kaposi's sarcoma-associated herpesvirus serological assays using clinically and serologically defined reference standards and latent class analysis. *J Clin Microbiol* 45: 715-720.

12. Renne R, Zhong W, Herndier B, et al. (1996). Lytic growth of Kaposi's sarcoma-associated herpesvirus (human herpesvirus 8) in culture. *Nat Med* 2: 342-346.

13. Engels EA, Atkinson JO, Graubard BI, et al. (2007). Risk factors for human herpesvirus 8 infection among adults in the United States and evidence for sexual transmission. *J Infect Dis* 196: 199-207.

14. Pica F and Volpi A (2007). Transmission of human herpesvirus 8: an update. *Curr Opin Infect Dis* 20: 152-156.

15. Zong JC, Ciufo DM, Alcendor DJ, et al. (1999). High-level variability in the ORF-K1 membrane protein gene at the left end of the Kaposi's sarcoma-associated herpesvirus genome defines four major virus subtypes and multiple variants or clades in different human populations. *J Virol* 73: 4156-4170.

16. Di Lorenzo G, Konstantinopoulos PA, Pantanowitz L, et al. (2007). Management of AIDS-related Kaposi's sarcoma. *Lancet Oncol* 8: 167-176.

17. Engels EA, Eastman H, Ablashi DV, et al. (1999). Risk of transfusion-associated transmission of human herpesvirus 8. *J Natl Cancer Inst* 91: 1773-1775.

18. Plancoulaine S, Abel L, van Beveren M, et al. (2000). Human herpesvirus 8 transmission from mother to child and between siblings in an endemic population. *Lancet* 356: 1062-1065.

19. Ferreira S, Sanabani S, Reis AD, et al. (2003). Human herpesvirus type 8 among Brazilian blood donors. *Transfusion* 43: 1764-1765.

20. Gao SJ, Kingsley L, Li M, et al. (1996). KSHV antibodies among Americans, Italians and Ugandans with and without Kaposi's sarcoma. *Nat Med* 2: 925-928.

21. Whitby D, Luppi M, Barozzi P, et al. (1998). Human herpesvirus 8 seroprevalence in blood donors and lymphoma patients from different regions of Italy. *J Natl Cancer Inst* 90: 395-397.

22. Simpson GR, Schulz TF, Whitby D, et al. (1996). Prevalence of Kaposi's sarcoma associated herpesvirus infection measured by antibodies to recombinant capsid protein and latent immunofluorescence antigen. *Lancet* 348: 1133-1138.

23. Ablashi D, Chatlynne L, Cooper H, et al. (1999). Seroprevalence of human herpesvirus-8 (HHV-8) in countries of Southeast Asia compared to the USA, the Caribbean and Africa. *Br J Cancer* 81: 893-897.

24. Enbom M, Urassa W, Massambu C, et al. (2002). Detection of human herpesvirus 8 DNA in serum from blood donors with HHV-8 antibodies indicates possible bloodborne virus transmission. *J Med Virol* 68: 264-267.

25. Newton R, Ziegler J, Bourboulia D, et al. (2003). The sero-epidemiology of Kaposi's sarcoma-associated herpesvirus (KSHV/HHV-8) in adults with cancer in Uganda. *Int J Cancer* 103: 226-232.

26. Wojcicki JM, Newton R, Urban M, et al. (2004). Low socioeconomic status and risk for infection with human herpesvirus 8 among HIV-1 negative, South African black cancer patients. *Epidemiol Infect* 132: 1191-1197.

CANCER INSTITUTE PROFILE: The Ocean Road Cancer Institute (ORCI)

The Ocean Road Cancer Institute (ORCI) in Dar es Salaam was established as the National Cancer Institute for Tanzania by an Act of Parliament in 1996. It is the only specialised cancer centre in the country that offers cancer treatment, training, research, surveillance and cancer prevention. Since its establishment, ORCI was designated as the National Coordinator for Cancer Control in Tanzania and given a mandate to formulate and ensure the development of cancer control actions in Tanzania. During its 10 years of existence, the ORCI has been a leader in terms of cancer control in Tanzania, implementing actions in strategic areas such as cancer prevention, early detection, cancer treatment, human resources development, research, surveillance, information and palliative care through the referral system of the Ministry of Health of Tanzania.

Currently ORCI has 160 beds and 200 staff members including 5 senior professionals with Academic status with the Muhimbili University of Health and Allied Sciences. As a renowned tertiary care centre, it accepts 3000 inpatients and 10 000 outpatients each year from all over Tanzania and neighbouring countries such as Malawi, Zambia and the Democratic Republic of Congo.

In 2006, following the endorsement of recommendations from the IAEA Programme of Action for Cancer Therapy (PACT) for strengthening cancer control capabilities by the government of Tanzania, the ORCI formed a secretariat for a Steering Committee appointed by the Minister of Health. The main tasks of the steering committee are to focus on formulating and strengthening each component of national cancer control system and develop action plans for the National Cancer Control programme.

5.10 Lung Cancer

Summary

- Lung cancer is the most common cause of cancer death worldwide
- Survival is poor and no effective screening is available
- In most populations, tobacco smoking accounts for 80% or more lung cancers
- Other causes of lung cancer include occupational (e.g. asbestos, heavy metals) and environmental exposures (e.g. secondhand smoke, radon decay products)
- Genetic susceptibility factors that might interact with tobacco smoking have been identified
- Tobacco control is the main tool in the fight against lung cancer

Lung cancer was a rare disease until the beginning of the twentieth century. Since then, its occurrence has increased rapidly; this neoplasm has become the most frequent malignant neoplasm among men in most countries and represents the most important cause of cancer death worldwide. It accounts for an estimated 960 000 new cases and 850 000 deaths each year among men, and 390 000 cases and 330 000 deaths among women. Survival from lung cancer is poor (5–10% at five years).

The geographical and temporal patterns of lung cancer incidence are to a large extent determined by consumption of tobacco. An increase in tobacco consumption is paralleled some 20–30 years later by an increase in the incidence of lung cancer; similarly, a decrease in consumption is followed by a decrease in incidence.

The highest incidence rates in men (>70/100 000) are recorded among blacks from the United States and in some Central and Eastern-European countries [2,3]. Rates are declining among US white men and among men in the United Kingdom and Northern Europe. The lowest incidence rates are reported from Africa and Southern Asia.

Rates in women are high in the USA, Canada, Denmark and the UK, and low in countries such as Japan and Spain, in which the prevalence of smoking in women has increased only recently. The lowest rates (<3 cases per 100 000 people) are recorded in Africa and India. China is a notable exception, with relatively high rates recorded among women (e.g. 37/100 000 in Tianjin during 1993–1997; [2], despite a low prevalence of smoking.

The main histological types of lung cancer are squamous-cell carcinoma, small cell carcinoma, adenocarcinoma, and large cell carcinoma. Over the last few decades, the proportion of squamous-cell carcinomas, which used to be the predominant type, has decreased and an increase of adenocarcinomas has taken place in both genders. This is probably due to changes in the composition of tobacco products and in smoking behaviour (e.g. use of filtered cigarettes, lower tar content, reduced inhalation). Despite some minor differences, the main risk factors for lung cancer are associated with all histological types.

A carcinogenic effect of tobacco smoke on the lung was demonstrated in the 1950s and has been recognised by public health and regulatory authorities since the mid-1960s [4]. The risk of lung cancer among smokers relative to the risk among never-smokers is of the order of tenfold or more. This overall risk reflects the contribution of the different aspects of tobacco smoking: average consumption, duration of smoking, time since quitting, age at start, type of tobacco product and inhalation pattern, with duration being the dominant factor. As compared to continuous smokers, the excess risk decreases in ex-smokers after quitting, but a small excess risk is likely to persist in long-term quitters throughout life. In the United Kingdom, the cumulative risk of lung cancer of a continuous smoker is 16%, and it is reduced to 10%, 6%, 3% and 2% among those who stopped at age 60, 50, 40 and 30, respectively. Smokers of black (air-cured) tobacco cigarettes are at higher risk of lung cancer than smokers of blond (flue-cured) tobacco cigarettes. A causal association with lung cancer has also been shown for consumption of cigars, cigarillos, pipes, bidis, water pipes and other smoking tobacco products [4], but not for use of smokeless tobacco products [5].

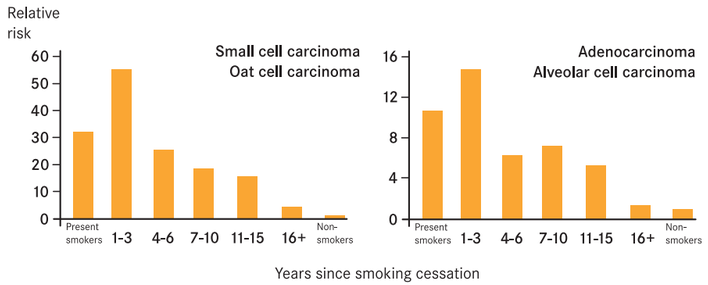


Fig. 5.10.1 *The relative risk of lung cancer is markedly lower five years after quitting, and decreases further with time (by comparison with those who continue to smoke)*

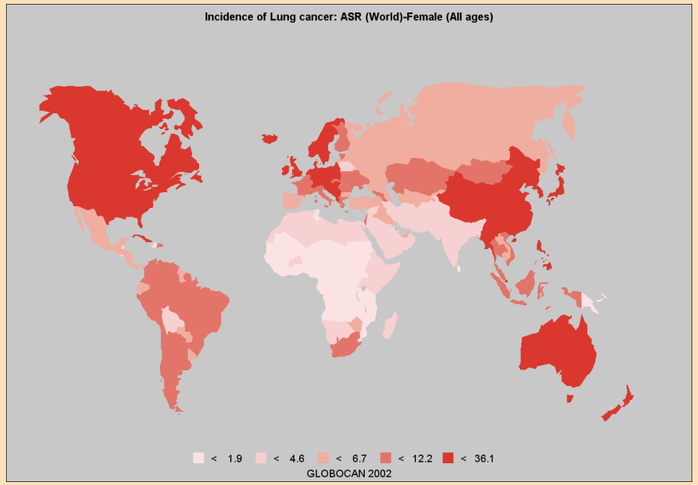
An association has been shown in many studies between exposure to involuntary smoking and lung cancer risk in non-smokers. The magnitude of the excess risk among non-smokers exposed to involuntary smoking is of the order of 20% [6].

There is limited evidence that a diet rich in vegetables and fruits exerts a protective effect against lung cancer [7]. In particular, a protective effect has been suggested for intake of cruciferous vegetables, possibly because of their high content in isothiocyanates [8]. Despite the many studies of intake of other foods, such as cereals, pulses, meat, eggs, milk and dairy products, the evidence is inadequate to allow a judgement regarding the evidence of a carcinogenic or a protective effect.

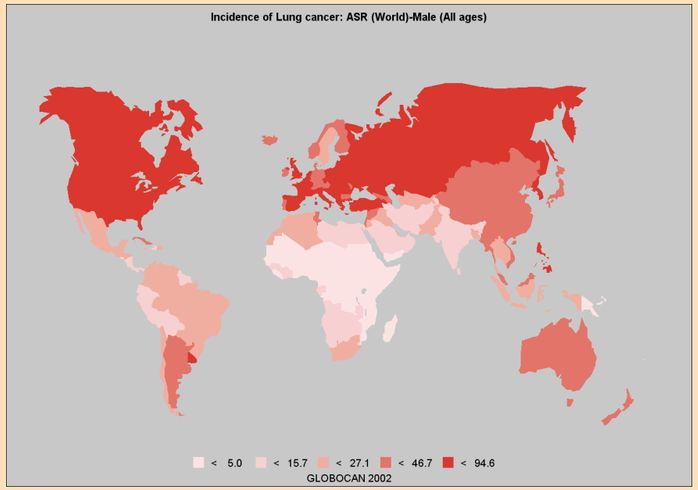
A large number of studies have reported a reduced risk of lung cancer for high intake of beta-carotene [9]. Similar results have been obtained in studies based on measurement of beta-carotene in prospectively collected sera. This evidence of a protective effect has been challenged by the results of intervention trials of beta-carotene supplementation [9]. In two of the studies, which included smokers and workers exposed to asbestos, an increase in the incidence of lung cancer was observed in the treated groups [10,11]: in the other studies, no difference was found between the treated and the control groups [12,13]. The differences in the results of observational studies and intervention trials can be explained either by a confounding effect due to other dietary components in observational studies, or by a paradoxical effect of beta-carotene at very high, non-physiological doses, in particular among smokers.

There is inadequate evidence of an increase in the risk of lung cancer from heavy alcohol drinking, independent from tobacco smoking , and for an association between body size and lung cancer risk [14].

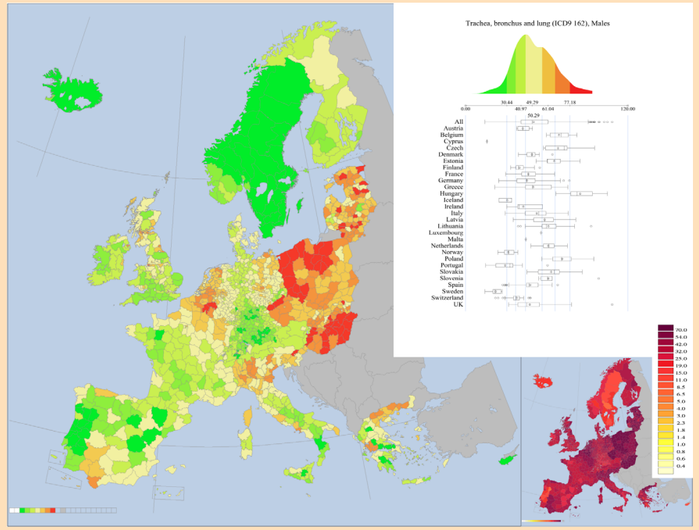
A positive familial history of lung cancer has been found to be a risk factor in several studies. Segregation analyses suggest that inheritance of a major gene, in conjunction with tobacco



World Map 5.10.1



World Map 5.10.2



European Map 5.10.1 *The most prominent feature of the geographical distribution of lung cancer in men in Europe is the large area of high rates extending from northern Italy through neighbouring Slovenia into Hungary, Slovakia, the Czech Republic, Poland, parts of northeast Germany and the Baltic Countries. There was a second, smaller, area with higher-than-average rates covering The Netherlands, Belgium and northern France. There were also small numbers of areas with high rates in central Scotland, southern Spain and the northern mainland of Greece. Rates were generally low in Portugal, central and northern Spain, southern France, Switzerland, southern Germany and Austria, as well as in all the Nordic Countries [1].*

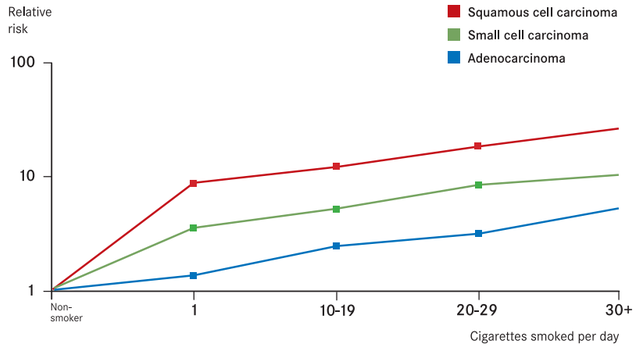


Fig. 5.10.2 *The relative risk of major histological types of cancer by average cigarette consumption*

smoking, might account for more than 50% of cases diagnosed below age 60 . A pooled analysis of high-risk pedigrees identified a major susceptibility locus to chromosome 6q23-25 . In addition, low-penetrance genes involved in the metabolism of tobacco carcinogens, DNA repair and cell cycle control might influence individual susceptibility to lung cancer [15]. Recently, three whole genome association studies have identified a susceptibility marker in chromosome 15q25.1, most likely located in a nicotine receptor gene [16-18]. It remains to be shown whether the effect of this gene is independent from tobacco dependence.

There is conclusive evidence that exposure to ionizing radiation increases the risk of lung cancer [19]. Atomic bomb survivors and patients treated with radiotherapy for ankylosing spondylitis or breast cancer are at moderately increased risk of lung cancer, while studies of nuclear industry workers exposed to relatively low levels of radiation, however, provided no evidence of an increased risk of lung cancer. Underground miners exposed to radioactive radon and its decay products, which emit alpha-particles, have consistently been found to be at increased risk of lung cancer [20]. The risk increased with estimated cumulative exposure and decreased with attained age and time since cessation of exposure .

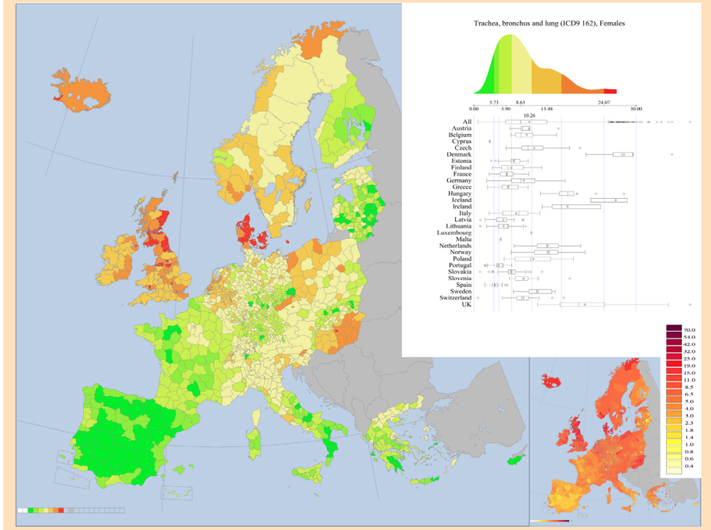
The risk of lung cancer is increased among workers employed in several industries and occupations. For several of these high-risk workplaces, the agent (or agents) responsible for the increased risk have been identified [21]. Of these, asbestos and combustion fumes are the most important. Occupational agents are responsible for an estimated 5–10% of lung cancers in industrialised countries.

Patients with pulmonary tuberculosis are at increased risk of lung cancer; it is not clear whether the excess risk is due to the chronic inflammatory status of the lung parenchyma or to the specific action of the mycobacterium. Chronic exposure to high levels of fibres and dusts might result in lung fibrosis (e.g. silicosis and asbestosis), a condition which entails an increase in the risk of lung cancer. Chronic bronchitis and emphysema have also been associated with lung cancer risk [22].

There is abundant evidence that lung cancer rates are higher in cities than in rural settings. Although this pattern might result from confounding by other factors, notably tobacco smoking and occupational exposures, the combined evidence from analytical studies suggests that urban air pollution might be a risk factor for lung cancer, although the excess risk is unlikely to be greater than 20% in most urban areas.

Indoor air pollution is thought to be responsible for the elevated risk of lung cancer experienced by non-smoking women living in several regions of China and other Asian countries. The evidence is strongest for coal burning in poorly ventilated houses, but also for burning of wood and other solid fuels, as well as for fumes from high-temperature cooking using unrefined vegetable oils such as rapeseed oil [23]. In some countries (e.g. Sweden), indoor exposure to radon decay particles may entail a sizeable increase of risk [22].

Control of tobacco smoking remains the key strategy for the prevention of lung cancer. Reduction in exposure to occupational and environmental carcinogens (in particular, indoor pollution and radon), as well as increase in consumption of fruits and vegetables are additional preventive opportunities. To date, no screening interventions have been demonstrated to be effective at reducing lung cancer mortality.



European Map 5.10.2 *The pattern of lung cancer mortality in women was quite different from that observed in males. The highest rates were in the United Kingdom (particularly the north), Ireland, Denmark and Iceland, and parts of Norway and Sweden, all of which had generally lower-than-average lung cancer mortality rates in males. There were, however, similar areas of higher-than-average rates in females as in males in Belgium and The Netherlands, in north and west Poland, and in Hungary. Low rates aggregated particularly in Portugal and Spain, but also in France, Greece, southern Italy and Finland. In terms of our understanding of lung cancer etiology, the current geographical patterns better represent the smoking habits in the various countries 20–30 years ago than those of today. In particular, the high mortality from lung cancer in women in Denmark and the United Kingdom reflects the early uptake of the smoking habit by large portions of females in those countries. An epidemic of tobacco-related lung cancer in women throughout Europe has yet to materialise (as it has previously in men) and effective intervention is now needed urgently to avoid this catastrophe [1].*

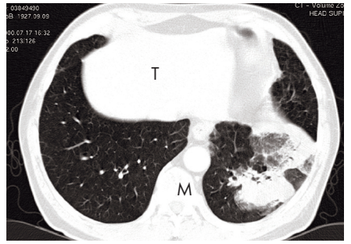


Fig. 5.10.3 *A lung tumour viewed by computed tomography. T= tumour, M= mediastinum*

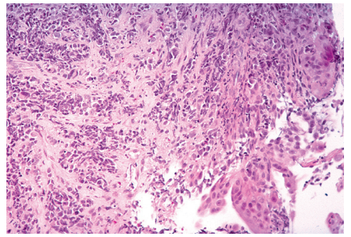


Fig. 5.10.4 *Biopsy of a small cell lung carcinoma, showing a monomorphic proliferation of small tumour cells with dense nuclei and poorly-defined cytoplasm, invading the deep parts of the bronchial wall*

REFERENCES

1. Boyle P, Smans M (2008). *IARC Scientific Publications, Number 159, Atlas of cancer mortality in the European Union and the European Economic Area 1993-1997*. Lyon, France: International Agency for Research on Cancer.

2. Parkin DM, Whelan SL, Ferlay J, et al (2007). (2002). *IARC Scientific Publications, Number 155, Cancer Incidence in Five Continents, Volume VIII*. Lyon, France: International Agency for Research on Cancer.

3. Curado MP, Edwards B, Shin HR, et al. *IARC Scientific Publications, Number 160, Cancer Incidence in Five Continents, Volume IX*. Available from: http://www-dep.iarc.fr/. Date Accessed: November 12 2008.

4. IARC (2004). Tobacco smoke. In: *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 83, Tobacco smoke and involuntary smoking* Lyon, France: International Agency for Research on Cancer. 51-1187.

5. IARC (2007). *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 89, Smokeless tobacco and some tobacco-specific N-nitrosamines*. Lyon, France: International Agency for Research on Cancer.

6. IARC (2004). Involuntary smoking. In: *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 83, Tobacco smoke and involuntary smoking* Lyon, France: International Agency for Research on Cancer. 1191-1413.

7. IARC (2003). *IARC Handbooks of Cancer Prevention, Volume 8, Fruits and vegetables*. Lyon, France: International Agency for Research on Cancer.

8. IARC (2004). *IARC Handbooks of Cancer Prevention, Volume 9, Cruciferous vegetables, isothiocyanates and indoles*. Lyon, France: International Agency for Research on Cancer.

9. IARC (1998). *IARC Handbooks of Cancer Prevention, Volume 2, Carotenoids*. Lyon, France: International Agency for Research on Cancer.

10. Omenn GS, Goodman GE, Thornquist MD, et al. (1996). Effects of a combination of beta-carotene and vitamin A on lung cancer and cardiovascular disease. *N Engl J Med* 334: 1150-1155.

11. The effect of vitamin E and beta-carotene on the incidence of lung cancer and other cancers in male smokers. The Alpha-Tocopherol, Beta-carotene Cancer Prevention Study Group (1994). *N Engl J Med* 330: 1029-1035.

12. Kamangar F, Qiao YL, Yu B, et al. (2006). Lung cancer chemoprevention: a randomized, double-blind trial in Linxian, China. *Cancer Epidemiol Biomarkers Prev* 15: 1562-1564.

13. Hennekens CH, Buring JE, Manson JE, et al. (1996). Lack of effect of long-term supplementation with beta-carotene on the incidence of malignant neoplasms and cardiovascular disease. *N Engl J Med* 334: 1145-1149.

14. IARC (2002). *IARC Handbooks of Cancer Prevention, Volume 6, Weight control and physical activity*. Lyon, France: International Agency for Research on Cancer.

15. Spitz MR, Wu X, Wilkinson A, et al. (2006). Cancer of the Lung. In: Schottenfeld D, Fraumeni JF, eds., *Cancer epidemiology and prevention*. New York: Oxford University Press 638-658.

16. Thorgeirsson TE, Geller F, Sulem P, et al. (2008). A variant associated with nicotine dependence, lung cancer and peripheral arterial disease. *Nature* 452: 638-642.

17. Hung RJ, McKay JD, Gaborieau V, et al. (2008). A susceptibility locus for lung cancer maps to nicotinic acetylcholine receptor subunit genes on 15q25. *Nature* 452: 633-637.

18. Amos CI, Wu X, Broderick P, et al. (2008). Genome-wide association scan of tag SNPs identifies a susceptibility locus for lung cancer at 15q25.1. *Nat Genet* 40: 616-622.

19. IARC (2000). X-radiation and γ-radiation. In: *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 75, Ionizing radiation, Part 1: x- and gamma (γ)-radiation and neutrons* Lyon, France: International Agency for Research on Cancer 121-362.

20. IARC (2001). *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 78, Ionizing radiation, Part 2: some internally deposited radionuclides*. Lyon, France: International Agency for Research on Cancer.

21. Siemiatycki J, Richardson L, Boffetta P (2006). Occupation. In: Schottenfeld D, Fraumeni JF, eds., *Cancer epidemiology and prevention*. New York: Oxford University Press 322-354.

22. Boffetta P, Trichopoulos D (2008). Biomarkers in cancer epidemiology. In: Adami HO, Hunter DJ, Trichopoulos D, eds., *Textbook of cancer epidemiology*. Oxford: Oxford University Press 109-126.

23. IARC (In Press). *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 95, Household combustion of solid fuels and high-temperature frying*. Lyon, France: International Agency for Research on Cancer.

CANCER INSTITUTE PROFILE: AORTIC

(African Organization for Research and Training in Cancer, or l'Organisation pour la Recherche et l' Enseigment sur le Cancer [OAREC] in French).

This organisation was formed by expatriate African cancer care workers, scientists and their friends and is dedicated to the promotion of cancer control in Africa.

AORTIC Mission

AORTIC's mission is to stimulate and promote research into cancer in Africa, to support and develop standardised training programmes in all aspects of cancer care and management and to enable African countries to develop national cancer control programmes. AORTIC is committed to creating awareness of the extent of cancer in Africa and to ensure that programmes to prevent, diagnose, treat and palliate cancer in Africa are firmly on the continent's health agenda. The Organisation will achieve this by working with other non-profit organisations, government agencies and businesses to advocate for improved resources and access to care. AORTIC will also organise symposia, workshops, meetings and conferences that support this mission.

AORTIC Vision

The African Organisation for Research and Training in Cancer (AORTIC) seeks to become the continent's preeminent non-profit organisation working for cancer control. AORTIC will achieve this through the facilitation of research and training as well as the provision of relevant and accurate information on the prevention, early diagnosis, treatment and palliation of cancer. Our organisation is dedicated to providing all Africans with these benefits, as well as to increasing public awareness of cancer and reducing the stigma associated with it.

AORTIC Objectives

AORTIC's key objectives are to further research relating to cancers prevalent in Africa, support the management of training programs in oncology for healthcare workers, and to deal with the challenges of creating cancer control and prevention programmes, as well as raising public awareness of cancer in Africa.

The executive members of AORTIC are high-profile scientists from all over Africa volunteering as knowledge workers for the plight of the cancer patient in Africa. Their main value is their ability to gather and analyse information and make decisions that will benefit the cancer patient. They work collaboratively with other cancer organizations via conferences and the internet, sharing knowledge, learning from each other and disseminating relevant ideas and research to the cancer community.

AORTIC is actively connected to the global community, with a vast electronic database as well as paper and electronic newsletters sent out quarterly in English and French. AORTIC has been represented at numerous cancer conferences around Africa and the world, and looks forward to their upcoming seventh AORTIC conference in Tanzania in November 2009.

website: www.aortic.org

CANCER INSTITUTE PROFILE: Institut Jules Bordet

Located in the heart of Europe, the Institut Jules Bordet (IJB) was among the first European centres to be fully dedicated to cancer, and is currently the only one in Belgium. IJB belongs to the academic research network of the Université Libre de Bruxelles. As a Comprehensive Cancer Centre, IJB fully integrates three key missions: patient care, education and research.

IJB provides a full range of services, including prevention, screening, diagnostics, therapeutics and rehabilitation using state-of-the-art technologies and the most up-to-date methods. With a capacity of 154 beds and a 13-bed day-care Unit, IJB insures 6000 hospitalisation admittances (together with 2000 new diagnoses) and 71 000 outpatient consultations a year.

IJB collaborates closely with the International Agency for Research on Cancer (IARC) and coordinates large pivotal multicentric clinical trials. The top-quality translational and clinical research activities at IJB lead annually to more than 200 scientific articles with a high impact factor (820 in 2006). IJB belongs to the Organization of European Cancer Institutes (OECI) and is strongly involved in the European Organization for Research and Treatment of Cancer (EORTC), which is currently chaired by the IJB Head of Medical Department, Prof Martine Piccart.

Institut Jules Bordet
1 rue Héger-Bordetstraat, 1000 Brussels
Belgium

www.bordet.be

5.11 Mesothelioma

Summary

> Mesothelioma of the pleura and the peritoneum is a rare cancer except in workers exposed to asbestos

> The clinical course of the disease is in most cases fatal

> Exposure to all types of asbestos increases the risk of developing mesothelioma, although the potency of amphibole asbestos (e.g. crocidolite, amosite) is greater than that of chrysotile asbestos

> Other known risk factors are environmental exposure to asbestos and asbestos-like fibres, as well as radiation

> Avoidance of exposure to asbestos and other fibres is the main approach to prevent mesothelioma

Mesothelioma is the most important primary tumour of the pleura. It can also originate from the peritoneum and the pericardium. Mesotheliomas were considered very rare tumours until large series of cases were reported in the 1960s among workers employed in asbestos mining and manufacturing. The descriptive epidemiology of pleural tumours, and mesothelioma in particular, is complicated by geographical and temporal differences in diagnostic accuracy. In most high-resource countries, the incidence of pleural mesothelioma is of the order of 1–1.5/100 000 in men and around 0.5/100 000 in women. Lower rates are reported from low-resource countries, where under-diagnosis might be a particularly serious problem. In areas with a high prevalence of occupational exposure to asbestos such as shipbuilding and mining centres, the rates might be as high as 5/100 000 in men and 4/100 000 in women [1]. Occurrence of mesothelioma has been linked conclusively to asbestos exposure, in particular to amphiboles such as crocidolite and amosite. Past occupational exposure to asbestos is the main determinant of pleural mesothelioma. High-exposure industries include mining, shipyard working, and especially asbestos, textile and cement manufacture [2].

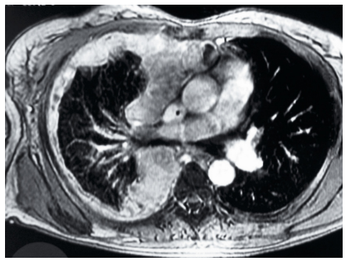
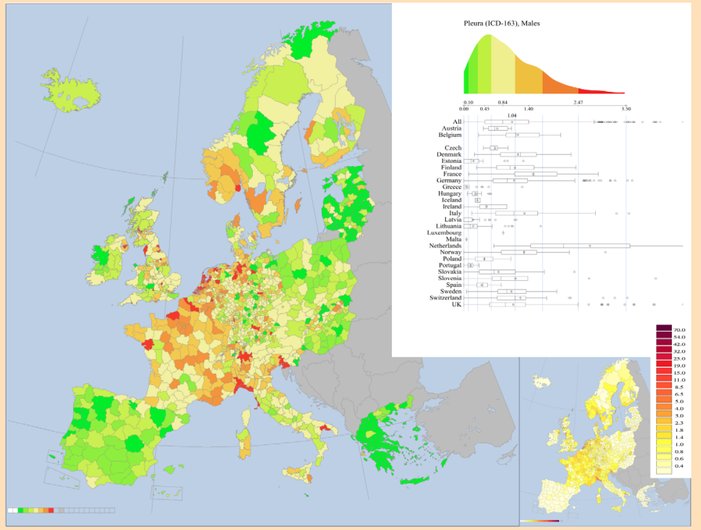


Fig. 5.11.1 *Diffuse malignant mesothelioma. In this CT scan, the pleura shows marked diffuse thickening by mesothelioma, with resulting encasement of the lung*

Despite a reduction or ban of asbestos use in many countries, the incidence of mesothelioma was increasing in the USA until the early 1990s, and in most Western European countries until the late 1990s, which reflects the long latency of the disease [3]. In the absence of occupational exposure to asbestos, incidence rates of the order of 0.1–0.2/100 000 are estimated in both genders. In heavily exposed workers, relative risks of the order of 1000 have been reported. There is evidence of an increased risk of pleural mesothelioma following environmental exposure to asbestos; epidemics of mesothelioma have been reported from areas with environmental contamination by other natural mineral fibres, such as some districts of central Turkey, where erionite, a fibrous substance similar to amphibole asbestos, contaminated the materials used for building construction.

In several populations, DNA of simian virus 40 has been reported in a high proportion of mesothelioma cases; however, a causal role of this virus, which contaminated polio vaccines used in the 1950s in many countries, has not been confirmed [4]. Exposure to ionising radiation entails an increased risk of pleural mesothelioma, as it has been shown in cohorts of patients treated with thorotrast, a radiological contrast medium [2]. Tobacco smoking, alcohol drinking and diet do not appear to be risk factors for pleural mesothelioma.

Peritoneal mesothelioma shares many of the epidemiological and biological features of the pleural form of the disease [5]. In particular, patients treated with thorotrast frequently developed peritoneal mesothelioma, probably because of local emission of alpha-particles by the contrast medium.



European Map 5.11.1 *This is the only form of cancer presented in the "Cancer Atlas of the Euroepan Union" in which the local rates are more important than the general geographic picture [Boyle and Smans, 2008].*

REFERENCES

1. Parkin DM, Whelan SL, Ferlay J, et al. (2002). *IARC scientific publications, Number 155, Cancer Incidence in Five Continents, Volume VIII*. Lyon, France: International Agency for Research on Cancer.

2. Boffetta P, Stayner L (2006). Pleural and peritoneal neoplasms. In: Schottenfeld D, Fraumeni JF, eds., *Cancer epidemiology and prevention*. New York: Oxford University Press.

3. Peto J, Decarli A, La Vecchia C, et al. (1999). The European mesothelioma epidemic. *Br J Cancer* 79: 666-672.

4. Shah KV (2007). SV40 and human cancer: a review of recent data. *Int J Cancer* 120: 215-223.

5. Boffetta P (2007). Epidemiology of peritoneal mesothelioma: a review. *Ann Oncol* 18: 985-990.

5.12 Non-Melanoma Skin Cancer

Summary

> Non-melanoma skin cancer includes squamous and basal cell carcinomas

> These two forms of skin cancer are the most frequent cancer in light-skinned populations, but are rarely a cause of death

> Their public health importance resides in the huge economic burden their treatment entails, and the loss of quality of life due to disfiguring scars

Basal cell carcinomas (BCC) and squamous-cell carcinomas (SCC) are the two main forms of non-melanoma skin cancer, accounting for the large majority of all skin tumours [1]. Non-melanoma skin cancer is the most frequent form of cancer in light-skinned populations [2].

Epidemiology

Incidence. Non-melanoma skin cancer is a disease of light-skinned (white) populations. Hispanic and Asian populations develop less skin cancer, and it is even less frequent in black populations [3,4]. The Squamous-cell carcinomas occur almost exclusively on chronically sun-exposed skin areas, whereas BCC may also occur on body sites only intermittently sun-exposed [5].

In white populations residing in areas close to the equator (e.g. Queensland in Australia), non-melanoma skin cancer incidence surpasses that of any other cancer site. BCC has the highest incidence rate and is 3 to 4 times more frequent than SCC (Table 5.12.1). Incidence of BCC and SCC increases with age, mainly for SCC whose incidence rises sharply after 65 years of age [6]. The incidence of SCC is about three times higher in men than in women, and the incidence of BCC is twice as high in men as in women [4].

An important variability in incidence rate exists between Europe, the USA and Australia: incidence rates are about 5 times higher in the US and 20–40 times higher in Australia than in Europe. This can partly be explained by differences in latitude of residence. A correlation between incidence and latitude of residence was initially described in the USA [4]. This observation contributed to the hypothesis related to chronic sun exposure and the risk of non-melanoma skin cancer.

A continuous increase in incidence over time is observed in different parts of the world [3,7-13] with no sign of levelling off in the most recent investigations [14]. The increase was more rapid for BCC than for SCC [9].

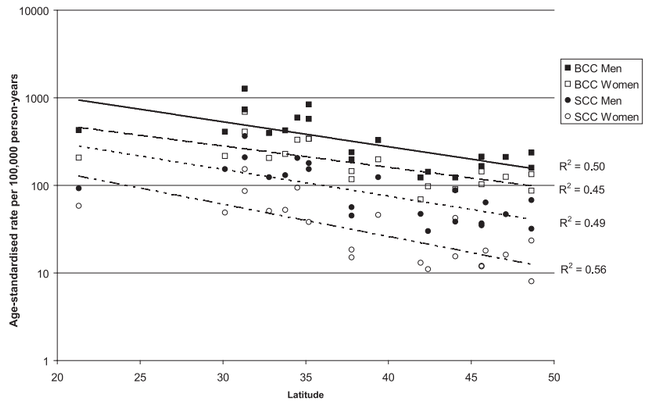


Fig. 5.12.1 *Incidence of BCC and SCC in the United States of America as a function of latitude in the white population from reports in peer-reviewed journals. R-squared corresponds to the log-linear correlation between incidence rate and latitude. Rates were standardised according to the US population of 1970*

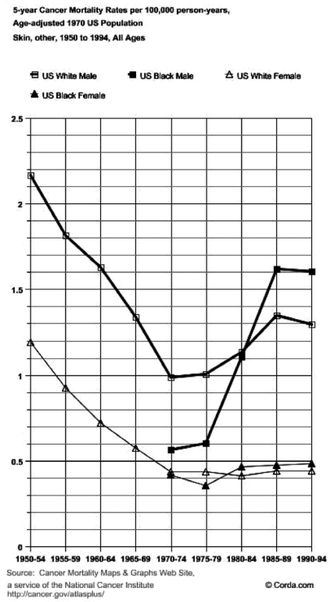


Fig. 5.12.2 *Non-melanoma skin cancer mortality rate in the USA*

Registration. In spite of its public health importance in white populations, and the continuous increase in incidence observed in all light-skinned populations, non-melanoma skin cancer remains poorly recorded by cancer registries. The main reason for the absence of registration data is the difficulty of obtaining systematic pathological assessment. Also, simultaneous BCC are often diagnosed, and both SCC and BCC have a high recurrence rate. In Australia, non-melanoma skin cancers are so frequent that around half of the population will develop a skin cancer during their lifetime, with many developing multiple recurrences. A complete registration of BCC and SCC in Australia would use all currently available resources for cancer registration and is therefore not feasible.

Mortality. BCC and SCC are slow-growing tumours that are locally invasive, but rarely result in distant metastasis. A small proportion of these cancers become life-threatening, and most countries with light-skinned populations record some deaths due to non-melanoma skin cancer. The majority of deaths are due to SCC, which are more invasive than BCC, and account for around 75% of all non-melanoma skin cancer deaths [15].

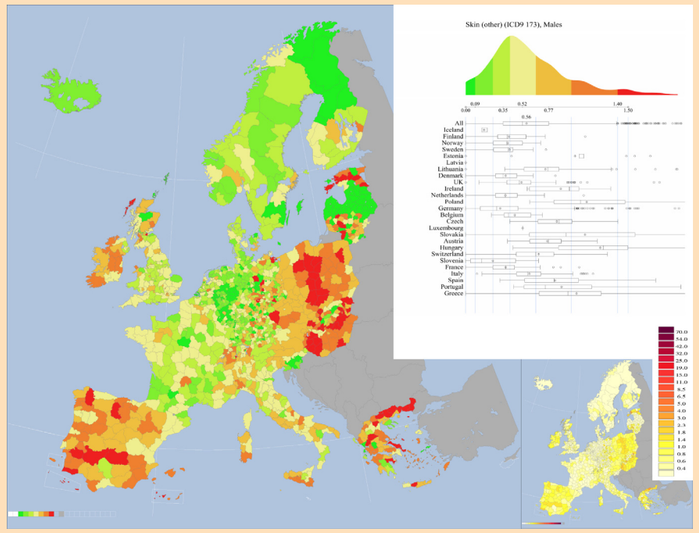
Etiology

Host factor - sun sensitivity. BCC and SCC arise predominantly in sun-sensitive people with light skin, red hair and an history of sunburn [16-18].

Publication	Geographical area	Years	BCC		SCC	
			Male	Female	Male	Female
North America*						
Scotto et al 1974	Dallas	1971-1972	394	205	124	51
	Iowa	1971-1972	123	69	47	13
	Minneapolis–Saint Paul	1971-1972	165	103	35	12
	San Francisco	1971-1972	198	117	45	15
Harris et al 2001	Southeastern Arizona	1996	936	497	271	112
Gallagher et al 1990	Canada	1973-1987	120	92	31	17
Australia**						
Giles et al 1988	Australia (survey)	1985	735	593	209	122
Marks et al 1993	Australia (survey)	1990	849	605	338	164
Buettner and Raasch 1998	Townsville, Australia	1997	2058	1194	1332	755
Europe**						
Osterlind et al 1988	Denmark	1978-1982	30	24	6.7	2.5
Holme et al 2000	South Wales, UK	1998	128	105	25	8.6
Hannuksela-Svahn et al 1999	Finland	1991-1995	49	45	7	4.2
Magnus 1991	Norway	1982,1984-1986	43	39	6.4	3.2
Coebergh et al 1991	Eindhoven, The Netherlands	1975-1988	46	30	11	3.4
Katalinic et al 2003	Schleswig-Holstein, Germany	1998-2001	54	44	11	5.3
Levi et al 1995	Vaud, Switzerland	1991-1992	69	62	29	18
Plesko et al 2000	Slovakia	1993-1995	38	29	6.7	3.8
Revenga et al 2004	Soria, Spain	1998-2000	65	53	23	13
Asia**						
Koh et al 2003	Singapore (Chinese)	1993-1997	6.4	5.8	3.2	1.8
	Singapore (Malay)	1993-1997	2.3	3.0	1.3	0.5
	Singapore (Indian)	1993-1997	1.2	1.4	1.8	1.9

Table 5.12.1 *Incidence per 100 000 person-years of BCC and SCC reported in different areas of the world*

** Standardised on the US population of 1970*
***Age-standardised incidence rate on the world population*



European Map 5.12.1 - *Mortality rates from non-melanoma skin cancer for men in Europe between 1993-1997*

Maps 5.12.1 and 5.12.2 present the distribution of mortality rates for men and women observed in the European Community including countries of the EFTA (Switzerland, Iceland and Norway). The main map represents the relative distribution of rates using a scale from lower rates in green to highest rates in red using percentiles of the distribution of rates (5,15,35,65,85 and 95). The second map represents the distribution of rates using an absolute scale and the upper right sub-figure contains the distribution of rates and boxplots of rates by country

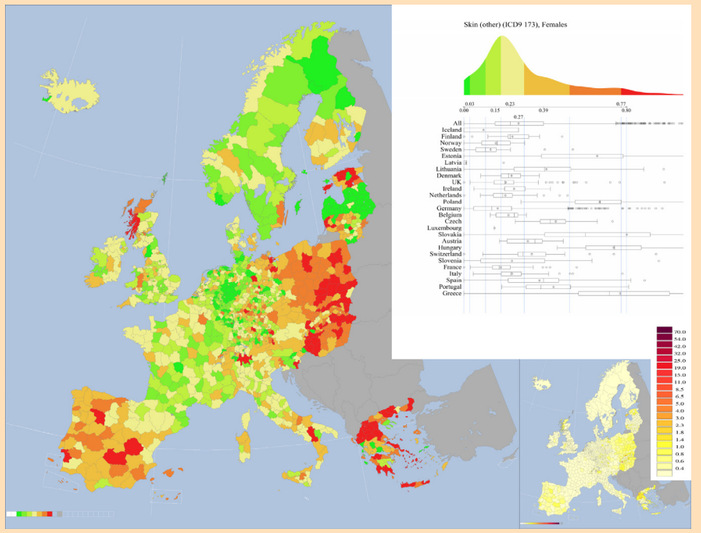
Sun exposure. The presence of actinic skin lesions, such as solar keratosis, lentigines, elastosis and telangiectasia, is frequently associated with BCC and SCC and reflects the role of chronic sun exposure in the risk of non-melanoma skin cancer [17]. The risk of SCC is strongly associated with increasing cumulative doses of sun exposure, independent of the pattern of sun exposure [19]. The association between sun exposure and BCC is more complex than that of SCC [16], and BCC seems more associated with intermittent exposure to high doses of solar radiation when compared to similar doses delivered more continuously [20].

Occupational exposure to untreated and mildly-treated mineral oil. The International Agency for Research on Cancer classified occupational exposure to untreated and mildly-treated mineral oil as carcinogenic to humans. This risk concerns squamous-cell carcinoma. These types of oils are used as lubricant bases for more refined oils such as engine oils, and the majority are used in automotive industries [21]. A case–control study evaluated that the risk of squamous-cell carcinoma is increased by 1.46 for those exposed to this carcinogen [22]. As the relative risk is low and the exposure concerns only a small fraction of the whole population, the number of SCC attributable to this exposure is very small.

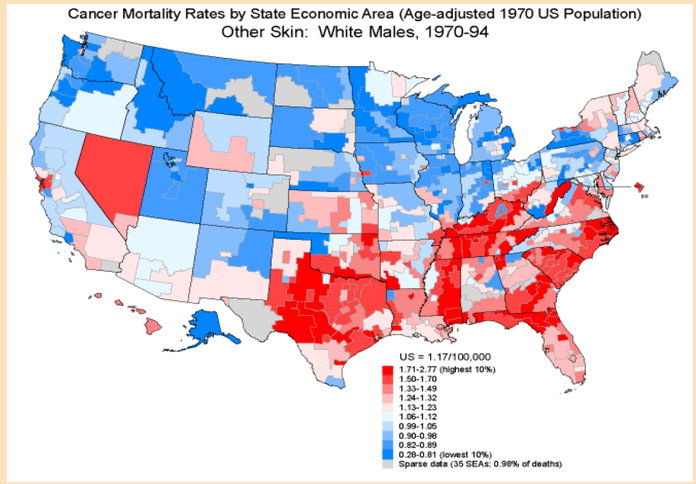
Immunodeficiency. Immunocompromised patients (renal transplant patients) have been repeatedly found to be at higher risk for non-melanoma skin cancer [23,24]. These observations strongly suggest that immune suppression could play a role in BCC and SCC etiology. This hypothesis could help in understanding the dramatic increase in the incidence of BCC and SCC with decreasing latitude, as solar radiation would cause SCC and BCC via two interacting mechanisms: the ultraviolet radiation-induced DNA damage of keratinocytes, and a decrease in immune control of carcinogenic events in the skin.

Skin infection with the Human papilloma virus. Non-melanoma skin cancer in immunocompromised subjects (e.g. organ transplant patients) was found to be associated with Human papilloma virus (HPV) infection of skin keratinocytes [25]. Persistent infections of the skin with high-risk genital HPV types (also known to be significant risk factors for cervical cancer) have also been found to represent a risk factor for non-melanoma skin cancer in non-immunocompromised subjects [26]. HPV infection of skin keratinocytes seems to be essentially associated with increased risk of SCC but not BCC [27] This association with HPV remains confined to SCC arising on chronically sun-exposed areas of the skin.

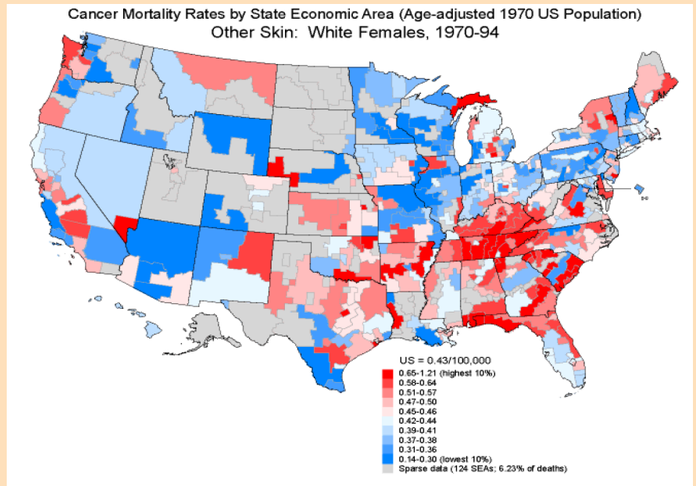
Genetics. Mutations of the TP53 gene are frequently observed in human SCC, and are associated with a history of sunburn [28]. In BCC, cell cycle regulatory factors other than TP53 are affected, such as mutations in the hedgehog signalling pathway genes [29].



European Map 5.12.2 *Mortality rates from non-melanoma skin cancer for women in Europe between 1993-1997*



US Map 5.12.1 *Mortality rates from non-melanoma skin cancer for men in US between 1970-1994*



US Map 5.12.2 *Mortality rates from non-melanoma skin cancer for women in US between 1970-1994*

REFERENCES

1. LeBoit PE, Burg G, Weedon D, et al. (2006). *World Health Organization Classification of Tumours. Pathology and genetics of skin tumours*. Lyon, France: International Agency for Research on Cancer.

2. Boyle P, Dore JF, Autier P, et al. (2004). Cancer of the skin: a forgotten problem in Europe. *Ann Oncol* 15: 5-6.

3. Koh D, Wang H, Lee J, et al. (2003). Basal cell carcinoma, squamous-cell carcinoma and melanoma of the skin: analysis of the Singapore Cancer Registry data 1968-97. *Br J Dermatol* 148: 1161-1166.

4. Scotto J, Kopf AW, Urbach F (1974). Non-melanoma skin cancer among Caucasians in four areas of the United States. *Cancer* 34: 1333-1338.

5. Gallagher RP, Ma B, McLean DI, et al. (1990). Trends in basal cell carcinoma, squamous-cell carcinoma, and melanoma of the skin from 1973 through 1987. *J Am Acad Dermatol* 23: 413-421.

6. Brewster DH, Bhatti LA, Inglis JH, et al. (2007). Recent trends in incidence of nonmelanoma skin cancers in the East of Scotland, 1992-2003. *Br J Dermatol* 156: 1295-1300.

7. Coebergh JW, Neumann HA, Vrints LW, et al. (1991). Trends in the incidence of non-melanoma skin cancer in the SE Netherlands 1975-1988: a registry-based study. *Br J Dermatol* 125: 353-359.

8. Hannuksela-Svahn A, Pukkala E, Karvonen J (1999). Basal cell skin carcinoma and other nonmelanoma skin cancers in Finland from 1956 through 1995. *Arch Dermatol* 135: 781-786.

9. Kaldor J, Shugg D, Young B, et al. (1993). Non-melanoma skin cancer: ten years of cancer-registry-based surveillance. *Int J Cancer* 53: 886-891.

10. Ko CB, Walton S, Keczkes K, et al. (1994). The emerging epidemic of skin cancer. *Br J Dermatol* 130: 269-272.

11. Levi F, Franceschi S, Te VC, et al. (1995). Trends of skin cancer in the Canton of Vaud, 1976-92. *Br J Cancer* 72: 1047-1053.

12. Marks R, Staples M, Giles GG (1993). Trends in non-melanocytic skin cancer treated in Australia: the second national survey. *Int J Cancer* 53: 585-590.

13. Plesko I, Severi G, Obsitnikova A, et al. (2000). Trends in the incidence of non-melanoma skin cancer in Slovakia, 1978-1995. *Neoplasma* 47: 137-142.

14. de Vries E, Louwman M, Bastiaens M, et al. (2004). Rapid and continuous increases in incidence rates of basal cell carcinoma in the southeast Netherlands since 1973. *J Invest Dermatol* 123: 634-638.

15. Dunn JE, Levin EA, Linden G, et al. (1965). Skin cancer as a cause of death. *Calif Med* 102: 361-363.

16. English DR, Armstrong BK, Kricker A, et al. (1997). Sunlight and cancer. *Cancer Causes Control* 8: 271-283.

17. Green A, Battistutta D, Hart V, et al. (1996). Skin cancer in a subtropical Australian population: incidence and lack of association with occupation. The Nambour Study Group. *Am J Epidemiol* 144: 1034-1040.

18. Kricker A, Armstrong BK, English DR (1994). Sun exposure and non-melanocytic skin cancer. *Cancer Causes Control* 5: 367-392.

19. English DR, Armstrong BK, Kricker A, et al. (1998). Case-control study of sun exposure and squamous-cell carcinoma of the skin. *Int J Cancer* 77: 347-353.

20. Kricker A, Armstrong BK, English DR, et al. (1995). Does intermittent sun exposure cause basal cell carcinoma? a case-control study in Western Australia. *Int J Cancer* 60: 489-494.

21. IARC (1984). *IARC Monographs on the Evaluation of Carcinogenic Risks to <umans, Volume 33, Polynuclear aromatic hydrocarbons, Part 2, Carbon blacks, mineral oils (lubricant base oils and derived products) and some nitroarenes*. Lyon, France: International Agency for Research on Cancer.

22. Kubasiewicz M, Starzynski Z, Szymczak W (1991). Case-referent study on skin cancer and its relation to occupational exposure to polycyclic aromatic hydrocarbons. II. Study results. *Pol J Occup Med Environ Health* 4: 141-147.

23. Ramsay HM, Reece SM, Fryer AA, et al. (2007). Seven-year prospective study of nonmelanoma skin cancer incidence in U.K. renal transplant recipients. *Transplantation* 84: 437-439.

24. Grulich AE, van Leeuwen MT, Falster MO, et al. (2007). Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis. *Lancet* 370: 59-67.

25. Shamanin V, zur Hausen H, Lavergne D, et al. (1996). Human papillomavirus infections in nonmelanoma skin cancers from renal transplant recipients and nonimmunosuppressed patients. *J Natl Cancer Inst* 88: 802-811.

26. Iftner A, Klug SJ, Garbe C, et al. (2003). The prevalence of human papillomavirus genotypes in nonmelanoma skin cancers of nonimmunosuppressed individuals identifies high-risk genital types as possible risk factors. *Cancer Res* 63: 7515-7519.

27. Karagas MR, Nelson HH, Sehr P, et al. (2006). Human papillomavirus infection and incidence of squamous cell and basal cell carcinomas of the skin. *J Natl Cancer Inst* 98: 389-395.

28. Ziegler A, Jonason AS, Leffell DJ, et al. (1994). Sunburn and p53 in the onset of skin cancer. *Nature* 372: 773-776.

29. Athar M, Tang X, Lee JL, et al. (2006). Hedgehog signalling in skin development and cancer. *Exp Dermatol* 15: 667-677.

5.13 Cutaneous Melanoma

Summary

> The risk of developing malignant melanoma varies markedly according to racial background (skin pigmentation) and geography (sunlight-derived ultraviolet irradiation); highest incidence rates occur in white populations in Australia

> In Nordic countries, a steep increase in melanoma incidence has been attributed to excessive sun exposure during vacations in lower latitudes

> While prognosis for patients with localised melanoma is good, metastatic melanoma is largely resistant to current therapies

Melanoma is a malignant proliferation of melanocytes, the pigment-forming cells of the skin, which is the site of most (>95%) melanoma. There are about 160 000 new cases of melanoma worldwide each year, of which almost 80% are in North America, Europe, Australia and New Zealand. Incidence is similar in men and in women [2].

Malignant melanoma of the skin occurs predominantly in white-skinned populations ("Caucasians") living in countries where there is high-intensity ultraviolet radiation, but this malignancy afflicts all ethnic groups to some degree.

Assessed in relation to skin colour, melanoma incidence falls dramatically as skin pigmentation increases, and the disease is very rare in dark-skinned people. The highest incidence of melanoma occurs in Australia where the population is predominantly white. In this country, there is an average of six hours of bright sunlight every day of the year, and there is an essentially outdoors lifestyle. The lifetime risk of developing melanoma in Australia is 4–6% in men and 3–4% in women [2].

In Oceania, cutaneous melanoma is the third most common cancer in males (after prostate and lung cancers and before colon cancer), and the second in females (after breast cancer and before colon cancer). In North America, melanoma is the fifth most common cancer in males and the sixth in females. In Europe, melanoma is less common, being the eighth and the sixth most common cancer in males and females, respectively [3].

Dark-skinned people have a low risk of melanoma. In Africa and South America, the sole of the foot, where the skin is not pigmented, is the most frequent site affected in the context of a low incidence. Asian peoples have a low risk of melanoma despite their paler skins; naevi in Asian people, though common, are predominantly of the acral-lentiginous type which have low malignant potential.

Marked increases in incidence and mortality are being observed in both sexes in many countries, even where rates were formerly low, such as Japan. In the Nordic countries, for example, this averages some 30% every five years. In Sweden, between calendar periods 1960–1964 and 2000–2004, melanomas increased most rapidly on the upper limbs (men 885%, women 1216%) on the trunk (men 729%, women 759%) and on the lower limbs (men 418%, women 289%) in both genders. The incidence increase of head tumours was slower. Melanomas of the trunk and lower limbs dominate among patients <70 years, whereas tumours of the head are most common among patients ≥70 years. Tumours of the trunk formed an increasing proportion of all melanomas during the period studied, particularly in females. The relative shift of melanomas from the head to the trunk with mostly intermittent UV exposure coincides with behavioural and societal changes with regard to sun exposure [4] and probably also with increasing sunbed use. In, several populations, there are indications that greater awareness and surveillance may result in an increase in the diagnosis of early thin melanomas, but no clear reduction in the incidence rate of more deeply invasive melanomas.

Mortality rates are slightly higher in men than in women, with Australia and New Zealand registering rates of 5.1 and 6.1 for men, and 2.6 and 3.6 for women, respectively [2].

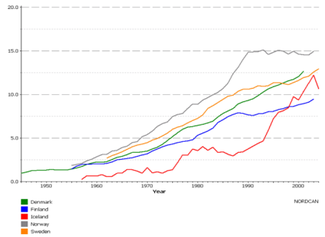


Fig. 5.13.1 *Melanoma of skin - Incidence: ASR (World), Male age (0-85+), (Rate per 100.000)*

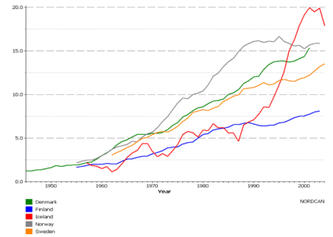


Fig. 5.13.2 *Melanoma of skin - Incidence: ASR (World), Female age (0-85+), (Rate per 100.000)*

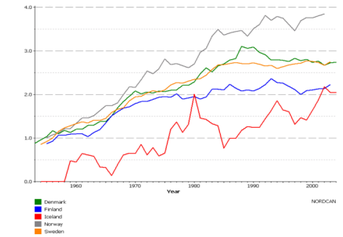


Fig. 5.13.3 *Melanoma of skin - Mortality: ASR (World), Male age (0-85+), (Rate per 100.000)*

Etiology

Melanoma risk factors include phenotypic pigmentation traits, naevi and sun exposure [5-7].

It is estimated that 80% of melanoma is caused by ultraviolet damage [8] to sensitive skin, i.e. skin that burns easily, fair or reddish skin, multiple freckles, skin that does not tan and develops naevi in response to early sunlight exposure. Prevention of melanoma is based on limitation of exposure to ultraviolet radiation, particularly in the first 20 years of life.

Ultraviolet radiation is particularly hazardous when it involves sporadic intense exposure and sunburn. Most damage caused by sunlight occurs in childhood and adolescence, making this the most important target group for prevention programmes. Other established risk factors include congenital naevi, immunosuppression and use of solaria [9].

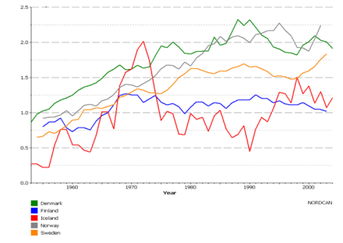


Fig. 5.13.4 *Melanoma of skin - Mortality: ASR (World), Female age (0-85+), (Rate per 100.000)*

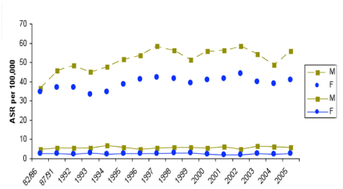
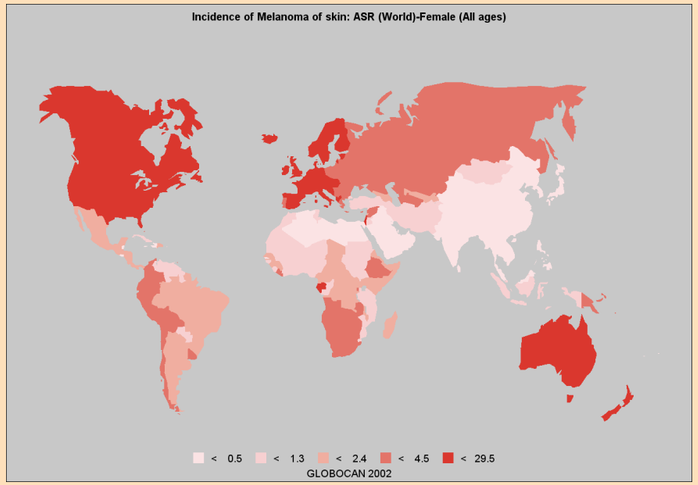
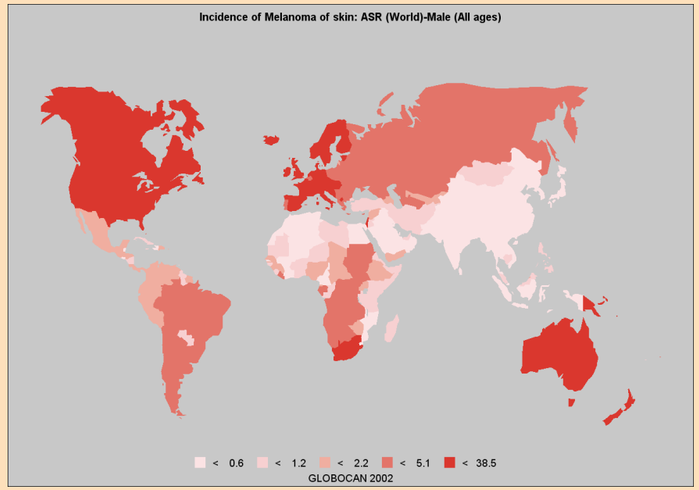


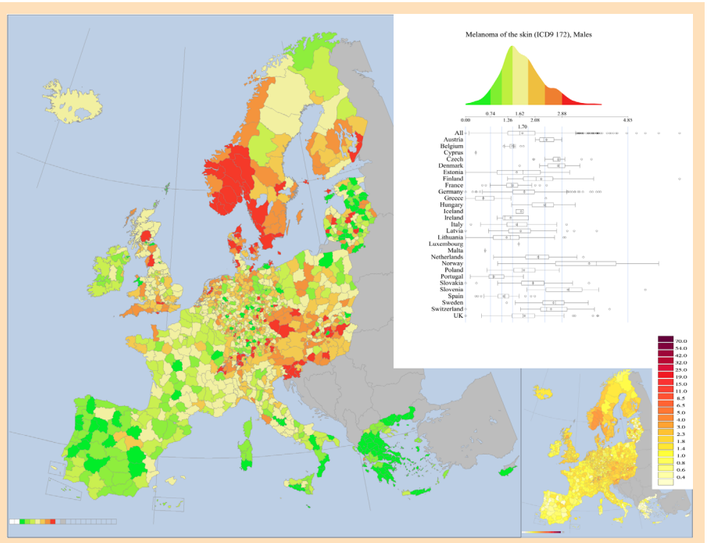
Fig. 5.13.5 *Incidence and mortality from cutaneous melanoma in Queensland, Austral (Queensland Cancer Registry (ASR per 100.000)*



World Map 5.13.1



Map 5.13.2



European Map 5.13.1 *The prominent features of the geographical distribution of melanoma in men are the high levels across (southern) Finland, Norway, Sweden and Denmark and into northern Germany and The Netherlands, in Austria, Switzerland, the Czech Republic, Slovakia, Hungary and Slovenia, and in southern England. Rates were low in most of Spain, Portugal, southern Italy and Greece [1].*

While melanoma may occur anywhere on the skin, the majority of melanoma in men is on the back, while in women the majority is on the legs. This difference in site incidence is not completely explained by differential exposure to ultraviolet light.

There is evidence from epidemiological studies that cutaneous melanomas arise through different causal pathways. Patterns of age-specific incidence of melanoma at different anatomical sites in fair-skinned populations show that melanomas arising on intermittently exposed body sites are significantly more common among younger and middle-aged adults, whereas melanomas of the head and neck are most common among older people. In younger patients the incidence of melanoma is higher on intermittently exposed skin areas than on continuously exposed areas: in both men and women under age 50 the highest melanoma density is on the back, while at ages over 50, the greatest density occurs on fully exposed sites, such as the face. Thus, intermittent sun exposure may have a greater potential for producing melanoma than continuous exposure at ages below about 50, though at older ages melanoma is more common on body sites with continuous sun exposure [10]. It was further shown that melanomas at different body sites arise through different pathways that have different associations with melanocytic nevi and solar keratoses. Patients who develop melanoma of the head and neck tend to have fewer naevi, greater lifetime exposure to sunlight and more evidence of chronic solar damage than those who develop melanoma of the trunk. Patients with Lentigo Maligna melanomas are also less likely than patients with truncal melanomas to have numerous naevi and tend toward more solar keratoses. Cutaneous melanomas may arise through two pathways, one associated with melanocyte proliferation and the other with chronic exposure to sunlight [11]. Most recently, molecular epidemiological studies have brought support to these views:

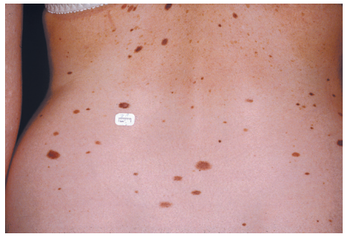


Fig. 5.13.6 *Dysplastic naevus syndrome, predisposing to non-familial malignant melanoma. The patient shows atypical cutaneous naevi, usually exceeding 5mm in diameter, with variable pigmentation and ill-defined borders*

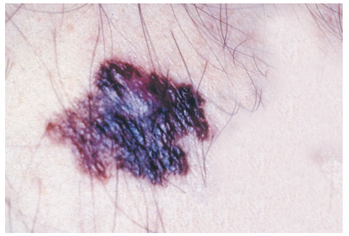


Fig. 5.13.7 *Primary melanoma with a coastline border and multiple colours, including classic blue black pigmentation*

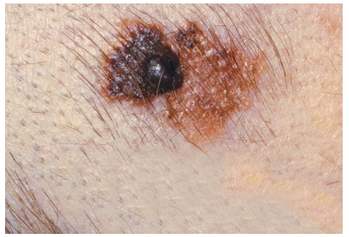
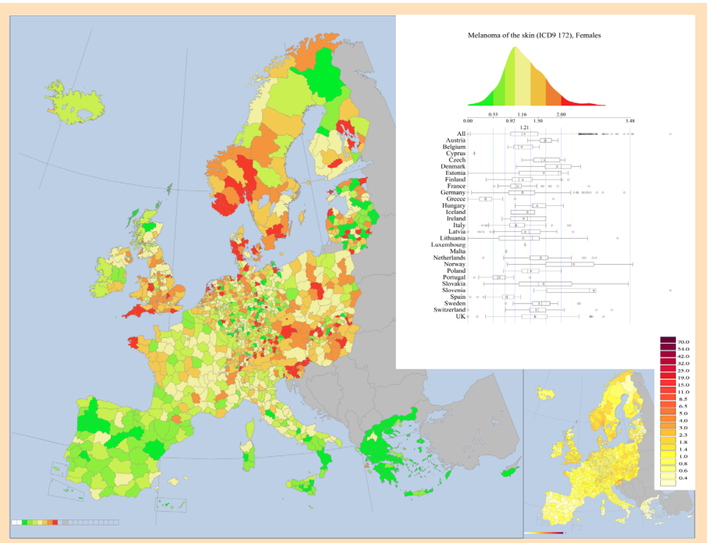


Fig. 5.13.8 *Melanoma with an elevated nodule*



European Map 5.13.2 *In females, the pattern was quite similar in broad terms with higher-than-average levels across (southern) Finland, Norway, Sweden and Denmark and into northern Germany and The Netherlands, in parts of Austria, Switzerland, the Czech Republic, Hungary and Slovenia, and in southern England. As in males, there were lower-than-average rates in Spain, Portugal, southern Italy and Greece [1].*

BRAF mutant melanomas tend to arise on the trunk and occur among younger people with many naevi.

Detection

Melanoma is usually asymptomatic, but a person with melanoma sometimes complains of an intermittent itch. Pain, bleeding and ulceration are rare in early melanoma. A melanoma often arises from a pre-existing pigmented lesion of the skin (a mole or "naevus") but these tumours can also develop in unblemished skin. The common predisposing skin lesions are dysplastic naevi, junctional and dermal naevi and blue naevi. However, the risk for melanoma development from mature dermal, junctional and blue naevi is quite small, estimated at approximately 1 in 200 000. Congenital naevi are also known precursors of melanoma, but the risk for malignant change is related specifically to the size of the naevus. Naevi greater than 20mm in diameter and, in particular, the large bathing trunk naevi have a high risk of malignant degeneration. The highest risk naevus is the dysplastic (atypical) naevus. These are naevi that are larger than 6mm in diameter, have irregular pigmentation, an ill-defined margin and often exist in multiples. Of particular risk is the dysplastic naevus syndrome (familial atypical mole syndrome) (Figure 5.13.6), in which the patient may have more than 100 of these irregular naevi; risk is highest in those patients with dysplastic naevus syndrome who have a near relative diagnosed with melanoma [12].

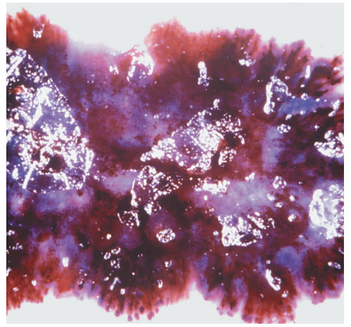


Fig. 5.13.9 *Surface microscopy of a melanoma, showing pseudopods, blue-grey veil and multiple colours*

The clinical features of melanoma are asymmetry (A), a coastline border (B), multiple colours and quite often some areas of blue/black pigmentation (C), and a diameter greater than 6mm (D). As the melanoma progresses, part or all of the lesion will become elevated (E) (Figure 5.13.7 and Figure 5.13.8). This ABCDE system has been the basis for clinical diagnosis for melanoma for many years. Surface microscopy [13] (dermoscopy, epiluminescence microscopy) has developed as an aid to the clinical diagnosis of melanoma. In this technique, the skin surface is rendered translucent by the application of oil, and a hand-held instrument providing magnification of at least ten times is used to view the internal details of the tumour. Many additional characteristics, such as pseudopods, radial streaming, blue/grey veil, peripheral black dots and multiple colours are visible and have been used in diagnostic systems now readily accessible to the clinician with an interest in cutaneous diagnosis (Figure 5.13.9).

Pathology and genetics

Melanoma occur primarily in the skin (where more than 95% of cases occur) but are also found in the mucous membranes of the mouth, nose, anus and vagina and, to a lesser extent, the intestine; melanocytes are also present in the conjunctiva, the retina and the meninges. The morphological classification system for melanoma defines four types: superficial

spreading melanoma, nodular melanoma, acral-lentiginous melanoma, and lentigo maligna melanoma. However, this classification has been superseded by a system based on the histopathological parameters of the excised lesion. Melanoma is now classified essentially on the vertical diameter of the lesion from the granular cell layer of the epidermis to the deepest detectable melanoma cell (tumour thickness). In recent years, one additional criterion, ulceration, has been shown to be important in prognosis and is included in the AJCC/UICC classification system (Table 5.13.1).

While it is clear that the genetic make-up of the melanoma-prone populations is very important, few melanomas can be ascribed to specific genetic defects in these populations. Loss-of-function mutations in the human melanocortin-1 receptor (MC1-R) have been associated with red hair, fair skin freckles and decreased ability to tan [14], all physical characteristics that affect susceptibility to skin cancer. While 10% of melanoma patients have a first-degree relative affected, less than 3% of melanomas in Australia (where the incidence of melanoma is high) can be ascribed to an inherited gene defect. Familial melanoma is even rarer in lower-incidence countries.

The familial melanoma syndromes are associated with germline mutations in highly penetrant genes [15]. About 20% of melanoma-prone families possess germline mutations in the CDKN2A gene, which encodes p16INK4A and p14ARF. Mutations in the pl6 binding domain of the gene encoding CDK4 have been identified in melanoma families without mutation of CDKN2A but are extremely rare [16]. The penetrance of the CDKN2A melanoma-predisposing gene varies with melanoma population incidence rates and is largely influenced by ultraviolet exposure across geographic latitude [17].

However, melanoma susceptibility genes identified in melanoma-prone families are rarely mutated in sporadic melanomas. Contrary to other skin cancers, only a small percentage (20%) of melanomas harbour mutations in the p53 gene. Nodular melanomas may display amplification of the MYC oncogene. Inactivation of p16INK4A is associated with a poorer prognosis. Different oncogenes and tumour suppressor genes may be involved in melanoma occurrence. Genes identified as having a role in sporadic melanoma development include CDKN2A, PTEN and BRAF, while cytogenetic studies have observed that genes located on chromosomes 1p, 6q, 7p, 9p and 11q are involved in the pathogenesis of melanoma. A high frequency of mutations of the BRAF gene, which resides on chromosome 7q, has been reported in primary melanomas [18]. The function of BRAF mutation in melanoma occurrence and development is currently being actively investigated. BRAF mutations are more common in melanomas arising on intermittently sun-exposed skin, but do not have the standard UVB signature [19]. It has recently been shown that genes involved in cellular signalling pathways may be inactivated in primary melanomas not only by mutation but also by deletion or epigenetic events [20]. Current data support a model in which genesis of melanoma requires changes that initiate clonal expansion, overcome cell senescence and reduce apoptosis. The inactivation of one critical pathway in the response to UV irradiation (such as p16 inactivation) may increase susceptibility to melanoma.

Cutaneous melanoma develops in a spatio/temporal sequence. Changes in expression of numerous melanoma associated genes can trace steps of melanoma progression from the early benign melanocytic lesions, to dysplastic naevi, to primary melanoma with radial (RGP) then vertical (VGP) growth pattern, to the acquisition of metastatic capacities. However, this sequence is currently challenged by the recent identification of malignant melanoma stem cells [21]. One of the major findings in cancer biology of recent years has been the identification of cells within tumours with stem cell-like properties. Such cancer stem cells were first identified in haematologic malignancies [22], then in solid tumours (breast cancers, glioblastomas, colon cancers and melanomas). It is not clear yet whether cancer stem cells arise from the malignant transformation of long-lived normal tissue stem cells or alternatively from the malignant transformation of lineage-restricted-progenitors or from differentiated cells [23]. Cancer stem cells share with normal tissue stem cells properties of self-renewal and the capacity to generate other sub-populations of cells within the tumour. Serial xenotransplantation experiments have shown that only a fraction of the cells in a tumour are essential for its propagation. Stem-like cancer cells are involved in the processes of progression and metastasis, and have been found to be highly resistant to drugs and toxins; hence they may constitute the small reservoir of drug-resistant cancer cells that survives chemotherapy and drives tumour recurrence and metastatic disease.

Classification	Melanoma thickness	Surgical excision margins
Tis	*in situ* melanoma/no invasion of the dermis	5 mm
T1	≤ 1 mm (in thickness)	10 mm
T2	1.1 mm – 2.0 mm	10 mm
T3	2.1 mm – 4.0 mm	Minimum 10 mm, maximum 20 mm
T4	> 4 mm	Minimum 20 mm, maximum 30 mm
Each T level is classified: A – if ulceration is present B – if no ulceration is present	There is no evidence that a margin greater than 1 cm improves survival but it may decrease local recurrence	There is no evidence that a margin greater than 1 cm improves survival but it may decrease local recurrence

Table 5.13.1 *Classification of melanoma (American Joint Committee on Cancer/International Union Against Cancer) and corresponding recommended excision margin*

Management

Treatment of primary melanoma is essentially surgical; the primary tumour is excised with a margin of normal skin, the excision being based on the tumour thickness measurement (Table 5.13.1) [24]. As the primary melanoma becomes thicker (deeper), the risk for metastatic spread rises; survival outcomes are thus related specifically to the tumour thickness measurement (Figure 5.13.10). Melanoma metastasises via the lymphatic system and also via the systemic circulation. Approximately 50% of melanomas metastasise first to the lymph nodes, thus making the management of lymph node metastases an important part of the treatment. Elective lymph node dissection (i.e. prophylactic removal of lymph nodes) is now rarely practised in the management of primary melanoma. The standard management for lymph nodes in patients with primary melanoma is an observation policy, with therapeutic node dissection if lymph nodes become involved. However, selective lymphadenectomy [25] is under clinical trial at the present time. This technique enables mapping of the lymphatics in the skin by lymphoscintigraphy: radioactive tracer is injected at the site of the primary and its flow through the skin to the first lymph node that takes up the tracer (the sentinel node) is identified. This lymph node is then removed for histopathological examination; only patients with positive lymph nodes are subjected to full lymph node dissection. An international trial has shown that the staging of intermediate-thickness (1.2–3.5mm) primary melanomas according to the results of sentinel-node biopsy provides important prognostic information and identifies patients with nodal metastases whose survival can be prolonged by immediate lymphadenectomy [26].

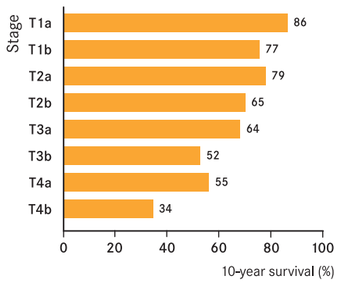


Fig. 5.13.10 *Ten-year relative survival for melanoma, according to stage*

The greater the number of nodes involved by melanoma cells, the higher the risk of systemic metastases and poor prognosis. As the thickness of the melanoma increases and as the number of lymph nodes involved rises, the risk of systemic metastases becomes greater. Melanoma metastasises widely, with the lungs, liver and brain being the most common sites. Vitiligo (a skin condition characterised by failure to form melanin) is a favourable prognostic sign in metastatic melanoma. At the present time, only a small proportion of people (<5%) live more than two years once systemic metastases become evident. The mainstay for the treatment of systemic metastases is chemotherapy. However, since the original introduction of dacarbazine 40 years ago, clinical trials conducted to date have failed to demonstrate a meaningful impact on survival. No highly effective single agent or combination has yet been developed, and metastatic melanoma is characterised by drug resistance [27]. Spontaneous regression of primary or metastatic melanoma, possibly as a result of natural and induced immune rejection, is rare but not uncommon (0.2–0.4% of cases), and this has led to increasing interest in immunotherapy. At the present time this modality remains experimental, although response rates of 15–20% to cytokines, such as interferon-α and interleukin-2, have been reported, and clinical trials of vaccines containing whole cells, lysates, dendritic cells or melanoma-associated antigens, such as MAGE, TRP and MART, are underway [28].

Recent progress in the understanding of melanoma biology has led to the identification of genetic lesions and intracellular signalling pathways that could serve as targets for novel therapy. An increasing number of new agents that have been shown to interfere with signalling pathways in melanoma, or to decrease proliferation, survival, migration or invasion, or to interfere with stromal components of melanoma such as angiogenesis and components of the immune system, are currently under evaluation [29].

REFERENCES

1. Boyle P, Smans M (2008). *IARC Scientific Publications, Number 156, Atlas of cancer mortality in the European Union and the European Economic Area 1993-1997*. Lyon, France: International Agency for Research on Cancer.

2. Ferlay J, Bray F, Pisani P, et al. (2004). *GLOBOCAN 2002: Cancer incidence, mortality and prevalence worldwide, IARC CancerBase No. 5. version 2.0*. Available from: http://www-dep.iarc.fr/ Date Accessed: November 8, 2008.

3. Curado MP, Edwards B, Shin HR, et al. (2007). *IARC Scientific Publications, Number 160, Cancer incidence in five continents, Volume IX*. Available from: http://www-dep.iarc.fr/ Date Accessed: November 8, 2008.

4. Dal H, Boldemann C, Lindelof B (2007). Does relative melanoma distribution by body site 1960-2004 reflect changes in intermittent exposure and intentional tanning in the Swedish population? *Eur J Dermatol* 17: 428-434.

5. Gandini S, Sera F, Cattaruzza MS, et al. (2005). Meta-analysis of risk factors for cutaneous melanoma: I. Common and atypical naevi. *Eur J Cancer* 41: 28-44.

6. Gandini S, Sera F, Cattaruzza MS, et al. (2005). Meta-analysis of risk factors for cutaneous melanoma: II. Sun exposure. *Eur J Cancer* 41: 45-60.

7. Gandini S, Sera F, Cattaruzza MS, et al. (2005). Meta-analysis of risk factors for cutaneous melanoma: III. Family history, actinic damage and phenotypic factors. *Eur J Cancer* 41: 2040-2059.

8. IARC (1992). *IARC monographs on the evaluation of carcinogenic risks to humans, Volume 55, Solar and ultraviolet radiation*. Lyon, France: International Agency for Research on Cancer.

9. IARC (2007). The association of use of sunbeds with cutaneous malignant melanoma and other skin cancers: A systematic review. *Int J Cancer* 120: 1116-1122.

10. Elwood JM and Gallagher RP (1998). Body site distribution of cutaneous malignant melanoma in relationship to patterns of sun exposure. *Int J Cancer* 78: 276-280.

11. Whiteman DC, Watt P, Purdie DM, et al. (2003). Melanocytic nevi, solar keratoses, and divergent pathways to cutaneous melanoma. *J Natl Cancer Inst* 95: 806-812.

12. Aitken JF, Duffy DL, Green A, et al. (1994). Heterogeneity of melanoma risk in families of melanoma patients. *Am J Epidemiol* 140: 961-973.

13. Kittler H, Pehamberger H, Wolff K, et al. (2002). Diagnostic accuracy of dermoscopy. *Lancet Oncol* 3: 159-165.

14. Schaffer JV and Bolognia JL (2001). The melanocortin-1 receptor: red hair and beyond. *Arch Dermatol* 137: 1477-1485.

15. Pho L, Grossman D, Leachman SA (2006). Melanoma genetics: a review of genetic factors and clinical phenotypes in familial melanoma. *Curr Opin Oncol* 18: 173-179.

16. Goldstein AM, Chidambaram A, Halpern A, et al. (2002). Rarity of CDK4 germline mutations in familial melanoma. *Melanoma Res* 12: 51-55.

17. Bishop DT, Demenais F, Goldstein AM, et al. (2002). Geographical variation in the penetrance of CDKN2A mutations for melanoma. *J Natl Cancer Inst* 94: 894-903.

18. Davies H, Bignell GR, Cox C, et al. (2002). Mutations of the BRAF gene in human cancer. *Nature* 417: 949-954.

19. Maldonado JL, Fridlyand J, Patel H, et al. (2003). Determinants of BRAF mutations in primary melanomas. *J Natl Cancer Inst* 95: 1878-1890.

20. Bennett DC (2008). How to make a melanoma: what do we know of the primary clonal events? *Pigment Cell Melanoma Res* 21: 27-38.

21. Schatton T, Murphy GF, Frank NY, et al. (2008). Identification of cells initiating human melanomas. *Nature* 451: 345-349.

22. Bonnet D and Dick JE (1997). Human acute myeloid leukemia is organized as a hierarchy that originates from a primitive hematopoietic cell. *Nat Med* 3: 730-737.

23. Reya T, Morrison SJ, Clarke MF, et al. (2001). Stem cells, cancer, and cancer stem cells. *Nature* 414: 105-111.

24. National Health and Medical Research Council (Australia) / Australian Cancer Network. *Clinical Practice Guidelines for the Management of Cutaneous Melanoma*. Available from: http://www.nhmrc.gov.au/publications/synopses/_files/cp68.pdf Date Accessed: November 8, 2008.

25. Morton DL (2001). Lymphatic mapping and sentinel lymphadenectomy for melanoma: past, present, and future. *Ann Surg Oncol* 8: 22S-28S.

26. Morton DL, Thompson JF, Cochran AJ, et al. (2006). Sentinel-node biopsy or nodal observation in melanoma. *N Engl J Med* 355: 1307-1317.

27. Tawbi HA and Kirkwood JM (2007). Management of metastatic melanoma. *Semin Oncol* 34: 532-545.

28. Keilholz U (2007). Antigen-specific cancer vaccines. *Recent Results Cancer Res* 176: 213-218.

29. Lejeune FJ, Rimoldi D, Speiser D (2007). New approaches in metastatic melanoma: biological and molecular targeted therapies. *Expert Rev Anticancer Ther* 7: 701-713.

CANCER INSTITUTE PROFILE: European Institute of Oncology (IEO)

The European Institute of Oncology (IEO) in Milan, Italy is the fastest-growing comprehensive cancer centre in Europe. The brainchild of Professor Umberto Veronesi, it opened in 1994, and the hospital has grown such that in 2007 over 11 000 new cancer patients were treated, 3000 of whom were suffering from breast cancer. A new Day Hospital and Hotel will be completed within eighteen months, adding 50% to our clinical capacity.

The science base has grown in parallel such that the total number of full-time scientists including the IFOM-IEO science campus is now over 380. In 2007 IEO staff published 322 peer-reviewed articles with a total impact factor of 1870.

Last year the hospital staff succeeded in entering around half of its patients in clinical trials ranging from prevention, imaging, staging and therapy to pain control and supportive care. The personnel at the hospital were the first to carry out a random trial of breast cancer conservation, the first to show the value of sentinel node imaging and biopsy, and the first to complete a random trial of intra-operative radiotherapy (IORT) in breast cancer.

A key focus in the science labs is the molecular biology of normal tissue stem cells and their cancerous counterparts.

In addition, IEO has recently launched the first new online Open Access cancer journal, www.ecancermedicalscience.com.

website: www.ieo.it/inglese/index.asp

5.14 Breast Cancer

Summary

> Breast cancer is the most common cancer in women worldwide. Mortality from breast cancer has been declining in developed countries over the last two decades due to improved diagnosis (mammography) and (mainly) improved treatment

> Breast cancer risk is related to nulliparity and late first birth, early menarche and late menopause; it is reduced by breastfeeding

> Current use of oral contraceptives and of combined HRT is associated with increased breast cancer risk, which reduces to that of never-users 5 to 10 years after stopping use

> Family history of breast cancer and high mammographic density are among the best recognised breast cancer risk factors, which assist in identifying high-risk women for screening purposes

Breast cancer is the most common cancer among women worldwide. It was estimated that 636 000 incident cases occurred in developed countries and 514 000 in developing countries during 2002 [2]. Breast cancer is also the most important cause of neoplastic deaths among women; the estimated number of deaths in 2002 was 410 000 worldwide. The incidence of breast cancer is low (less than 20/100 000) in most countries from sub-Saharan Africa, in China and in other countries of eastern Asia, except Japan. The highest rates (80-90/100 000) are recorded in North America, in regions of South America, including Brazil and Argentina, in northern and western Europe, and Australia. With reference to time trends in incidence and mortality from breast cancer, the incidence has grown rapidly during the last decades in many developing countries, and slowly in developed countries. Mortality rates have remained fairly stable between 1960 and 1990 in most of Europe and the Americas, then showed appreciable declines, which have reached 25-30% in northern Europe [3]. The incidence increases linearly with age up to menopause, after which a further increase is less marked, or almost absent in developing countries.

Over 80% of the neoplasms of the breast originate from the ductal epithelium, while a minority originate from the lobular epithelium. However, the proportion of ductal carcinomas has been increasing over recent calendar periods. Survival from breast cancer has slowly increased in developed countries, where it now achieves 85%, following improvements in screening practices and treatments. On the other hand, survival in developing countries remains around 50-60%.

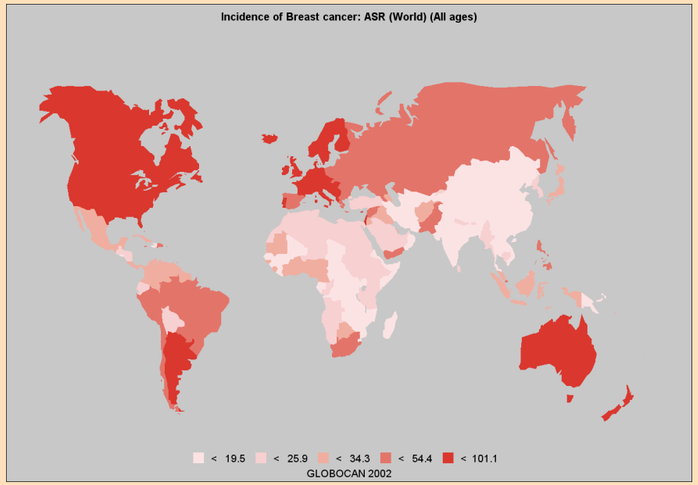
The risk of breast cancer increases with cumulative number of ovarian cycles. The risk decreases by about 15% for each year of delay in age at menarche and increases by 3% for each year of delay in age at menopause. Artificial menopause exerts a similar or somewhat stronger protective effect than natural menopause [4].

Pregnancy increases in the short term the risk of breast cancer, probably because of increase in the level of free estrogens during the first trimester. In the long run, however, pregnancy has a beneficial effect, since parous women have a higher level of prolactin and a lower level of sex hormone-binding globulin than nulliparous women. These two effects result in a protective role of early age at first pregnancy and a small residual protective effect of other pregnancies. An additional protective effect of lactation has been shown in several populations, probably attributable to the suppression of the ovulatory function caused by nursing. In a collaborative reanalysis of 47 studies, breast cancer risk decreased by 4.3% for each year of lactation (Figure 5.14.1) [5]. The Collaborative Group also reconsidered data from 53 epidemiological studies providing information on history of spontaneous or induced abortions, and found no association with breast cancer [6].

With reference to exogenous hormones, the risk of breast cancer is 15-25% higher in current and recent users of oral contraceptives (OC) as compared to never users (Figure 5.14.2) [7]. Further, 10 or more years after stopping OC use the risk levels off to approach that of never users, independently from duration of use. This is of particular importance since most women who use OC are young and have low baseline incidence of breast cancer. Therefore, their increased risk during and shortly after OC use has little relevance [8]. The evidence derived both from observational epidemiological studies (cohort and case-control) and randomised clinical trials indicates that the risk of breast cancer (mainly ductal cancer) is elevated among women using (combined) hormonal replacement therapy (HRT) [9]. The risk of breast cancer depends on duration of HRT use and is reduced after cessation of use, levelling off after 5 or more years since quitting HRT. The Women's Health Initiative, a randomised controlled trial conducted on post-menopausal women, provided comprehensive information on the risk of breast cancer in users of conjugated estrogen alone or in combination with progestin. In the estrogen-alone trial, after about 7 years of follow-up, there was no significant difference in breast cancer incidence comparing conjugated estrogen users to the placebo group (hazard ratio, HR=0.80) [10]. On the other hand, a higher incidence of invasive breast cancer was observed in the estrogen plus progestin group as compared to women receiving placebo. Further, breast cancers were diagnosed at a more advanced stage in the estrogen plus progestin group [11].

First-degree relatives affected with breast cancer	Cases : Controls	Risk ratio (99% FCI)
0	50,713 : 94,548	1.00 (0.97-1.03)
1	6810 : 6998	1.80 (1.70-1.91)
2	603 : 404	2.93 (2.37-3.63)
≥3	83 : 36	3.90 (2.03-7.49)

Table 5.14.1 *Risk ratios of breast cancer and 99% floating confidence intervals (FCI) in relation to family history of breast cancer in first-degree relatives. RRs are stratified by study, age, menopausal status, parity, age at first birth and number of sisters. (Data from Lancet (2001) 358, 1389-99)*



World Map 5.14.1

Besides exogenous hormones, the combined evidence from reproductive factors points towards a role of endogenous hormones in breast carcinogenesis. A direct assessment of the role of estrogen and testosterone is also available from recent prospective studies collecting epidemiological data and biological samples. Estradiol concentrations in the blood have been directly associated with breast cancer risk in post-menopausal women, particularly with estrogen and progesterone receptor positive tumours. Similarly, testosterone and other androgens have been found to increase breast cancer risk, but the data are inconsistent for all endogenous hormones across major cohort studies [12].

Fibrocystic disease and fibroadenoma, the most common benign breast diseases, are associated with a 2-3-fold higher breast cancer risk. Likely, these lesions are not pre-neoplastic conditions, but epithelial proliferation, linked to hormonal alterations, is a feature they share with breast cancer.

Family history of breast cancer is associated with a 2-3-fold higher risk of the same disease, and risk increases with the number of affected first-degree relatives (Table 5.14.1) [13]. This role of familial history is likely to result from low-penetrance genes associated with hormonal metabolism and regulation, DNA damage and repair. There is some evidence of an increased risk of breast cancer associated with polymorphisms of genes involved in the biosynthesis of estradiol, particularly the CYP19 gene. Several other low-penetrance genes have been analysed, but studies have generally reported null or inconsistent findings. In addition, breast cancer risk is greatly increased in carriers of mutations of several high-penetrance genes, in particular BRCA1, BRCA2 and p53. Although the cumulative lifetime risk in carriers of these genes might be over 50%, they are rare in most populations and explain only a small fraction (2-5%) of total cases.

Although a role of nutrition in breast cancer risk is strongly suggested by international comparisons, the combined evidence from epidemiological studies is inconclusive for most aspects of diet [14]. Several studies have been conducted to investigate whether intake of fruit, vegetables and related micronutrients, dietary fibre, total and saturated fats, dairy products, glycaemic index and load, and intake of phytoestrogens have an influence on breast cancer risk. No association emerged consistently from prospective studies, although there is some evidence for a protective role played by soy intake [15] and folate (by neutralising the enhancing effect of alcohol in moderate and high drinkers) [16]. Hormonal levels and nutritional factors during the intrauterine period and childhood are also likely to be important in breast carcinogenesis. In fact, energy intake during childhood is one of the determinants of adult height, which in turn has been directly associated with breast cancer risk in most epidemiological studies [17].

Besides height, other anthropometric factors are involved in the etiology of breast cancer. Weight gain during adult life has been consistently associated with postmenopausal breast

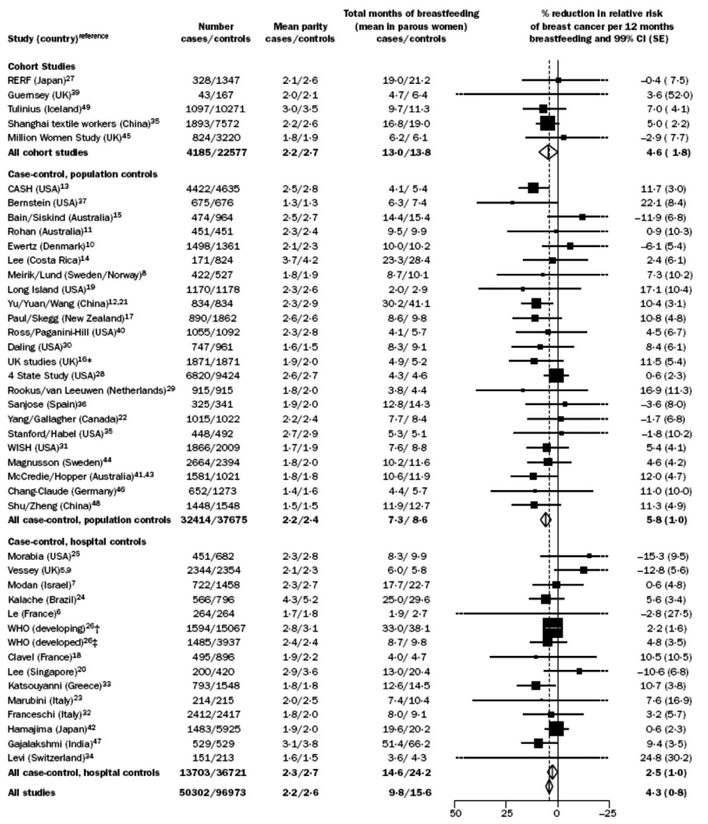


Fig. 5.14.1 *Details and results from cohort and case–control studies that contributed data on breastfeeding and breast cancer. (Figure from Lancet (2002), 360, 187-95)*

cancer incidence [14]. There is an inverse relationship between body mass index and breast cancer in pre-menopausal women and a direct relationship in post-menopausal women [18]. Further, in post-menopausal women, there is consistent evidence of a modifying effect of HRT use, as the increase in risk of breast cancer related to a high body weight and/or weight gain is stronger or limited to non-users of HRT.

Alcohol drinking is an established aetiological factor for breast cancer. Consumption of three or more alcoholic drinks per day increases the risk by 30–50%, with each daily drink accounting for an about 7% higher risk (Figure 5.14.3) [19]. It is likely that both obesity and heavy alcohol drinking act on breast cancer through mechanisms involving hormonal levels or metabolism. With reference to other lifestyle factors, tobacco smoking is not associated with development of breast cancer, while frequent physical activity is likely to moderately decrease the risk. Studies of occupational factors and of exposure to organochlorine pesticides have failed to provide evidence of an etiological role.

Male breast cancer is a rare disease. Less than 1% of all breast cancer patients are men [20]. Incidence rates in developed countries provide limited evidence of geographical and interracial variations, except for Jewish men who have higher than average rates. There is no clear correlation between incidence rates in men and women. Conditions involving high oestrogen level, such as gonadal dysfunction and liver damage, alcohol abuse and obesity, are risk factors for breast cancer in men. BRCA2 mutations are more frequent than BRCA1 in male familial breast cancers [21].

Primary prevention of breast cancer has been attempted via nutritional intervention, involving reduction of energy intake, reduction of proportion of calories from fat, and increase in fruit and vegetable consumption. No evidence of efficacy has been produced so far. However,

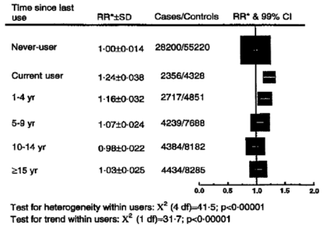


Fig. 5.14.2 *Relative risks (RR) of breast cancer and 99% confidence intervals (CI) in relation to time since last use of combined oral contraceptives. RRs are stratified by study, age, parity, age at first birth and age when risk of conception ceased. (Figure from Lancet (1996), 347, 1713-27)*

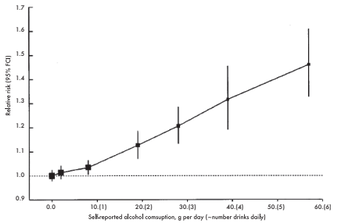
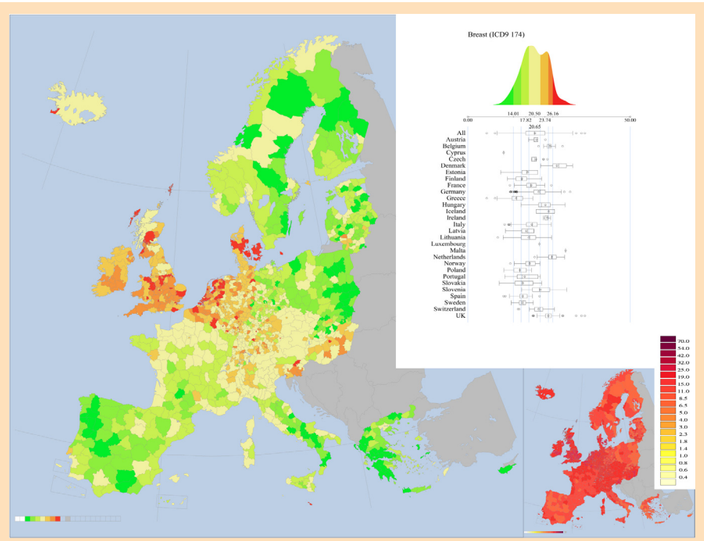


Fig. 5.14.3 *Relative risks (RR) of breast cancer and 95% floated confidence intervals (FCI) in relation to self-reported alcohol consumption. RRs are stratified by study, age, parity, age at first birth and smoking. (Figure from Br J Cancer (2002) 87, 1234-45)*

control of weight gain and of overweight and obesity in postmenopausal women would have favourable implications in breast cancer risk.

Tamoxifen, an anti-oestrogen drug used in chemotherapy, has shown a chemopreventive action against breast cancer, although the magnitude of the protection is uncertain [22]. Aspirin and other nonsteroidal anti-inflammatory drugs might also have a chemopreventive effect on breast cancer risk, although results from epidemiological studies are heterogeneous [23].

Secondary prevention through mammography is the most suitable approach for breast cancer control. The effectiveness of screening by mammography in women older than 50



European Map 5.14.1 *There are several notable features of the geographic distribution of breast cancer mortality in women in Europe.*
There is an aggregation of high rates that covers Denmark and westwards through northern Germany, The Netherlands and Belgium and then across to the United Kingdom and Ireland; mortality was also slightly above average in parts of Slovenia and Hungary. Rates were low in the Nordic Countries (apart from Denmark), Portugal, Spain, France, southern Italy and Greece.
There is nothing known about the etiology of breast cancer that can explain the geographic pattern demonstrated on the map. The pattern will change in the future as national breast screening programmes make their effects in reducing breast cancer mortality [1].

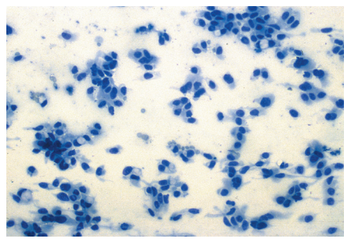


Fig. 5.14.4 *Fine needle aspirate of cells from a breast tumour*

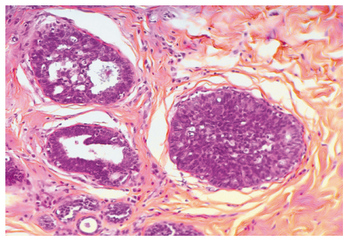


Fig. 5.14.5 *An example of lobular carcinoma in situ, comprising a well-differentiated malignant proliferation without signs of invasion*

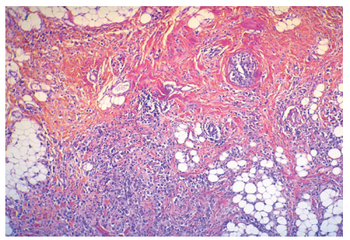


Fig. 5.14.6 *Infiltrating ductal carcinoma. This is a poorly-differentiated adenocarcinoma infiltrating the adipose tissue*

years has been demonstrated, and education programmes have been established in various countries. The effectiveness in women younger than 50 is not yet demonstrated, though there is some evidence for a reduction in risk of dying from breast cancer in women aged 40–49 years who undergo annual mammography. MRI has also been valuable in the screening of high-risk (BRCA-positive) young women [24].

REFERENCES

1. Boyle P, Smans M (2008). *IARC Scientific Publications, Number 156, Atlas of cancer mortality in the European Union and the European Economic Area 1993-1997*. Lyon, France: International Agency for Research on Cancer.

2. Parkin DM, Bray F, Ferlay J, et al. (2005). Global cancer statistics, 2002. *CA Cancer J Clin* 55: 74-108.

3. Bosetti C, Bertuccio P, Levi F, et al. (2008). Cancer mortality in the European Union, 1970-2003, with a joinpoint analysis. *Ann Oncol* 19: 631-640.

4. Colditz GA, Baer HJ, Tamimi RM (2006). Breast Cancer. In: Schottenfeld D, Fraumeni JF, eds., *Cancer epidemiology and prevention*. New York: Oxford University Press 995-1012.

5. Breast cancer and breastfeeding: collaborative reanalysis of individual data from 47 epidemiological studies in 30 countries, including 50302 women with breast cancer and 96973 women without the disease (2002). *Lancet* 360: 187-195.

6. Beral V, Bull D, Doll R, et al. (2004). Breast cancer and abortion: collaborative reanalysis of data from 53 epidemiological studies, including 83 000 women with breast cancer from 16 countries. *Lancet* 363: 1007-1016.

7. Breast cancer and hormonal contraceptives: collaborative reanalysis of individual data on 53 297 women with breast cancer and 100 239 women without breast cancer from 54 epidemiological studies. Collaborative Group on Hormonal Factors in Breast Cancer (1996). *Lancet* 347: 1713-1727.

8. La Vecchia C, Altieri A, Franceschi S, et al. (2001). Oral contraceptives and cancer: an update. *Drug Saf* 24: 741-754.

9. La Vecchia C (2004). Estrogen and combined estrogen-progestogen therapy in the menopause and breast cancer. *Breast* 13: 515-518.

10. Stefanick ML, Anderson GL, Margolis KL, et al. (2006). Effects of conjugated equine estrogens on breast cancer and mammography screening in postmenopausal women with hysterectomy. *JAMA* 295: 1647-1657.

11. Chlebowski RT, Hendrix SL, Langer RD, et al. (2003). Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: the Women's Health Initiative Randomized Trial. *JAMA* 289: 3243-3253.

12. Key T, Appleby P, Barnes I, et al. (2002). Endogenous sex hormones and breast cancer in postmenopausal women: reanalysis of nine prospective studies. *J Natl Cancer Inst* 94: 606-616.

13. Familial breast cancer: collaborative reanalysis of individual data from 52 epidemiological studies including 58,209 women with breast cancer and 101,986 women without the disease (2001). *Lancet* 358: 1389-1399.

14. Michels KB, Mohllajee AP, Roset-Bahmanyar E, et al. (2007). Diet and breast cancer: a review of the prospective observational studies. *Cancer* 109: 2712-2749.

15. Trock BJ, Hilakivi-Clarke L, Clarke R (2006). Meta-analysis of soy intake and breast cancer risk. *J Natl Cancer Inst* 98: 459-471.

16. Larsson SC, Giovannucci E, Wolk A (2007). Folate and risk of breast cancer: a meta-analysis. *J Natl Cancer Inst* 99: 64-76.

17. Lagiou P and Trichopoulos D (2008). Birth size and the pathogenesis of breast cancer. *PLoS Med* 5: e194 DOI:10.1371/journal.pmed.0050194.

18. van den Brandt PA, Spiegelman D, Yaun SS, et al. (2000). Pooled analysis of prospective cohort studies on height, weight, and breast cancer risk. *Am J Epidemiol* 152: 514-527.

19. Hamajima N, Hirose K, Tajima K, et al. (2002). Alcohol, tobacco and breast cancer–collaborative reanalysis of individual data from 53 epidemiological studies, including 58,515 women with breast cancer and 95,067 women without the disease. *Br J Cancer* 87: 1234-1245.

20. Fentiman IS, Fourquet A, Hortobagyi GN (2006). Male breast cancer. *Lancet* 367: 595-604.

21. Ottini L, Rizzolo P, Zanna I, et al. (2008). BRCA1/BRCA2 mutation status and clinical-pathologic features of 108 male breast cancer cases from Tuscany: a population-based study in central Italy. *Breast Cancer Res Treat*.

22. Forbes JF, Cuzick J, Buzdar A, et al. (2008). Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 100-month analysis of the ATAC trial. *Lancet Oncol* 9: 45-53.

23. Bosetti C, Gallus S, La Vecchia C (2006). Aspirin and cancer risk: an updated quantitative review to 2005. *Cancer Causes Control* 17: 871-888.

24. Veronesi U, Boyle P, Goldhirsch A, et al. (2005). Breast cancer. *Lancet* 365: 1727-1741.

5.15 Cervical Cancer

Summary

> Cervical cancer is the second most common cancer among women worldwide; more than 80% of the global burden of cervical cancer is found in developing countries

> Cervical cancer is caused by persistent infection with one or more of the 15 oncogenic types of human papillomaviruses (HPV)

> Invasive cervical cancer is preceded by well-defined precancerous lesions that can be detected early by screening tests

> Population-based screening, leading to early detection of cervical precancerous lesions and their treatment, has led to greatly reduced cervical cancer incidence and mortality in developed countries

> HPV vaccination offers a promising option for cervical cancer prevention

Cervical cancers arise in the epithelium covering the uterine cervix, particularly at the junction between the columnar epithelium of the endocervix and the squamous epithelium of the ectocervix, a site of continuous metaplastic change, especially *in utero*, at puberty and after first pregnancy through to menopause. Persistent infection of the cervical epithelium with one or more oncogenic types of human papillomaviruses (HPV) lead to the development of precancerous lesions therein, a proportion of which, if not detected and treated, progress to invasive cervical cancer over a period of 10–20 years. Squamous-cell carcinomas are the most common type of epithelial tumours of the cervix, accounting for 85–90% of the epithelial cancers. Adenocarcinomas and adenosquamous cancers, among others, constitute the remaining 10–15%. Adenocarcinoma cases constitute a quarter of cervical cancer cases in western countries as a consequence of cytological screening.

Epidemiology

Cervical cancer is an important global public health problem. It accounted for an estimated 493 000 incident cases, 1.4 million prevalent cases and 273 000 deaths in the world in 2002, constituting approximately 8% of the global burden of cancer among women and the second most common cancer among women worldwide. Developing countries accounted for four fifths of this global burden, reflecting the grim reality of the lack of effective control measures in many high-risk countries. It is a major cause of mortality and premature death among women in their most productive years in low- and medium-resource countries in Asia, Africa and Latin America, despite the fact that it is an eminently preventable cancer.

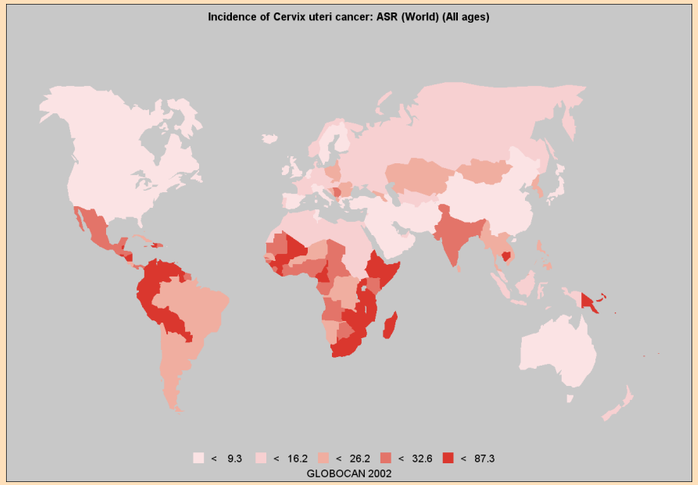
There is a more than twentyfold difference between the highest and lowest incidence rates of cervical cancer worldwide (Figure 5.15.1) [2,3]. In sub-Saharan Africa, Central and South America, South Asia and Southeast Asia, age-standardized incidence rates of cervix cancer exceed 25/100 000 in many countries. Rates lower than 7/100 000 women are observed in West Asian countries and in urban China, while these are lower than 10/100 000 women in most developed countries. The highest risk is observed in sub-Saharan Africa, Melenasia, Latin America and the Caribbean, and South and East Asia (World map 5.15.1). The incidence of cancer of the cervix begins to rise at ages 30–39, and then increases rapidly to reach a peak in the fifth or sixth decade of life. The high incidence rates in developing countries are mainly due to the lack of or ineffective screening programmes. Estimated age-adjusted cervical cancer mortality rates range between 3–8/100 000 women in most developed countries and 10–25/100 000 women in most developing countries [2]. The high mortality in developing countries is due to advanced clinical stage at presentation and to the fact that a significant proportion of patients do not avail themselves of or complete prescribed courses of treatment due to deficiencies in treatment availability, accessibility and affordability. Incidence and mortality declined markedly over the 5 decades after the introduction of population-based cervical screening programmes in the 1950s and 60s in Western Europe, USA, Canada, Australia and New Zealand. However, in recent years, notably in the UK, Nordic countries, Australia, New Zealand and eastern Europe. Increases in incidence have been observed in young women, particularly for adenocarcinoma [4,5].

A large variation in survival from cervical cancer is observed among countries due to the differences in clinical stages at presentation and the level of development of cancer-related health services. Five-year survival rates less than 25% are reported for black patients in Uganda [6] and Zimbabwe [7]; survival ranged between 30–50% in Cuba, India, and Philippines; 50–60% in Thailand and mainland China [8]; and 65% in Singapore [9]; rates range between 60–75% in developed countries [10,11].

Etiology

Persistent infection with one or more of the oncogenic types of HPV is the central and necessary cause of cervical cancer [12,13]. The recent IARC monograph concluded that there is sufficient evidence in humans for the carcinogenicity of HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 66 in the cervix [14]. HPV DNA has been detected in virtually all cervical cancer specimens [15,16]. The association of HPV with cervical cancer is equally strong for the two main histological types: squamous-cell carcinoma and adenocarcinoma.

However, since most cervical abnormalities caused by HPV infection are unlikely to progress to high-grade CIN or cervical cancer, as most of them regress by themselves, other exogenous or endogenous factors acting in conjunction with HPV may be necessary for progression of the disease. Epidemiological studies have identified a number of other risk factors that contribute to the development of cervical cancer precursors and cervical cancer. These include sexual intercourse at an early age, multiple sexual partners, multiparity, long-term oral contraceptive use, tobacco smoking, low socioeconomic status, infection with Chlamydia trachomatis, and micronutrient deficiency in vegetables and fruits. [12,13,17]. It is now clear that the well-established risk factors associated with sexual behaviour, such as multiple sexual partners and early age at initiation of sexual activity, simply reflect the probability of being infected with HPV. The assessment of the role of these co-factors requires that the central and strong effect of HPV be taken into account. A review of studies fulfilling this requirement has revealed that high parity, smoking and long-term use of oral contraceptives are co-factors that increase the risk of cervical cancer [18]. Additional co-factors such as herpes simplex virus type 2 (HSV-2), *Chlamydia trachomatis* infection, HIV and immunosuppression, certain micronutrient deficiencies and genetic susceptibility, are also implicated in cervical carcinogenesis [19-23].



World Map 5.15.1

Natural history

The cervical columnar epithelium is replaced by metaplastic squamous epithelium over several years after first pregnancy. The area of the cervical epithelium where this squamous metaplasia occurs is called the transformation zone (TZ), and this is where cervical neoplasia occur. The peak risk of HPV infection occurs soon after the onset of sexual activity, and HPV infects the basal cells or parabasal cells of the metaplastic epithelium. In most women HPV infection resolves spontaneously, but it may persist in some. If the infection persists, integration of viral genome into the host cellular genome may occur. The normal differentiation and maturation of the immature squamous metaplasia into the mature squamous metaplastic epithelium may be disrupted as a result of expression of E6/E7 oncoproteins and the loss of normal growth control. This may then lead to the occurrence, persistence and progression of precancerous lesions such as cervical intraepithelial neoplasia (CIN), particularly grade 3 CIN and adenocarcinoma *in situ* in some women. If undetected and untreated, these precursor lesions may progress traversing the basement membrane invading cervical stroma over a period of 5–20 years. The invasion may then involve blood and lymphatic vessels and the disease may spread to the lymph nodes and distant organs. While early detection of asymptomatic precancerous lesions by screening and their effective treatment lead to the prevention of invasive cervical cancer, prevention of oncogenic HPV infection by vaccination is an important emerging prevention option.

Pathology

Persistent HPV infection followed by a long phase of preinvasive disease precedes invasive cervical cancer. Precursor lesions of the cervix microscopically present as a spectrum ranging from cellular atypia to various grades of dysplasia or CIN. CIN are subclassified into 3 grades depending upon the thickness of the epithelium affected by the dysplastic cells. In grade 1, dysplastic cells are confined to the lower third of the epithelium (Figure 5.15.2), while CIN 2 is characterised by dysplastic cells restricted to the lower half of the epithelium (Figure 5.15.3). In CIN 3, differentiation and stratification may be totally absent and dysplastic cells present throughout the thickness of the epithelium, but the basement membrane is intact (Figure 5.15.4). In the case of adenocarcinoma *in situ* (AIS), normal columnar epithelium is replaced by dysplastic glandular epithelium showing loss of polarity and dysplastic features.

Histologically 85–90% of invasive cervical cancers are squamous-cell carcinoma, appearing as infiltrating networks of neoplastic cells in the stroma, with varying degree of differentiation, with or without keratinization (Figure 5.15.5). Other uncommon types of squamous carcinoma include verrucous carcinoma, papillary squamous-cell carcinoma, squamo-transi-

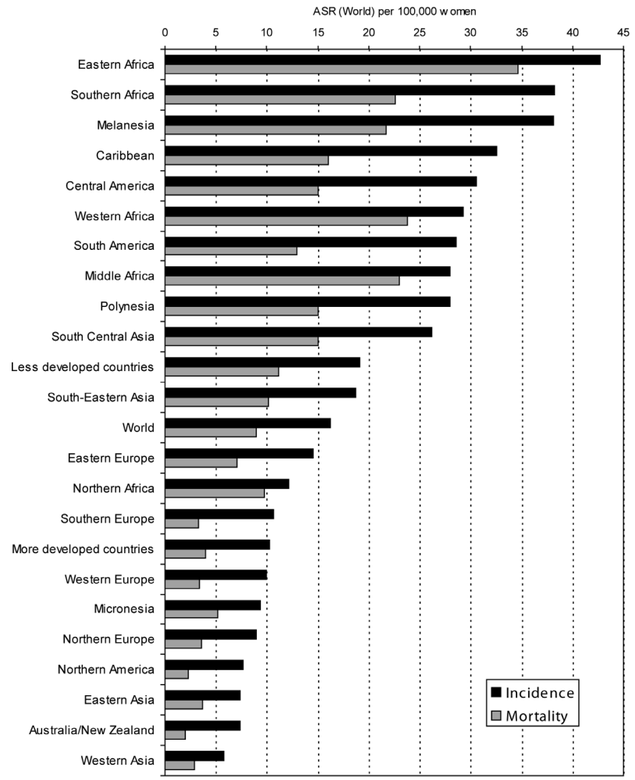


Fig. 5.15.1 *Cervical cancer incidence and mortality rates in selected regions*

tional cell carcinoma and lympho-epithelioma cell-like carcinoma. Adenocarcinoma and its variants constitute 10–15% of cervical cancers.

The most common type of adenocarcinoma is the endocervical cell type showing abnormal glands with varying size and shape with budding and branching, infiltrating the stroma (Figure 5.15.6).

Prevention by HPV vaccination

Primary prevention through vaccination offers a promising new tool to prevent cervical cancer. However, vaccines are currently expensive and there are several challenges and uncertainties in the widespread implementation of HPV vaccines. The currently available HPV vaccines based on virus-like particles produced by recombinant technology target preventing infection by HPV types 16 and 18, and are given using a regimen of three intramuscular injections over a six-month period. Monovalent (HPV 16), bivalent (HPV 16 and 18) and quadrivalent (HPV 6, 11, 16 and 18) virus-like particle (VLP) vaccines have been evaluated in randomised Phase II and III trials. Recent studies indicate that HPV vaccines are safe, highly immunogenic inducing high levels of serum antibodies in virtually all vaccinated women, and confer a high degree of protection (~99%) against HPV 16/18 infection and related CIN in fully vaccinated women [24,25]. The current information is based on a maximum of 5-year follow-up after vaccination and long-term immunogenicity and efficacy in preventing cervical neoplasia, cross-protection against HPV types not targeted by the vaccine antigens, the need for boosters and the efficacy of different, more logistically feasible dose regimes in inducing and maintaining immunogenicity, remain to be established.

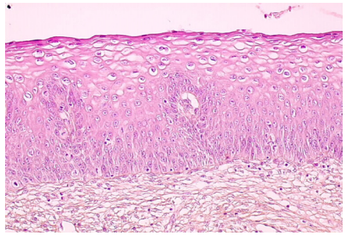


Fig. 5.15.2 *Histology of CIN 1 characterised by the dysplastic cells confined to the lower third of the epithelium*

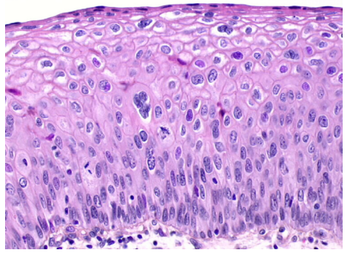


Fig. 5.15.3 *Histology of CIN 2 characterised by dysplastic cells restricted to the lower half of the epithelium*

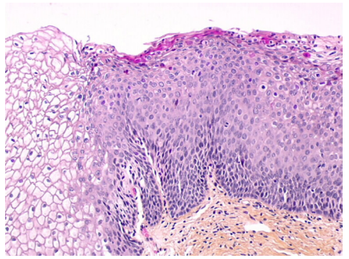


Fig. 5.15.4 *Histology of CIN 3 characterised by lack of differentiation and stratification and dysplastic cells are present throughout the thickness of the epithelium while the basement membrane is intact*

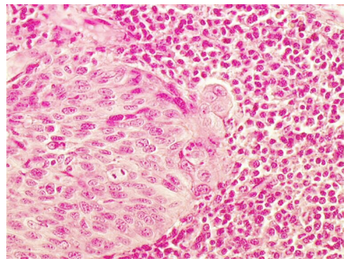


Fig. 5.15.5 *Squamous-cell carcinoma: note infiltrating networks of neoplastic cells in the stroma, varying degrees of differentiation, with keratinization*

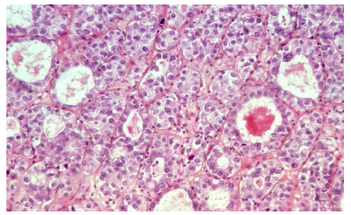
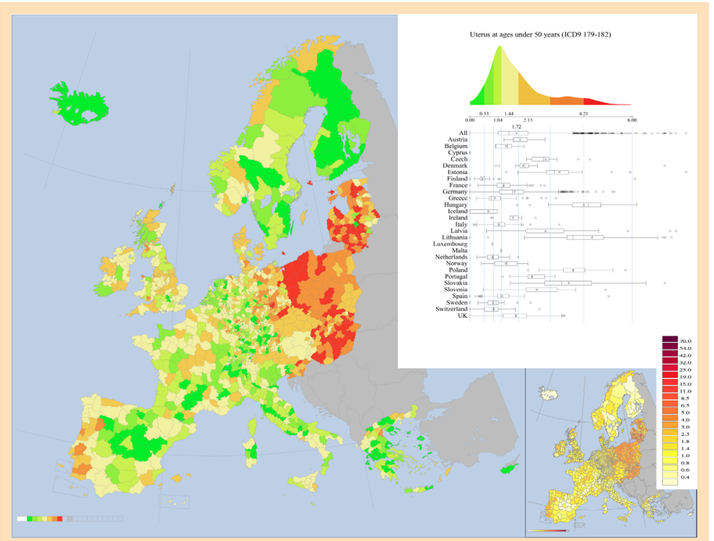


Fig. 5.15.6 *Adenocarcinoma of the cervix showing abnormal glands of varying sizes and shapes infiltrating the stroma*



European Map 5.15.1 *When consideration is restricted to mortality in women under the age of 50, the band of higher rates from Denmark southwards to Austria and Slovenia was still present but less prominent, as were the higher rates in Portugal. Rates were again highest in central Europe and low in Italy and Greece as well as Finland and Sweden [1].*

Prevention by screening

Early changes in the cervix, specifically CIN, can be detected years before invasive cancer develops by screening tests such as conventional cytology (Pap smear), liquid-based cytology, HPV testing and visual screening with acetic acid or Lugol's iodine [26]. An affordable, fast and simple new HPV test (careHPV) developed to detect 14 high-risk types of HPV is a promising test to screen women in developing countries [27]. Women with abnormal screening results are further investigated with colposcopy (a 4–20X magnified inspection of the cervix with a binocular endoscope), directed biopsies from abnormal areas identified on colposcopy [28]. For women whose TZ is not or only partially visible, a tissue specimen may be obtained using endocervical curettage (ECC) or by excising the cervical tissue by the loop electrosurgical excision procedure (LEEP) and subjecting these for histological examination.

The treatment of CIN has evolved from in-patient procedures like hysterectomy and cold knife conisation towards more conservative, safer, simpler and more effective approaches. CIN may be treated by destructive therapy such as cryotherapy, electrocoagulation, cold coagulation or laser vaporisation or by local excision methods such as the LEEP, large loop excision of the transformation zone (LLETZ), or laser excision. The basic principle of treatment of CIN is that the entire TZ of the cervix including the extension into the crypts (average depth 5mm) should be destroyed or removed [28]. Currently, cold knife conisation under local or general anaesthesia is reserved only for the treatment of micro-invasive cancer where evaluation of the margin is of prime importance. Hysterectomy should be reserved only for a

select few cases of CIN coexisting with associated gynaecological conditions requiring removal of the uterus.
CIN 2 and 3 being true cervical cancer precursors are always treated. CIN 1 lesions should be treated if follow-up cannot be ensured (as in most low-resource settings) or the lesion persists for 2 years or worsens in grade or size.

Diagnosis and management of invasive cervical cancer

Public and professional awareness are important in the early detection and management of invasive cervical cancer. Awareness of early symptoms and signs lead to clinical early diagnosis. Education and awareness are critical for the success of this approach. Clinical early diagnosis has been responsible for the reduction in mortality from cervical cancer achieved in developed countries before cervical screening programs were introduced [29,30].

Early, aymptomatic preclinical invasive cervical cancers may be detected during colposcopic assessment of screen-positive women. As invasion progresses, symptoms manifest with characteristic clinical features, depending on the clinical spread of the disease. Women with invasive cervical cancer often present with one or more of the following symptoms: intermenstrual bleeding, postcoital bleeding, heavier menstrual flows, excessive seropurulent discharge, recurrent cystitis, backache and lower abdominal pain. In advanced stages, patients may present with breathlessness due to severe anemia, edema of the lower limbs, haematuria, bowel obstruction, cachexia, a non-functioning kidney (due to ureteral obstruction), invasion of sacral nerve branches or extranodal extension.

Awareness of symptoms and signs of invasive cancer should prompt visual inspection of the cervix to rule out cancer. Clinical suspicion and speculum examination are important in the early detection of invasive cancer. Once a diagnosis of invasive cancer is made, it is mandatory to stage the clinical extent of disease, according to the International Federation of Gynaecology and Obstetrics (FIGO) classification, to guide treatment and prognosis (Table 5.15.1).

A diagnosis of invasive squamous-cell carcinoma or adenocarcinoma requires prompt referral for definitive treatment with surgery or radiotherapy, with or without chemotherapy. Women with microinvasive (stage I A) cancers may be treated with cold knife conisation or simple hysterectomy. Early cervical cancers (stage I B and IIA) may be treated with radical surgery or radiotherapy. Radical surgery for these stages involves the removal of the uterus with a cuff of vagina and the parametrial tissue. Radiotherapy with or without concomitant chemotherapy with platinum compounds is the treatment of choice once the disease has spread beyond the confines of the cervix and vaginal fornices (stages IIB and III). The management of cervical cancer with radical radiotherapy involves a combination of external beam therapy and intracavitary radiation. Concomitant chemotherapy with radiotherapy has improved local control rates in advanced cervical cancer. Treatment for locally very advanced stage IV A and distally spread (IVB) cancers is often palliative.

Clinical stage of disease at presentation is the single most important predictor of long-term survival; survival rates also decline with advancing age. The 5-year survival in stage I A disease ranges from 90–95%, 80–85% in stage I B, 50–65% for stage IIA, 25–35% for stage III and <5% for stage IV disease (Table 5.15.1).

Stage	Description of the stage of disease	5-year survival %
IA	Invasive cancer identified only microscopically. Invasion is limited to measured stromal invasion with a maximum depth of 5 mm and no wider than 7 mm. Stage IA_1: Measured invasion of the stroma 3 mm or less in depth and 7 mm or less in diameter. Stage IA_2: Measured invasion of stroma more than 3 mm but 5 mm or less in depth and 7 mm or less in diameter.	90-95%
IB	Clinical lesions confined to the cervix or preclinical lesions greater than stage IA. Stage IB_1: Clinical lesions 4 cm or less in size. Stage IB_2: Clinical lesions more than 4 cm in size.	80-85%
II	Stage II is carcinoma that extends beyond the cervix but has not extended onto the pelvic wall. The carcinoma involves the vagina but not as far as the lower third section. Stage IIA: No obvious parametrial involvement. Involvement of as much as the upper two thirds of the vagina. Stage IIB: Obvious parametrial involvement but not onto the pelvic sidewall.	50-65% for II A disease 40-50% II B disease
III	Carcinoma that has extended onto the pelvic sidewall and/or involves the lower third of the vagina. On rectal examination, there is no cancer-free space between the tumor and the pelvic sidewall. All cases with a hydronephrosis or nonfunctioning kidney are stage III B, unless they are known to be due to other causes. Stage IIIA: No extension onto the pelvic sidewall but involvement of the lower third of the vagina. Stage IIIB: Extension onto the pelvic sidewall or hydronephrosis or nonfunctioning kidney.	25-30%
IV	Carcinoma that has extended beyond the true pelvis or has clinically involved the mucosa of the bladder and/or rectum. Stage IVA: Spread of the tumor onto adjacent pelvic organs such bladder or rectum. Stage IVB: Spread to distant organs.	<5%

Table 5.15.1 *Clinical staging and survival of cervical cancer*

REFERENCES

1. Boyle P, Smans M (2008). *IARC Scientific Publications, Number 159, Atlas of cancer mortality in the European Union and the European Economic Area 1993-1997*. Lyon, France: International Agency for Research on Cancer.

2. Ferlay J, Bray F, Pisani P, et al. (2004). *GLOBOCAN 2002: Cancer Incidence, Mortality and Prevalence Worldwide*. Available from: http://www-dep.iarc.fr/ Date Accessed: November 10, 2008.

3. Parkin DM, Whelan SL, Ferlay J, et al. (2002). *IARC Scientific Publications, Number 155, Cancer incidence in five continents, Volume VIII*. Lyon, France: International Agency for Research on Cancer.

4. Bray F, Loos AH, McCarron P, et al. (2005). Trends in cervical squamous-cell carcinoma incidence in 13 European countries: changing risk and the effects of screening. *Cancer Epidemiol Biomarkers Prev* 14: 677-686.

5. Bray F, Carstensen B, Moller H, et al. (2005). Incidence trends of adenocarcinoma of the cervix in 13 European countries. *Cancer Epidemiol Biomarkers Prev* 14: 2191-2199.

6. Gondos A, Brenner H, Wabinga H, et al. (2005). Cancer survival in Kampala, Uganda. *Br J Cancer* 92: 1808-1812.

7. Chokunonga E, Ramanakumar AV, Nyakabau AM, et al. (2004). Survival of cervix cancer patients in Harare, Zimbabwe, 1995-1997. *Int J Cancer* 109: 274-277.

8. Sankaranarayanan R, Black RJ, Parkin DM (1998). *IARC Scientific Publications, Number 145, Cancer survival in developing countries*. Lyon, France: International Agency for Research on Cancer.

9. Wang H, Chia KS, Du WB, et al. (2003). Population-based survival for cervical cancer in Singapore, 1968-1992. *Am J Obstet Gynecol* 188: 324-329.

10. Sant M, Aareleid T, Berrino F, et al. (2003). EUROCARE-3: survival of cancer patients diagnosed 1990-94-results and commentary. *Ann Oncol* 14 Suppl 5: s61-118.

11. Ries LAG, Eisner MP, Kosary CL, et al. *SEER Cancer Statistics Review, 1975-2001*. Available from: http://seer.cancer.gov/csr/1975_2001/ Date Accessed: November 10, 2008.

12. Bosch FX, Lorincz A, Munoz N, et al. (2002). The causal relation between human papillomavirus and cervical cancer. *J Clin Pathol* 55: 244-265.

13. IARC (1995). *IARC monographs on the evaluation of carcinogenic risks to humans, Volume 64, Human papillomaviruses*. Lyon, France: International Agency for Research on Cancer.

14. IARC (2007). *IARC monographs on the evaluation of carcinogenic risks to humans, Volume 90, Human papillomaviruses*. Lyon, France: International Agency for Research on Cancer.

15. Walboomers JM, Jacobs MV, Manos MM, et al. (1999). Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. *J Pathol* 189: 12-19.

16. zur Hausen H (1999). Viruses in human cancers. *Eur J Cancer* 35: 1878-1885.

17. Munoz N, Bosch FX, de Sanjose S, et al. (2003). Epidemiologic classification of human papillomavirus types associated with cervical cancer. *N Engl J Med* 348: 518-527.

18. Castellsague X and Munoz N (2003). Chapter 3: Cofactors in human papillomavirus carcinogenesis-role of parity, oral contraceptives, and tobacco smoking. *J Natl Cancer Inst Monogr* 20-28.

19. Castle PE and Giuliano AR (2003). Chapter 4: Genital tract infections, cervical inflammation, and antioxidant nutrients--assessing their roles as human papillomavirus cofactors. *J Natl Cancer Inst Monogr* 29-34.

20. Garcia-Closas R, Castellsague X, Bosch X, et al. (2005). The role of diet and nutrition in cervical carcinogenesis: a review of recent evidence. *Int J Cancer* 117: 629-637.

21. Palefsky JM and Holly EA (2003). Chapter 6: Immunosuppression and co-infection with HIV. *J Natl Cancer Inst Monogr* 41-46.

22. Smith JS, Herrero R, Bosetti C, et al. (2002). Herpes simplex virus-2 as a human papillomavirus cofactor in the etiology of invasive cervical cancer. *J Natl Cancer Inst* 94: 1604-1613.

23. Smith JS, Bosetti C, Munoz N, et al. (2004). Chlamydia trachomatis and invasive cervical cancer: a pooled analysis of the IARC multicentric case-control study. *Int J Cancer* 111: 431-439.

24. Future II Study Group (2007). Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. *N Engl J Med* 356: 1915-1927.

25. Koutsky LA and Harper DM (2006). Chapter 13: Current findings from prophylactic HPV vaccine trials. *Vaccine* 24: S3/114-S3/121.

26. Sankaranarayanan R, Gaffikin L, Jacob M, et al. (2005). A critical assessment of screening methods for cervical neoplasia. *Int J Gynaecol Obstet* 89 Suppl 2: S4-S12.

27. Qiao YL, Sellors JW, Eder PS, et al. (2008). A new HPV-DNA test for cervical cancer screening in developing regions: a cross-sectional study of clinical accuracy in rural China. *Lancet Oncol* 9: 929-936.

28. Sellors JW, Sankaranarayanan R (2003). *Colposcopy and treatment of cervical intraepithelial neoplasia: A beginner's manual*. Lyon, France: International Agency for Research on Cancer.

29. Ponten J, Adami HO, Bergstrom R, et al. (1995). Strategies for global control of cervical cancer. *Int J Cancer* 60: 1-26.

30. Sparen P, Gustafsson L, Friberg LG, et al. (1995). Improved control of invasive cervical cancer in Sweden over six decades by earlier clinical detection and better treatment. *J Clin Oncol* 13: 715-725.

5.16 Ovarian Cancer

Summary

> Parity and oral contraceptive use reduce ovarian cancer risk. Late menopause and use of hormonal therapy in menopause are associated with moderate excess risk

> Overweight and obesity are moderately related to the risk

> The prevention of ovarian cancer is hampered by the lack of availability of early diagnostic techniques and the absence of a proven screening test

Most malignant neoplasms of the ovary originate from the coelomic epithelium; less frequent tumours originate from the germ cells (dysgerminomas and teratomas) and the follicular cells (granulosa cell tumours). In 2002 the estimated number of new cases worldwide was 204 000 with 125 000 cancer deaths, ranking ovarian cancer as the 6th most common cancer in women, and 7th most common cause of cancer death. High incidence rates (on the order of 10–12/100 000) are found in western and northern Europe and in North America; the lowest rates (<3/100 000) are from China and central Africa. In high-risk countries the rates have remained stable in recent decades.

Menstrual, reproductive and hormonal factors are the most widely investigated and best-recognised risk factors for ovarian cancer. Early age at menarche is a risk factor, but only has a modest effect on ovarian cancer risk. Lifelong number of menstrual cycles has also been associated with ovarian cancer risk, suggesting that ovulation may be implicated in the process of ovarian carcinogenesis. Several studies showed a direct relation between late age at menopause and the risk of ovarian cancer [2].

Nulliparity and low parity have been consistently related to ovarian cancer. Most studies showed a decline in risk associated with number of full-term pregnancies beyond the first one, thus suggesting that the inverse association is not due to infertility per se, and additional risk reduction is conferred by events accompanying each pregnancy [3].

The protection afforded by combined oral contraceptives (OC) is the other established, and most important from a public health perspective, feature of epithelial ovarian cancer. The overall estimated protection is approximately 40% in ever OC users and increases with duration of use to about 60% for users for 10 years or longer. The favourable effect of OC against ovarian cancer risk seems to persist for at least 15–20 years after OC use has ceased, and it is not confined to any particular type of OC formulation [4]. The issue of fertility drugs and ovarian cancer has also attracted lively interest, but the findings of various studies remain inconsistent. Hormone therapy in menopause has also been related to increased ovarian cancer risk, although the association is less consistent than that of breast cancer [5].

The implication of reproductive factors in the etiology of ovarian cancer suggests a major role of endogenous hormones in the disease. Several hypotheses have been postulated, as excessive gonadotropins stimulation [6] (see *Reproductive factors*, Chapter 2.7). To date, however, the epidemiological evidence of such an involvement is rather limited: only a few studies with limited sample size have been published on the association of endogenous sex steroids and ovarian cancer risk, with discordant results. Conversely, two case–control studies nested within large cohorts have shown an increase in ovarian risk with increasing circulating insulin-like growth factor concentrations in blood in young women (pre or peri-menopausal age)[7,8].

Additional support for an involvement of hormones in ovarian cancer comes from studies exploring the relationship between endometriosis and ovarian cancer risk. Endometriosis is an inflammatory disease, very often becoming clinically apparent during the reproductive years, that seems to be regulated by estrogens and progestins. Risk factors for endometriosis are similar to those for ovarian cancers, viz. age at menarche, irregular menstrual cycles and height, while pregnancy and oral contraceptive use seem to lower the risk of developing the disease. Apart from hormones, the chronic inflammatory state caused by endometriosis may also explain its implication in the disease, since other known epidemiological risk factors, such as talc use and pelvic inflammation, are related to chronic inflammation. A consistent association between endometriosis and ovarian cancer risk has been shown in many epidemiological and clinical studies. Prospective as well as case–control studies suggest an overall doubling in ovarian cancer risk in women who have endometriosis compared to women who do not [9].

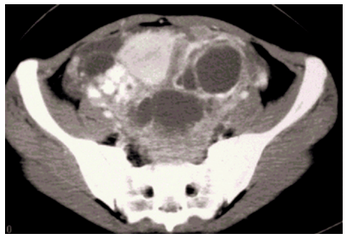


Fig. 5.16.1 *Magnetic resonance image (MRI) of a large, partly cystic ovarian carcinoma*

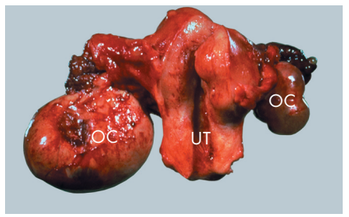


Fig. 5.16.2 *Surgical specimen of a bilateral ovarian carcinoma (OC). UT = uterus*

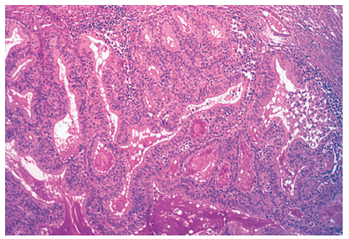
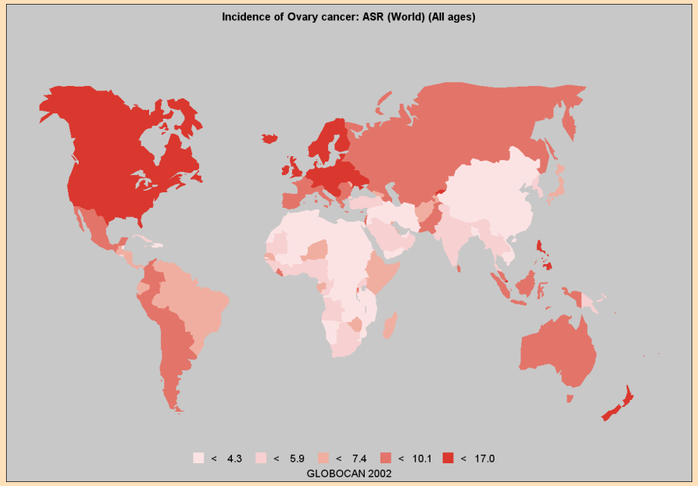


Fig. 5.16.3 *Histopathology of a well-differentiated, mucus-secreting, endometrial-like adenocarcinoma of the ovary*

Factors leading to greater adult height, including genetic, environmental, hormonal and nutritional factors, have been judged by the World Cancer Research Fund panel experts to be probable causes of ovarian cancer [10]. Results from cohort studies suggest an overall 15% increase in ovarian cancer risk with a 10cm increase in adult height, even though this relationship with risk is not supported by results from case–control studies. The association between ovarian cancer risk and adult height seems to be more related to specific subtypes of cancer (borderline mucinous) [11].

Potential links between ovarian cancer and diet were originally suggested on the basis of international differences or correlation studies. Overweight and obesity are moderately related to the risk of ovarian cancer: The estimated RR was 1.14 (95% CI 1.03–1.27) in the Million Women study [12]. Positive correlations were observed with fat, protein and total caloric intake and are generally in the same direction as those of endometrial and breast cancer. A relationship between ovarian cancer and intake of meat and fats has also been reported from some cohort and case–control studies, whereas fruit and vegetables appear to be inversely related. Some case–control studies found direct associations between measures of fat intake and risk of ovarian cancer. Starchy foods, and consequently diets with a high glycemic index and glycemic load, have also been related to excess ovarian cancer risk. The possibility that the milk sugar lactose or its metabolites have some effect on oocytes with a compensatory gonadotropic stimulation resulting in excess ovarian cancer risk has been investigated. Several, but not all, studies have found excess risk with lactose consumption and absorption, but the issue remains unsettled. Studies from Greece and Italy suggested that monounsaturated fats (olive oil) and fibre intake may be protective [13,14]. The role of diet on ovarian cancer incidence and mortality rates across Europe remains, however, unquantified [15].

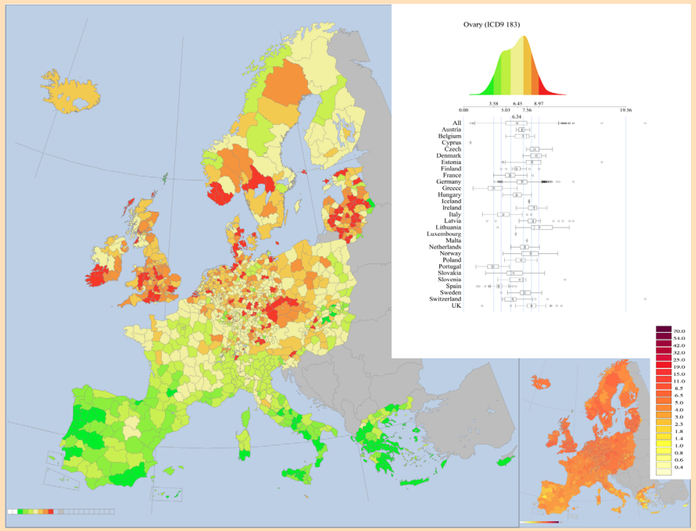


World Map 5.16.1

A relationship between smoking and ovarian cancer risk has also been suggested, even though results from studies are not totally consistent and largely negative. A recent meta-analysis including 910 women with mucinous ovarian cancer and 5564 women with non-mucinous ovarian cancer suggests a doubling in mucinous ovarian cancer risk in current smokers compared to never-smokers, but no increase in risk with other types of ovarian cancer [16].

There have long been clinical observations suggesting familial aggregations of ovarian cancer. Besides the clustering of ovarian cancer, an excess of breast cancer and a more general excess of several cancers (including colon and endometrium) have been described. These patterns are consistent with an autosomal dominant gene with variable penetration. The estimated relative risks from case–control studies that included data on family history range between 3 and 5 in most studies [17]. Women carrying BRCA1 or BRCA2 mutations have been seen to be at higher risk of developing ovarian cancer. The average cumulative risk of developing ovarian cancer by the age of 70 is 39% (22–51%) in BRCA1-mutation carriers and 11% (4.1–18%) in BRCA2 carriers [17].

The prevention of ovarian cancer is currently hampered by the limited knowledge of its causes and the lack of availability of early diagnostic techniques.



European Map 5.16.1 *While there are certain similarities with breast cancer in the geographic distribution of mortality from cancer of the ovary, there are also some potentially interesting differences [1].*

REFERENCES

1. Boyle P, Smans M (2008). *IARC Scientific Publications, Number 159, Atlas of cancer mortality in the European Union and the European Economic Area 1993-1997.* Lyon, France: International Agency for Research on Cancer.

2. La Vecchia C (2001). Epidemiology of ovarian cancer: a summary review. *Eur J Cancer Prev* 10: 125-129.

3. Hankinson SE, Danforth KN (2006). Ovarian cancer. In: Schottenfeld D, Fraumeni JF, eds., *Cancer epidemiology and prevention.* New York: Oxford University Press 1013-1026.

4. La Vecchia C (2006). Oral contraceptives and ovarian cancer: an update, 1998-2004. *Eur J Cancer Prev* 15: 117-124.

5. Anderson GL, Judd HL, Kaunitz AM, et al. (2003). Effects of estrogen plus progestin on gynecologic cancers and associated diagnostic procedures: the Women's Health Initiative randomized trial. *JAMA* 290: 1739-1748.

6. Lukanova A and Kaaks R (2005). Endogenous hormones and ovarian cancer: epidemiology and current hypotheses. *Cancer Epidemiol Biomarkers Prev* 14: 98-107.

7. Lukanova A, Lundin E, Toniolo P, et al. (2002). Circulating levels of insulin-like growth factor-I and risk of ovarian cancer. *Int J Cancer* 101: 549-554.

8. Peeters PH, Lukanova A, Allen N, et al. (2007). Serum IGF-I, its major binding protein (IGFBP-3) and epithelial ovarian cancer risk: the European Prospective Investigation into Cancer and Nutrition (EPIC). *Endocr Relat Cancer* 14: 81-90.

9. Ness RB and Modugno F (2006). Endometriosis as a model for inflammation-hormone interactions in ovarian and breast cancers. *Eur J Cancer* 42: 691-703.

10. World Cancer Research Fund / American Institute for Cancer Research (2007). *Food, Nutrition, Physical Activity and the Prevention of Cancer: a Global Perspective.* Washington, DC: AICR.

11. Jordan SJ, Webb PM, Green AC (2005). Height, age at menarche, and risk of epithelial ovarian cancer. *Cancer Epidemiol Biomarkers Prev* 14: 2045-2048.

12. Reeves GK, Pirie K, Beral V, et al. (2007). Cancer incidence and mortality in relation to body mass index in the Million Women Study: cohort study. *BMJ* 335: 1134.

13. Edefonti V, Decarli A, La Vecchia C, et al. (2008). Nutrient dietary patterns and the risk of breast and ovarian cancers. *Int J Cancer* 122: 609-613.

14. Tzonou A, Hsieh CC, Polychronopoulou A, et al. (1993). Diet and ovarian cancer: a case-control study in Greece. *Int J Cancer* 55: 411-414.

15. Bosetti C, Negri E, Franceschi S, et al. (2002). Olive oil, seed oils and other added fats in relation to ovarian cancer (Italy). *Cancer Causes Control* 13: 465-470.

16. Jordan SJ, Whiteman DC, Purdie DM, et al. (2006). Does smoking increase risk of ovarian cancer? A systematic review. *Gynecol Oncol* 103: 1122-1129.

17. Negri E, Pelucchi C, Franceschi S, et al. (2003). Family history of cancer and risk of ovarian cancer. *Eur J Cancer* 39: 505-510.

CANCER INSTITUTE PROFILE: Karolinska Comprehensive Cancer Centre

Recently there was a merger of the two university hospitals in Stockholm, Sweden into the Karolinska University Hospital. The aim was to integrate research and education at the Karolinska Institute with the health care system in Stockholm and build a structure for translational medicine. The hospital and the campus of the Karolinska Institute together form an organisation with more than 18 000 employees. The decision has been made to develop a more visible and functional comprehensive cancer centre within this structure in order to form an environment for improved translational cancer research. With about 120 research groups involved in cancer research, there is a strong platform for basic, preclinical and epidemiological research. There is also important infrastructure for translational research, with experimental cancer research laboratories linked to oncological health care (Cancer Center Karolinska, a translational research structure), patient data registries containing population-based data, a clinical trial unit, a structure for biobanking and a platform for biomics. A particularly strong area of interest is proteomics, evidenced by the collaboration with the human proteome resource at the Royal School of Technology. The Centre provides oncologic service for the 2 million inhabitants in the Stockholm area. About 700 to 800 scientific reports in the area of cancer are published each year, as well as around 80 PhD theses.

5.17 Endometrial Cancer

Summary

> The "unopposed estrogens" hypothesis (long-term exposure to relatively high levels of estrogens, not counterbalanced by the presence of progesterone) is the most widely accepted hypothesis on the etiology of endometrial cancer

> Obesity is the most important risk factor for endometrial cancer worldwide, and has been estimated to account for up to 40% of endometrial cancer incidence

> The use of oral contraceptives is associated with a long-lasting decrease in endometrial cancer risk

> Much of the effects of dietary habits and physical activity on endometrial cancer risk may be explained by the link between energy intake, expenditure and body weight

Endometrial cancer is the seventh most-common cancer in women worldwide, and the fourth in developed countries, after breast, lung and colorectal cancers. This cancer appears more important in terms of number of new cases than in terms of mortality (representing 3.9% of new cancer cases in women compared to 1.7% cancer deaths) [2]. The highest incidences are in North America and in Western Europe, where it is about 10 times higher than in Asia or in rural Africa[2] . In these areas, endometrial cancer is the most common cancer of the female genital tract. The wide differences in incidence of endometrial cancer between rural and urban areas, as well as results of studies on migrations from low- to high-risk areas, strongly suggest strong environmental rather than genetic risk factors.

The overall incidence of endometrial cancer is rising as life expectancy increases. This cancer mostly arises in post-menopausal women: more than 90% of cases occur in women who are older than 50, with the highest incidence reached after 65 years of age [2]. Survival is rather good and parallels that of breast cancer (86% according to the SEER registries, and 78% in European registries) [2].

There are two major types of endometrial cancers. About 80% are of endometrioid type, are well to moderately differentiated, and are generally associated with endometrial hyperplasia (type I). They have favourable prognosis, and are strongly related to hormonal imbalances [3]. About 10% of endometrial cancers are type 2 (high-grade or poorly differentiated). Type 2 tumours are more often serous papillary, squamous cell or clear cell carcinomas, and seem to be unrelated to estrogens [3]. Women with type 2 tumours are at high risk of relapse and of metastatic disease. Type-I carcinomas are associated with mutations in the ras oncogene and PTEN tumour suppressor gene, as well as with microsatellite instability, while the majority of type-2 tumours are associated with p53 mutations.

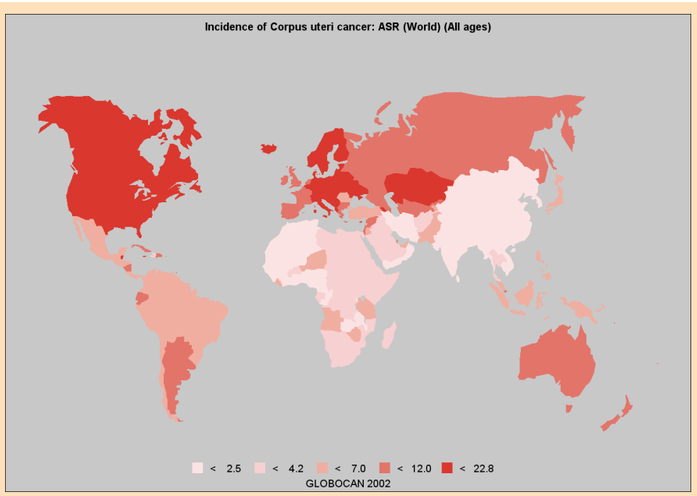
Since endometrium is a tissue that is very responsive to hormone stimulation, hormones seem to play an important role in the etiology and in the development of this cancer. Endometrial cell mitotic rate is sensitive to estrogens, especially to estrogens that are unopposed by progestins: the proliferation rate of endometrial cells seems to reach its maximum during the first 18 days of the menstrual cycle (follicular and early luteal phases), phases in which progesterone levels are particularly low. The "unopposed estrogens" hypothesis (long-term exposure to relatively high levels of estrogens, not counterbalanced by the presence of progesterone) [4] is the most widely accepted hypothesis on the etiology of endometrial cancer and can explain most of the risk factors already identified: early age at menarche, late age at menopause, nulliparity, hormone replacement therapy (HRT) use and obesity. An early age at menarche and a late age at menopause increase the exposure of a woman to estrogens over her lifespan, while pregnancies mainly increase her exposure to progestogens (through placental production).

Obesity is the most important risk factor for endometrial cancer worldwide, and has been estimated to account for about 40% of endometrial cancer incidence. In pre-menopausal women, obesity is associated with anovulatory cycles during which the endometrial tissue receives continuous stimulation. In post-menopausal women, increased body fat mass increases the concentration of endogenous estrogens, because in this population estrogens are not produced by the ovary anymore, but are mainly produced by the aromatisation of androgens in the adipose tissues. Excess weight is associated with insulin resistance and chronically elevated insulin concentrations in blood, and with increasing concentrations of bioavailable sex steroids [5], factors that are associated with increased endometrial cancer risk (Figure 5.17.1). Type-2 and type-1 diabetes are strongly associated with an increase in endometrial cancer risk, as well as hypertension. Hyperglycaemia has also been associated with an increase in endometrial cancer risk, especially in overweight women.

	Premenopausal		Postmenopausal
	Normoandrogenic	Hyperandrogenic (PCOS)	
SHBG	↓	↓	↓
E_1	↑	↑	↑
E_2 (total)	~	~	↑
E_2 unbound to SHBG	~	~	↑
Δ-4A	~	↑	~↑[α]
T (total)	~	↑	~↑ [α]
T unbound to SHBG	↑	↑↑	↑

Fig. 5.17.1 *Effects of obesity and chronic hyperinsulinemia on plasma sex steroids in women [5]*
[α]Observed relationships between obesity/plasma insulin and plasma androgen levels in postmenopausal women are inconsistent across studies, and might depend on genetic factors predisposing to hyperandrogenism.

The use of OC is associated with a long-lasting decrease in endometrial cancer risk, but only when the contraceptives used contain progesterone in addition to estrogens [6] (Figure 5.17.2). Since in these drugs the concentrations of progestagens are dominant compared to oestrogen concentrations, the proliferation of endometrial cells happens only during the few days of the menstrual cycle when OC are not taken. Based on this assumption, the decrease in endometrial cancer risk has been calculated to be about 10% per year of OC use. Oestrogen-containing pills only, conversely, increase the risk of endometrial cancer. The use of HRT in post-menopausal women increases about twofold the risk of developing endometrial cancer [7] (Figure 5.17.3), and the risk increases with duration of use and with increasing oestrogen concentrations in the medications. Adding progesterone daily to estrogen therapy seems to lower the risk of endometrial cancer similar (or lower) to that of non-estrogen users [6]. A recent publication suggests that the risk of endometrial cancer in women taking HRT may be associated with relevant genotypes regulating steroid hormone sulfation.



World Map 5.17.1

Relatively higher endogenous estrogen concentrations in blood are associated with an increase in endometrial cancer risk mainly in post-menopausal women, while higher endogenous androgen concentrations are associated with an increase in endometrial cancer risk in both pre- and post-menopausal women [5]. Polycystic ovary syndrome (PCOS) (a syndrome associated with increased blood androgen levels, and with infertility, amenorrhea, hirsutism and diabetes) has been repeatedly associated with an increase in endometrial cancer risk [5].

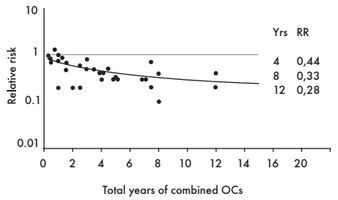


Fig. 5.17.2 *Relative risk of endometrial cancer by duration of use of combined oral contraceptives [11]*

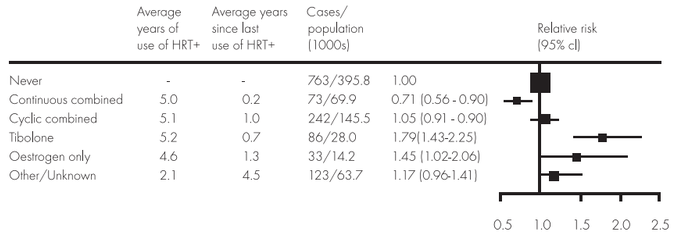


Fig. 5.17.3 *Relative risk of endometrial cancer according to type of hormone replacements therapy used (Million Women study) [7]*

In respect to dietary factors, phytoestrogen, antioxidant and vegetable consumptions have been associated with a decrease in risk of endometrial cancer [8,9]. Conversely, recent publications have suggested an increase in endometrial cancer risk with high consumption of meat.

Women who develop breast cancer are at increased risk of developing endometrial cancer, and are more likely to develop type-2 rather than type-I endometrial carcinoma. This increase in risk could be partly explained by common risk factors between breast and endometrial malignancies (as nulliparity or late age at menopause), but the use of tamoxifen for the treatment of breast cancer has also been questioned: women under tamoxifen therapy had more than a twofold increase in endometrial cancer risk compared to non-users. Physical activity has been shown to decrease the risk of endometrial cancer, although further studies are needed to finally assess its influence on the disease. Epidemiological evidence suggests that smoking may be protective against endometrial cancer in post-menopausal women, but it seems to be associated with an increase in endometrial cancer risk in pre-menopausal women. Much, if not all, of the reported effects of dietary habits and physical activity on endometrial cancer risk may be explained by the link between energy intake and expenditure, and body weight. The same may be true for the apparent lower risk among smoking women, as they tend to be leaner than non-smoking women.

As stated previously, genetic causes of endometrial cancer are uncommon, although having a first-degree relative with endometrial cancer has been associated with double the risk of developing the disease, and an association with hereditary non-polyposis colon cancer (HNPCC) syndrome has been observed [3]. Screening for endometrial cancer does not seem to improve survival or reduce mortality from endometrial cancer, since most of the cancers detected with screening would be most likely low-risk cancers [3,10]. Post-menopausal bleeding is the most common symptom of endometrial cancer, which is present in 75% of women with the disease. Women should therefore be aware of the importance of detecting post-menopausal bleeding or spots. Conversely, no tests have so far been validated or are recommended for endometrial cancer screening [10].

REFERENCES

1. Boyle P, Smans M (2008). *IARC Scientific Publications, Number 159, Atlas of cancer mortality in the European Union and the European Economic Area 1993-1997*. Lyon, France: International Agency for Research on Cancer.

2. Parkin DM, Bray F, Ferlay J, et al. (2005). Global cancer statistics, 2002. *CA Cancer J Clin* 55: 74-108.

3. Amant F, Moerman P, Neven P, et al. (2005). Endometrial cancer. *Lancet* 366: 491-505.

4. Key TJ and Pike MC (1988). The dose-effect relationship between 'unopposed' oestrogens and endometrial mitotic rate: its central role in explaining and predicting endometrial cancer risk. *Br J Cancer* 57: 205-212.

5. Kaaks R, Lukanova A, Kurzer MS (2002). Obesity, endogenous hormones, and endometrial cancer risk: a synthetic review. *Cancer Epidemiol Biomarkers Prev* 11: 1531-1543.

6. Cogliano V, Grosse Y, Baan R, et al. (2005). Carcinogenicity of combined oestrogen-progestagen contraceptives and menopausal treatment. *Lancet Oncol* 6: 552-553.

7. Beral V, Bull D, Reeves G (2005). Endometrial cancer and hormone replacement therapy in the Million Women Study. *Lancet* 365: 1543-1551.

8. Horn-Ross PL, John EM, Canchola AJ, et al. (2003). Phytoestrogen intake and endometrial cancer risk. *J Natl Cancer Inst* 95: 1158-1164.

9. Tao MH, Xu WH, Zheng W, et al. (2005). A case-control study in Shanghai of fruit and vegetable intake and endometrial cancer. *Br J Cancer* 92: 2059-2064.

10. Robertson G (2003). Screening for endometrial cancer. *Med J Aust* 178: 657-659.

11. Schlesselman JJ (1997). Risk of endometrial cancer in relation to use of combined oral contraceptives. A practitioner's guide to meta-analysis. *Hum Reprod* 12: 1851-1863.

BRIEF REPORT FROM THE WHO REGIONAL OFFICE FOR AFRICA

Cancer is an emerging public health problem in the WHO African Region. The commonest cancers are Kaposi sarcoma and cancers of the liver and prostate gland in men, and cancers of the cervix and breast in women. In Africa the cancer situation is characterised by 80–90% of cancer cases being incurable at presentation, 10–15% curable when given appropriate treatment and less than 5% prevention actions implemented. According to GLOBOCAN, 412 100 people in sub-Saharan Africa died from cancer in 2002. If no interventions are put in place, it is projected that by the year 2020 the number of new cancer cases will be 804 000 and the number of deaths due to cancer will be 626 400. The main risk factors for cancer are infectious conditions, tobacco use, unhealthy diet, environmental pollution, excessive alcohol intake and physical inactivity. Use of traditional diets, farming and pasturing are protective factors.

In the WHO African Region, a few countries including Guinea, Senegal, South Africa and Tanzania have national cancer control policies and programmes. Data on the magnitude of cancer are scanty or nonexistent. Cancer registries exist but not many countries have published national data in global outlets. Cervical cancer prevention programmes have been implemented in many countries including Guinea, Uganda, South Africa, Zimbabwe and Tanzania; these initiatives must be scaled up. Well-equipped infrastructure and facilities for early cancer detection or management requiring surgery, chemotherapy and radiotherapy are very lacking in most countries. While there is an acute shortage of cancer specialists such as pathologists for diagnosis, oncologists for treatment and oncology nurses for care, some national universities, especially in South Africa, Nigeria, Kenya and Senegal, have started training programmes for health personnel specialists in various cancer domains. There is increasing political will to address cancer-related issues and challenges.

The WHO Regional Office for Africa (AFRO) is committed to public health actions designed to reduce cancer incidence and mortality and to improve quality of life of patients through the systematic implementation of evidence-based strategies for prevention, early detection, diagnosis, treatment and palliative care. The WHO-AFRO Regional Director has made cancer prevention and control a priority for the Region and provided the Regional office with resources to tackle the problem. There have been:

- actions of *advocacy* to increase commitment, such as a roundtable held on August 2007 during the AFRO Regional committee to underline the best approaches to increase awareness and put cancer high on the national agenda;
- *statements of commitment* facilitated among member states including the adoption of resolutions and, a regional strategy for cancer control to be submitted to next regional committee in September 2008 for adoption by Member States;
- *normative guidance and technical support* for national programme development and implementation, such as a tool for key interventions in cancer prevention and control to be published soon and an integrated approach for non-communicable diseases that incorporates comprehensive health promotion components;
- at regional and country levels, many *specific interventions* have been implemented with AFRO's support including capacity-building, mobilisation and allocation of resources, collaboration and partnerships (with other UN agencies such as IAEA and IARC, and international NGOs including UICC and the American Cancer Society), strategic information and surveillance including STEPs and tobacco surveys; and research.

The future perspective for the WHO African Region is the adoption and implementation of a regional strategy for cancer control where prevention, early detection, treatment and cure of cancers are systematically implemented or scaled up and where all cancer patients receive the best possible care.

website: www.afro.who.int)

5.18 Testicular Cancer

Summary

- A rapid increase in the incidence of germ-cell testicular cancer has been reported, particularly in young white men
- Little is known about the etiology and the cause(s) of the observed increase in incidence of the disease. Exposure to sex hormones and hormone-like chemicals in utero and/or during puberty appears to be important to the occurrence and the progression of the disease
- Genetic susceptibility is likely to explain the uniformly low rate and lack of increase in black populations worldwide
- Epigenetic or other cellular changes may be responsible for the rapid decrease of the disease after age 35

During the last several decades, epidemiological studies conducted in various parts of the world have demonstrated a rapid increase in the incidence of germ-cell testicular cancer, predominantly in young men. Birth cohort analyses suggest that the observed long-term increasing trend of testicular cancer is real. While considerable efforts have been made in studying the etiology of testicular cancer, little is known about the etiology and the cause(s) of the observed increase in incidence of the disease. Nevertheless, the following descriptive epidemiological features of germ-cell testicular cancer as summarised by Zheng et al. [2] offer important clues for searching for the risk factors of germ-cell testicular cancer:

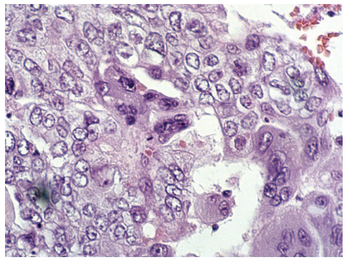


Fig. 5.18.1 *Testicular teratoma, Wellcome Images*

1. Different populations or different birth cohorts of the same population have wide differences in magnitude in the incidence of testicular cancer. For example, there is a fivefold difference in incidence rates between Denmark and Finland, with Denmark (along with Switzerland) having the highest reported incidence rate of germ-cell testicular cancer in the world. Danish men born during World War II, however, had lower-than-expected rates in most age groups [3]. These observations indicate that environmental exposures may be of significant importance in the occurrence and/or the progression of the disease.

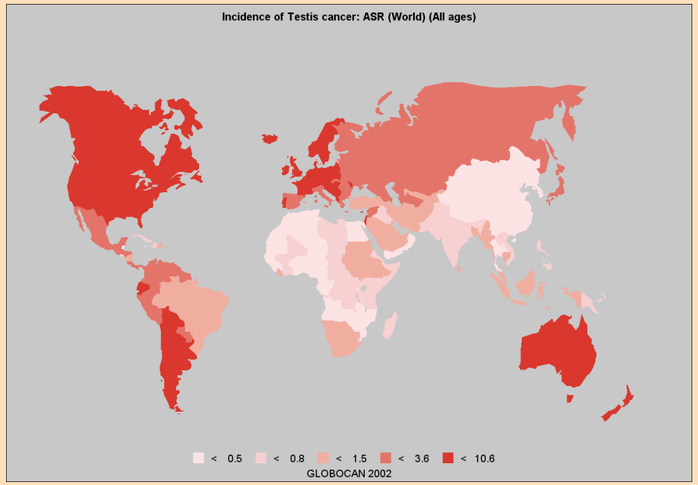
2. Different populations or different birth cohorts of the same population have very similar age-incidence patterns. Testicular cancer has a very small peak in the postnatal period (particularly for non-seminoma), followed by a rapid increase after puberty, and peak at around age 25 for non-seminoma and age 35 for seminoma. The vast majority of the cases of germ-cell testicular cancer are diagnosed between ages 15–45. The early onset of the disease, the rapid increase in rate after puberty and the peak at young age suggest that early-life exposure and male sex hormones are related to the occurrence and/or progression of germ-cell testicular cancer.

3. Black populations living in different parts of the world, whether in North America, Europe or Africa, have very low and similar incidence rates of germ-cell testicular cancer (<1/100 000 for the majority of the black populations). They also have not shown a long-term increase during the past decades as observed in the white populations. It is difficult to argue that blacks have universally had lower exposure to testicular cancer risk factors than whites. Rather, lower genetic susceptibility to environmental exposures may be responsible for the uniformly low rate and lack of increase in the black populations. A recent study by Zhang et al. [4] found that black mothers had a significantly lower ratio of sex hormones (estradiol/testosterone) in the first and the third trimesters; the authors suggested that this lower ratio might be responsible for the lower risk of germ-cell testicular cancer observed among black men.

Etiology

Analytical epidemiologic studies of risk factors for testicular cancer have thus far not provided convincing evidence to explain these descriptive features of germ-cell testicular cancers. The results linking major suspected risk factors (such as endogenous hormones and environmental hormone disruptors) to testicular cancer risk have been inconsistent, possibly due to small sample sizes in the majority of studies. Few studies so far have investigated the relationship between genetic susceptibility and gene-environment interaction in the risk of developing the disease. The following summarises the major suspected risk factors for germ-cell testicular cancer:

High levels of endogenous hormones during early pregnancy or adolescences. Henderson et al. [5] and Depue et al. [6] hypothesised that the major risk factor for testis cancer is a relative excess of certain hormones (in particular estrogen) during early pregnancy, perhaps at the time of differentiation of the testes. Several indices of early-life exposure to elevated levels of circulating maternal estrogens have been linked to testicular cancer risk, though the results have been inconsistent. These indices include bleeding, spotting, excessive nausea and vomiting during early pregnancy, neonatal jaundice, early birth order, preterm birth, low birth weight or abnormally high birth weight, high placenta weight, hypospadias, cryptorchidism and inguinal hernia of the subject, and dizygotic twins. High maternal age at pregnancy and high maternal body mass index at the time of conception with the index pregnancy have also been associated with the risk of testicular cancer in their sons.



World Map 5.18.1

The observed relationship between these prenatal exposure surrogates and testicular cancer risk has generally been considered to be due to a raised maternal level of available estrogens early in life. For example, the cause of severe nausea in pregnancy is considered to be due to the rapid rise of estrogen levels in the mother in the first 2 months of gestation. Higher risk of testicular cancer for early birth order is consistent with the fact that pregnancy estrogen concentrations are higher during the first pregnancy. Cryptorchidism is related to an excess of available maternal estrogen during early pregnancy. Thus, rather than as a cause of testicular cancer, cryptorchidism may simply share common risk factor(s) with testicular cancer [7]. Neonatal jaundice is also related to high estrogen levels among infants. Abnormally high birth weights are associated with testicular cancer risk since foetal growth was reported to be positively correlated with pregnancy estrogen levels in both blood and in urine. Pregnancy estrogen concentrations were also reported to be higher among older women. Dizygotic twin pregnancies have higher estrogen levels because dizygotic twins tend to have two placentas.

Moller [8] proposed a "carcinoma in situ model", according to which germ-cell testis cancer is a process initiated by causes acting very early in life, most probably before birth, and leading to carcinoma in situ (CIS). Adulthood exposures, whether male sex hormones or environmental exposures, would only influence the further progression of the existing CIS to invasive testis cancer or different types of germ-cell testis cancers. A rapid increase of testis cancer incidence after puberty indicates that male sex hormones may be responsible for the further progression of the existing CIS to invasive testis cancer. The relationship between severe acne at puberty and testicular cancer risk further supports the role of male sex hormones in the progression of the disease because severe acne at puberty is associated with increasing testosterone levels. Thus, prenatal exposure to excess estrogens (while subnormal androgen exposure has also been proposed as a risk factor) may play a major role in the development of the CIS, while adolescent exposure to excess male sex hormones may play a critical role for the progression of the CIS to invasive testicular cancer.

No study has systematically examined the relationships between prenatal exposures and various prenatal exposure surrogates at different critical periods of pregnancy. Several epidemiological studies actually do not support the estrogen hypothesis as recently reviewed by Zhang et al. [4]. Studies showed that both Chinese women and black women had significantly higher serum levels of estradiol and estriol during early gestation than US white women, but both Chinese men and black men have a much lower incidence rate of germ-cell testicular cancer than do US white men. Based on these results, Zhang et al. [4] suggested that increased testosterone levels during early pregnancy, rather than estrogen levels, are associated with a reduced risk of germ-cell testicular cancer. They considered that more critical is the ratio of estrogen to androgen; that is, a lower ratio of sex hormones (estrogens/androgens) is associated with a reduced risk of germ-cell testicular cancer. More studies clearly are needed to clarify the role of both the estrogen hypothesis and the androgen hypothesis in the risk of testicular cancer.

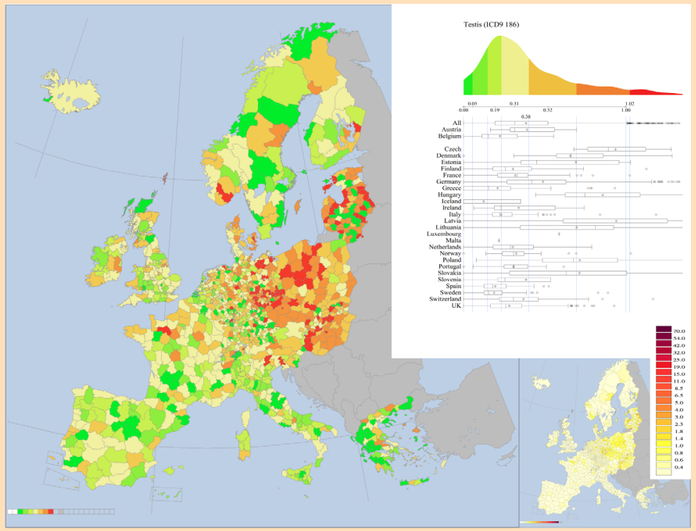
Environmental hormone disruptors. Although prenatal exposure to high levels of endogenous hormones and adolescent exposure to high levels of male sex hormones might be related to the risk of testicular cancer (the age-incidence pattern), this excess hormone hypothesis itself, however, cannot explain the increasing trend of testicular

cancer observed during the past decades (the secular incidence pattern). Based on recent laboratory studies in animal systems, investigators have suggested that environmental hormone disruptors may be risk factors for testicular cancer, and population-wide increasing exposure to estrogenic or other hormonally active (e.g. antiandrogenic) compounds may be at least in part responsible for the observed increasing trend of the disease [9,10]. Specifically, there is concern over the relationship between environmental exposure to organochlorines (e.g. polychlorinated biphenyls, organochlorine insecticides such as DDT and its analogues, and others), polybrominated diphenyl ethers (PBDEs) and the risk of testicular cancer.

While there has been considerable interest in the relationship between environmental endocrine disruptors and human testicular cancer, few epidemiological studies have directly examined these relationships. Thus, a relationship between environmental endocrine disruptors and increased risk of testicular cancer risk is mainly based on the following observations:

1. Experimental studies show that exposure to both endogenous and exogenous hormones produces testicular cancer and other male reproductive disorders.

2. Results from a pilot study support a potential relationship between environmental hormone disruptors and testicular cancer risk. In this small study, Hardell et al. [11] reported that the mothers of testicular cancer cases had significantly higher serum levels of PCBs, hexachlorobenzene (HCB), transnonachlordane (TNC), cisnonachlordane (CNC) and the sum of chlordanes than did the mothers of noncancerous controls. When using the median concentration for the controls as cut-off value, the OR was 3.8 (95% CI 1.4–10) for PCBs, 4.4 (1.7–12) for HCB, 4.1 (1.5–11) for TNC, 3.1 (1.2–7.8) for CNC and 1.9 (0.7–5.0) for sum of chlordanes.



European Map 5.18.1 *The main feature of the geographic distribution of testicular cancer mortality is the grouping of areas with high rates in the former communist countries - the eastern part of Germany, Poland, the Czech Republic, Slovakia, Hungary, and the three Baltic countries. The patchwork appearance of the remainder of the map simply reflects the wide random variation inherent in rates based on very small numbers of deaths [1].*

3. Men exposed in utero to diethylstilbestrol (DES) showed an increased risk of testicular cancer in some studies, and the combined estrogenic effects of environmental estrogens may exceed those of DES.

4. Pesticide applicators were reported to have an increased risk of testicular cancer, though the results are inconsistent.

5. While testicular cancer is increasing, other male reproductive disorders, such as cryptorchidism, hypospadias, reduced sperm count and quality, and infertility, are also increasing. These disorders are now collectively called testicular dysgenesis syndrome (TDS). TDS and testicular cancer may share a common risk factor—environmental hormones.

6. The hormone properties, carcinogenicity, tumour promotion activity and enzyme induction ability of these chemicals strongly support that exposure to environmental hormone disruptors may increase the risk of testicular cancer.

In summary, the hypothesis that environmental hormone disruptors are risk factors for testicular cancer is plausible based on animal data and limited human data. Organochlorines, for example, possess estrogenic and antiandrogenic activity, are known animal carcinogens and suspected human carcinogens, and have tumour promotion activity. Due to these properties, along with the continued widespread exposure to environmentally persistent organochlorine compounds and PBDEs among the general population, there exists a need to determine whether these compounds are risk factors for testicular cancer.

Family history and genetic susceptibility. It is estimated that about 2% of the cases of testicular cancer may be explained by family history of testicular cancer. As described previously, epidemiological studies have strongly suggested a role of genetic susceptibility in the risk of testicular cancer. While few studies have investigated the relationship between testicular cancer risk and genetic polymorphisms, it seems reasonable to assume that major genes that have been associated with either the regulation, metabolism or functional activities of endogenous and exogenous hormones (such as genes of the CYP family, the oxidative stress defense enzyme genes and the hormone receptor genes) should play a major role in the risk of occurrence and progression of testicular cancer.

In a study of estrogen receptor polymorphisms and risk of testicular cancer, for example, Heimdal et al. [12] found that the variant-B allele was somewhat more frequent in cancer patients who were firstborn compared to controls, although this was not statistically significant. They also found that the frequency of the variant B allele seemed to decrease in cancer patients born later in the sibship. This observation is consistent with the hypothesis that firstborn testicular cancer patients, who presumably are exposed to higher maternal estrogen levels, in some instances may have an ER variant that interacts differently with maternal estrogen than do later-born patients. Sexual differentiation to the male phenotype is dependent on activation of the androgen receptor by androgens during foetal development [13]. Testosterone is converted to dihydrotestosterone (DHT) and DHT binds to the AR to form a complex, which translocates to the nucleus and transactivates target genes [14]. It is conceivable that variant forms of the gene for AR affect the function and efficiency of its gene products, thus influencing the development and progression of testicular cancer. CYP1A1 genetic polymorphism may affect the relationship between endogenous hormones, environmental hormone disruptors and testicular cancer risk because AHH is 17-beta-estradiol hydroxylase, therefore involved in steroid hormone metabolism [15]. The enhanced CYP1A1 activity from exposure to environmental hormone disruptors could lead to increased activation of environmental carcinogens; thus increased testicular cancer risk. Studies of environmental hormone disruptors and breast cancer risk have reported a strong interaction between CYP1A1 m2 genetic polymorphisms, PCB exposures and risk of breast cancer [16].

Other suggested risk factors. Several factors, such as testicular trauma, viral exposure, unusual amounts of heat to the testis, vasectomy, EMF exposure, farming and farm-related exposures, maternal dietary intakes, maternal viral or bacterial infection before pregnancy, smoking and alcohol consumption during pregnancy, and immunologic reaction during foetal life have also been inconsistently associated with the risk of testicular cancer [17,18]. These factors, however, can hardly explain the observed age-incidence pattern and the reported increase in rates during the past decades. The reported effect due to these factors is also not great enough to explain the increase in incidence rates of testicular cancer among young men.

Similar risk profiles for seminoma and nonseminoma? Both seminoma and nonseminoma are considered to have a common cell of origin, the carcinoma in situ germ cell [19]. The similar secular trend for both seminoma and nonseminoma supports that these two types of testis cancer are likely to have similar risk profiles. Analytical epidemiological studies so far have not provided strong evidence demonstrating separate etiologies of seminoma and nonseminoma. Even if some differences exist in the risk factors for these two types of testis cancer as suggested by some of the studies [20], the major risk factors responsible for the time trend must be similar between seminoma and nonseminoma.

Prevention

The descriptive epidemiological features of testicular cancer as summarised previously suggest that environmental factors may play a major role on the occurrence and/or progression of testicular cancer, thus a large proportion of the disease is potentially preventable. However, since so little is known about the etiology of testicular cancer, it is not possible at this stage to develop effective preventive measures to reduce the disease. Greater efforts must be made to better understand the etiology of testicular cancer and to better understand the underlying causes for the observed increase of the disease during the past few decades. If indeed in-utero exposure to high levels of free estrogens is responsible for the occurrence of testicular cancer, modification of the factors that directly affect the secretion and metabolism of the estrogen of pregnancy might prove to be effective [21]. If indeed human exposure to environmental hormone disruptors increases the risk of development and progression of testicular cancer, greater effort needs to be made to reduce human exposure to these man-made environmental pollutants. While it is difficult to develop effective preventive measures to reduce disease incidence, testicular cancer could almost be eliminated as a cause of death worldwide if the political will, adequate finance, and the necessary training and logistics to deliver appropriate treatment were implemented [22].

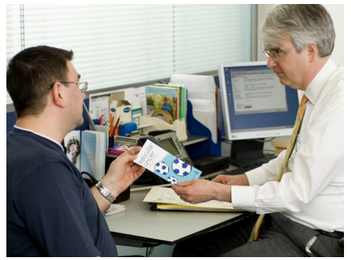


Fig. 5.18.2 *Discussion of testicular cancer between a young man and family doctor*

In summary, much of the etiology of testicular cancer remains unexplained, and hitherto unidentified risk factors remain to be identified. The question that must be answered is to what extent are endogenous hormones, environmental hormone disruptors, and genetic polymorphisms not only responsible for the observed age-incidence pattern, but also for the observed secular-incidence trend of testicular cancer. Unless major risk factors of testicular cancer are identified, no effective preventive measures can be developed to reduce the disease.

REFERENCES

1. Boyle P, Smans M (2008). *IARC Scientific Publications, Number 159, Atlas of cancer mortality in the European Union and the European Economic Area 1993-1997*. Lyon, France: International Agency for Research on Cancer.

2. Zheng T, Holford TR, Ma Z, et al. (1996). Continuing increase in incidence of germ-cell testis cancer in young adults: experience from Connecticut, USA, 1935-1992. *Int J Cancer* 65: 723-729.

3. Moller H (1989). Decreased testicular cancer risk in men born in wartime. *J Natl Cancer Inst* 81: 1668-1669.

4. Zhang Y, Graubard BI, Klebanoff MA, et al. (2005). Maternal hormone levels among populations at high and low risk of testicular germ cell cancer. *Br J Cancer* 92: 1787-1793.

5. Henderson BE, Benton B, Jing J, et al. (1979). Risk factors for cancer of the testis in young men. *Int J Cancer* 23: 598-602.

6. Depue RH, Pike MC, Henderson BE (1983). Estrogen exposure during gestation and risk of testicular cancer. *J Natl Cancer Inst* 71: 1151-1155.

7. Moller H, Prener A, Skakkebaek NE (1996). Testicular cancer, cryptorchidism, inguinal hernia, testicular atrophy, and genital malformations: case-control studies in Denmark. *Cancer Causes Control* 7: 264-274.

8. Moller H (1993). Clues to the aetiology of testicular germ cell tumours from descriptive epidemiology. *Eur Urol* 23: 8-13.

9. Sharpe RM and Skakkebaek NE (1993). Are oestrogens involved in falling sperm counts and disorders of the male reproductive tract? *Lancet* 341: 1392-1395.

10. Skakkebaek NE, Rajpert-De Meyts E, Jorgensen N, et al. (1998). Germ cell cancer and disorders of spermatogenesis: an environmental connection? *APMIS* 106: 3-11.

11. Hardell L, van Bavel B, Lindstrom G, et al. (2003). Increased concentrations of polychlorinated biphenyls, hexachlorobenzene, and chlordanes in mothers of men with testicular cancer. *Environ Health Perspect* 111: 930-934.

12. Heimdal K, Andersen TI, Skrede M, et al. (1995). Association studies of estrogen receptor polymorphisms in a Norwegian testicular cancer population. *Cancer Epidemiol Biomarkers Prev* 4: 123-126.

13. Wolf C, Ostby J, Furr J, et al. (2002). Anti-androgenic effects of vinclozolin on male rats are partially attenuated by testosterone propionate. *Workshop Abstracts - Endocrine Disruptors Program Review Worskhop* October 29-31, 2002: 115.

14. Irvine RA, Ma H, Yu MC, et al. (2000). Inhibition of p160-mediated coactivation with increasing androgen receptor polyglutamine length. *Hum Mol Genet* 9: 267-274.

15. Chen I, McDougal A, Wang F, et al. (1998). Aryl hydrocarbon receptor-mediated antiestrogenic and antitumorigenic activity of diindolylmethane. *Carcinogenesis* 19: 1631-1639.

16. Zhang Y, Wise JP, Holford TR, et al. (2004). Serum polychlorinated biphenyls, cytochrome P-450 1A1 polymorphisms, and risk of breast cancer in Connecticut women. *Am J Epidemiol* 160: 1177-1183.

17. Boyle P and Zaridze DG (1993). Risk factors for prostate and testicular cancer. *Eur J Cancer* 29A: 1048-1055.

18. Wanderas EH, Grotmol T, Fossa SD, et al. (1998). Maternal health and pre- and perinatal characteristics in the etiology of testicular cancer: a prospective population- and register-based study on Norwegian males born between 1967 and 1995. *Cancer Causes Control* 9: 475-486.

19. Skakkebaek NE, Berthelsen JG, Giwercman A, et al. (1987). Carcinoma-in situ of the testis: possible origin from gonocytes and precursor of all types of germ cell tumours except spermatocytoma. *Int J Androl* 10: 19-28.

20. Akre O, Ekbom A, Hsieh CC, et al. (1996). Testicular nonseminoma and seminoma in relation to perinatal characteristics. *J Natl Cancer Inst* 88: 883-889.

21. Prener A, Hsieh CC, Engholm G, et al. (1992). Birth order and risk of testicular cancer. *Cancer Causes Control* 3: 265-272.

22. Boyle P (2004). Testicular cancer: the challenge for cancer control. *Lancet Oncol* 5: 56-61.

BRIEF REPORT FROM THE WHO REGIONAL OFFICE FOR EUROPE (WHO EURO)

Cancer in the WHO European Region

Cancer was estimated to cause 19% of deaths and 11% of the disease burden (as measured by DALYs) in the WHO European Region in 2005. There were approximately 1.8 million deaths from cancer in the Region in 2005; leading causes of cancer death are lung, colorectal, stomach and breast, with the leading cancers for incidence burden being lung, colorectal, breast cancer and prostate.

Disease patterns cannot simply be generalised–overall cancer incidence and mortality rates vary at least two-fold between European countries, and differences are often greater for specific cancers. Across WHO European Region as a whole, death rates from cancer have been decreasing since late 1980s; however the picture is mixed and complex according to age, sex, type of cancer and country. Cancer incidence is rising for the Region as whole–trends largely reflect changes in the age structure of the population and its risk factor profile, which is in turn related to the success of primary prevention programmes. Irrespective of changes in risk, the demographic changes alone are projected to substantially increase cancer incidence in next few decades.

There are marked disparities within countries and between countries in cancer survival, which partly reflects success of the health system in early detection and effective care. There are some indications that this survival gap is narrowing, suggesting improvements in care in countries with previously poor survival.

Steps being taken by WHO Regional Office for Europe

WHO EURO promotes a comprehensive approach to cancer: prevention; early detection; diagnosis and treatment; palliative care. All countries, no matter what their resource level, can mount an effective response to cancer; only their prioritisation will differ. During 2008–09, WHO EURO is working in-depth with 8 countries in development or review of National Cancer Control Programmes, and at least another 10 countries on strategies for the prevention and control of Noncommunicable diseases (NCD) including cancer.

Primary prevention, particularly tobacco control, is key. Cancer shares common risk factors with other NCDs such as heart disease and stroke. EURO promotes an integrated approach to prevention across such diseases through the European Strategy on Prevention and Control of Noncommunicable Diseases, as well as through WHO strategies, frameworks and action plans for individual risk factors such as tobacco control, food and nutrition, alcohol, counteracting obesity, physical activity, environment and health. There are now 41 Member States of the WHO European Region that are parties to the Framework Convention for Tobacco Control (WHO FCTC), and a further 5 that are signatories. Regarding infectious agents, EURO works with countries and partners to strengthen immunisation in Europe, control sexually transmitted infections and develop policy advice, for example on Human Papilloma Virus (HPV) vaccination. By 2003, 43 Member States had included hepatitis B in their national immunisation programmes. In May 2007, WHO EURO held a meeting with policymakers from more than 40 countries in Europe on strengthening cervical cancer prevention in Europe, and is following up during 2008–09 with support to a number of countries in developing and strengthening cervical cancer prevention programmes. This work is underpinned by the broader work of the office to strengthen health systems in particular to improve quality assurance systems.

Good palliative care and access to morphine could significantly improve the lives of many. Working closely with its WHO Collaborating Centres and other partners, WHO EURO is promoting a public health approach to palliative care and the rational use of drugs for cancer treatment. A meeting of countries is planned for autumn 2008.

website: www.euro.who.int

5.19 Kidney Cancer

Summary

> Populations with a high incidence of kidney cancer include Central Europe and the black population in the USA

> Tobacco smoking is a recognised risk factor for kidney cancer, as are obesity and hypertension

> Apart from rare high-risk variants, susceptibility genes for kidney cancer are yet to be discovered

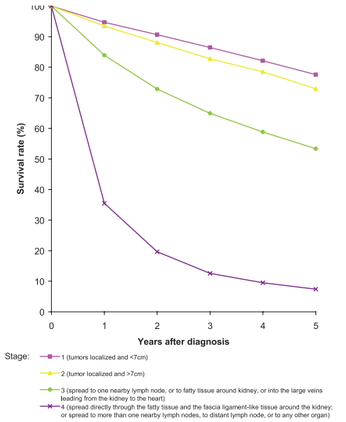


Fig. 5.19.1 *5-year relative survival rates (%) for kidney cancer cases diagnosed in 1990–94, in selected countries and by age at diagnosis (source: Eurocare-3 study)*
Relative survival rates were based on 474 000 kidney cancer cases diagnosed in Europe in 1990–94. The prognosis of patients with kidney cancer improved at younger ages of diagnosis, with the 5-year relative survival rates falling from 71% for patients diagnosed at 15–44 years old to 45% for patients diagnosed at 75 years or older. On average, Germany showed the highest survival rates, whereas Wales had the lowest rates, with greater difference between countries than for bladder cancer survival rates

Histological types

The vast majority of cancers which arise in the renal parenchyma are clear cell carcinomas.[2] Non-clear cell types include papillary, chromophobe, collecting duct and oncocytoma, although whether the epidemiology of these rarer types differs from that of clear cell has not been established. Finally, nephroblastoma (Wilms' tumour) occurs in children. The epidemiology of cancers of the renal pelvis differs markedly from that of the renal parenchyma, the former having histology similar to that of transitional cell bladder cancer.

Stage at diagnosis and survival

In the USA in 2003, 49% of cases of kidney cancer were diagnosed at stage 1, 10% at stage 2, 13% at stage 3, 18% at stage 4, and the stage was unknown in 10% of cases (2003 data from the National Cancer Data Base, NCDB).[3] The five-year relative survival after kidney cancer in the third version of the Eurocare study, comprising 47 000 kidney cancer cases diagnosed 1990–1994, is shown in Figure 5.19.1.[4] Overall, the 5-year relative survival rate kidney cancer was 56% in males and 58% in females. The prognosis of patients improved at younger ages of diagnosis, with the 5-year relative survival rates falling from 71% for patients diagnosed at 15–44 years old with kidney cancer to 45% for patients diagnosed at 75 years or older.

Incidence

Worldwide geographical variations in incidence rates (age-standardised for the world population) of kidney cancers in men and women respectively are shown in 5.19.2.[5] the highest rate was found for both sexes in

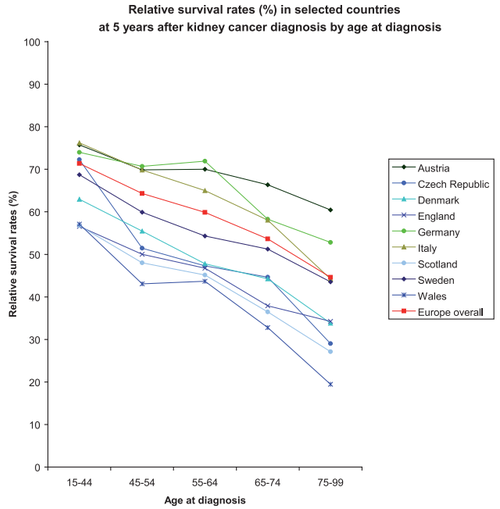


Fig. 5.19.2 *Observed survival rates (%) for kidney cancer cases diagnosed in 1998 in the USA (source: National Cancer DataBase). Important differences were found between the survival rates for different stages at diagnosis*

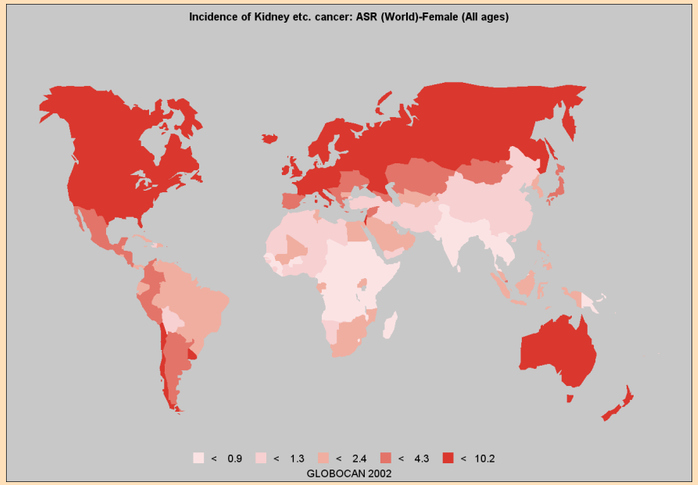
Czech Republic (21.1/100 000 in men and 10.2/100 000 in women). In men, other regions with high incidence rates included Estonia (17.3/100 000), Lithuania (14.7/100 000), Hungary (14.7/100 000), Slovakia (13.7/100 000), and Poland (13.5/100 000). Among females, the intermediate high incidence rates were found in Lithuania (8.4/100 000), Estonia (7.1/100 000), Austria (6.8/100 000), Slovakia (6.6/100 000) and Hungary (6.6/100 000). In both sexes, the lowest rates were found in Africa and Asia.

A sharp increase in the incidence of kidney cancer was observed in numerous registries. Some of the greatest increases were observed in the Czech Republic and among the black population in the USA.[6]

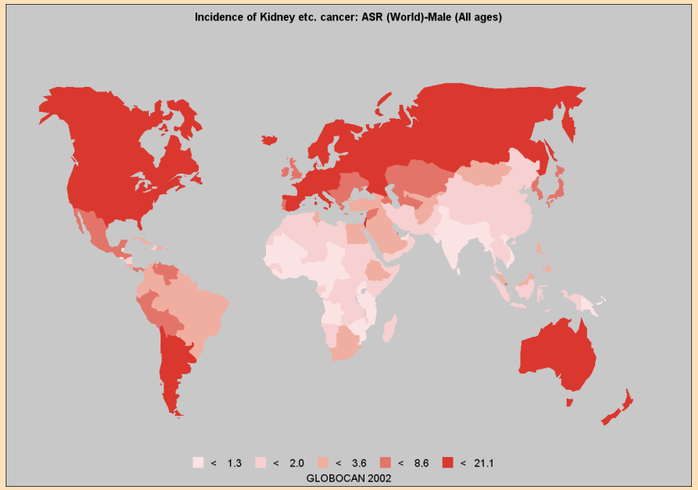
Regarding time trends for kidney cancer and using data reported in two volumes of the CI5 series from various cancer registries for the calendar periods 1983–1987[7] and 1993–1997 [8], a sharp increase in incidence was observed in numerous registries. Some of the greatest increases were observed in the Czech Republic and among the black population in the USA.[6] These increasing trends are unlikely to be explained by increasing detection of presymptomatic tumours, and are instead likely to reflect real increases in the numbers of new cases.[9]

Risk factors for kidney cancer

Cigarette smoking. Cigarette smoking has been consistently observed to be a risk factor for kidney cancer, with increased risks compared to never smokers in the order of 50%.[10,11] A number of studies have also demonstrated a dose-response relationship with increasing consumption, with risks of developing kidney cancer for heavy smokers ranging from 2.0 to 3.0 above that of people who have never smoked. The risk appears to decline with increasing years of smoking cessation. Population attributable risk estimates indicate that cigarette smoking, both past and present, is responsible for approximately 20% of kidney cancer cases among men and 10% of cases



World Map 5.19.1



World Map 5.19.2

among women.[12,13] Approximately half of this attributable risk is due to current smoking. The mechanism by which cigarette smoking increases the risk of kidney cancer has not been elucidated, although this clearly represents a major opportunity for prevention.

Obesity. A recent overview of the relationship between obesity and kidney cancer concluded that there was sufficient evidence to conclude that weight gain led to an increased risk of developing renal cancer.[14] The review was based on consistent evidence from four cohort and fifteen case–control studies that reported a steadily increasing risk with increasing weight gain, and indicated that the effects among men and women were similar. Approximately 25% of kidney cancer cases among both men and women are likely to be due to being overweight and obese.[15,16] The mechanism by which obesity causes kidney cancer is unclear, although hormonal changes such as increased levels of endogenous oestrogens might be responsible. Other correlates of obesity, such as hypertension and lack of physical exercise, have not been found to explain this relationship.

Medical conditions and treatment. A history of hypertension has also been consistently linked to kidney cancer.[17-22] The increase in risk appears to occur in a dose-response manner, with even moderately increased blood pressure resulting in an increased risk of kidney cancer. Several studies have tried to separate the effect of hypertension and a possible effect from diuretic and non-diuretic antihypertensive medications. Given the strong correlation between hypertension and the use of these drugs, this has been very difficult. However, evidence that reductions in blood pressure over time may lead to a decrease in kidney cancer risk would appear to indicate that the primary effect is with hypertension and is not treatment related.[17] It is also likely to account for a substantial proportion of cases. The attributable risk of reported hypertension or treatment with anti-hypertensive drugs has been estimated to be 21% overall, and 39% among women.[23]

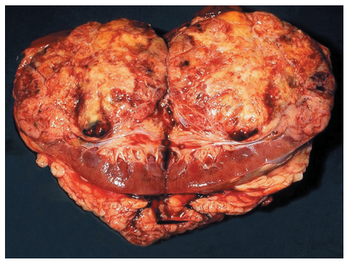
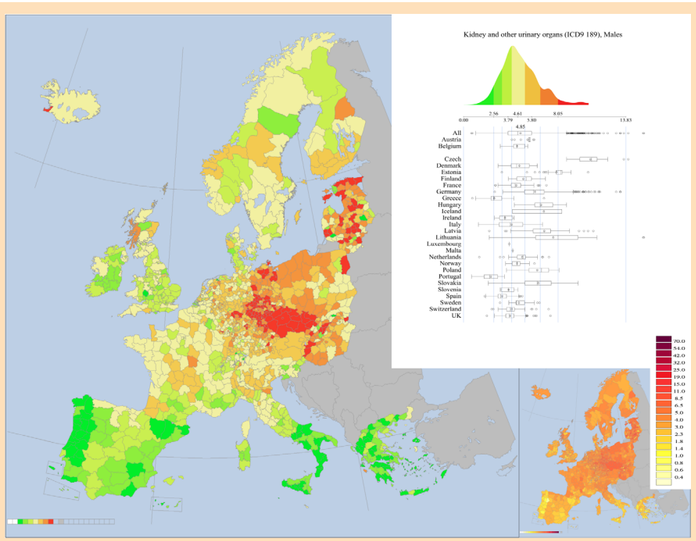


Fig. 5.19.3 *Surgical specimen of a bisected kidney showing a large renal cell carcinoma. Much of the kidney has been replaced by tumour tissue*



European Map 5.19.1 *The strongest feature of the geographic distribution of kidney cancer mortality in men is the strong gradient from the low rates in Portugal, Spain, southern Italy and Greece through rates generally close to the average in France, northern Italy, Switzerland, Slovenia, Belgium, The Netherlands and the United Kingdom and Ireland, to high rates in eastern Germany and Austria, the Czech Republic, and western parts of Poland, Slovakia and Hungary. Rates were also generally high in all three Baltic countries. Mortality rates in all the Nordic countries were generally close to the average [1]*

There is also strong evidence for a role of diabetes mellitus in the etiology of kidney cancer. Two large nationwide cohort studies in Sweden and Denmark both identified an increased risk of kidney cancer among inpatients with diabetes, in the order of 40% among men and 70% among women.[24,25] The risk appeared to be constant with follow-up and was restricted to type II diabetes.

Acquired cystic kidney disease, which occurs in end-stage renal disease, is associated with the development of kidney cancer, as are both kidney stones and kidney infections.[26]

Dietary factors. A recent IARC evaluation on the potential cancer preventative effect of diets high in fruits and vegetables reported that higher intake of both fruits and vegetables possibly reduce the risk of kidney cancer.[27] The amount of evidence from prospective cohort studies was, however, sparse, with only two studies reporting on fruit consumption and one on vegetable consumption. A more recent report from the European Prospective Investigation into Cancer and Nutrition (EPIC) reported no overall protective effect for high consumption of fruits and vegetables, although an increased risk at very low levels of consumption could not be ruled out.[28]

High protein consumption from meat and dairy products has been associated with chronic renal conditions that may predispose to kidney cancer, although the evidence is inconsistent.[29] The role of coffee and alcohol have also been studied extensively for kidney cancer, although no increase in risk with increased consumption of coffee or alcohol appears to exist.[30]

Occupational risk factors. Consistent and strong increases in risk with occupational exposures have not been detected for kidney cancer. Suggestive increases in risk have been observed for a variety of occupations with exposure to polycyclic aromatic hydrocarbons such as coke and coal oven workers, fire-fighters, and asphalt and tar workers.[31] Excess risks have also been reported for occupations with exposure to gasoline and other petroleum products such as oil refinery workers and gas station attendants, as well as with exposure to asbestos.[32]

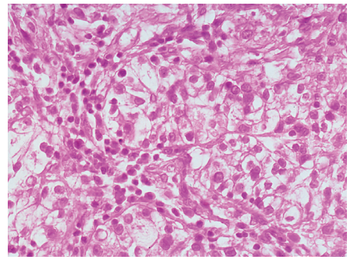
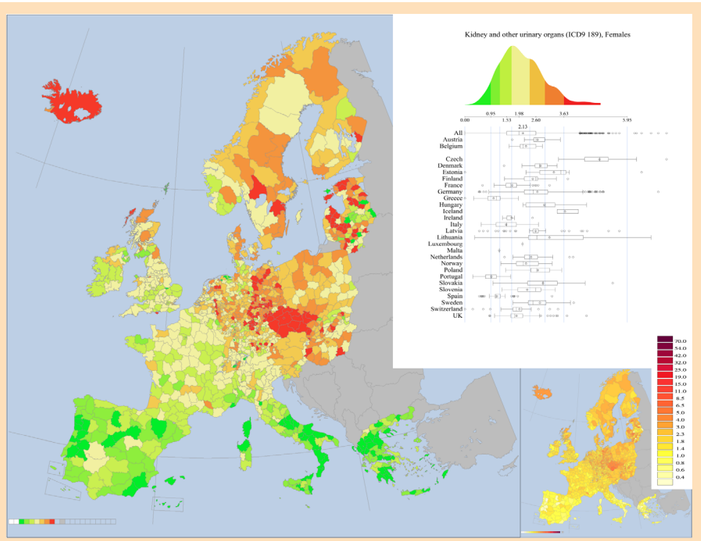


Fig. 5.19.4 *Clear cell carcinoma of the kidney showing a monomorphic proliferation of distinctive tumour cells, with an abundant clear, lipid-containing cytoplasm, arranged in a trabecular pattern*

Exposure to organic solvents, in particular to chlorinated aliphatic hydrocarbons, has also been suggested as a risk factor in occupations including dry-cleaning and printing. A report from a German series of individuals with kidney cancer that exposure to trichlorethylene was associated with a specific mutation pattern in the von Hippel-Lindau (VHL) tumour suppressor gene is of interest although requires confirmation.[33] Overall, the evidence for associations of specific occupational exposures with kidney cancer is still inconclusive.



European Map 5.19.2 *The map for females shows that both the between- and the within-country variability in mortality rates were closely similar to the patterns in males. There were generally low rates in Portugal, Spain, Italy and Greece and around average rates in Ireland, the southern parts of the UK, France, Belgium and Switzerland. High rates, as in males, occurred in northeast Germany, the Czech Republic, eastern Austria, and western Poland, Slovakia and Hungary, and in the Baltic countries. Many areas in the Nordic countries had above average rates in females but not in males [1].*

Family history and genetic risk factors. Several registry-based studies including the Swedish Family Cancer Database, deCODE Genetics, and the Utah database have reported an increased risk of renal cell carcinoma (RCC) for subjects with affected first-degree relatives, with a familial relative risk of 2–2.5.[34,35] The familial risk for kidney cancer appears to be greater between siblings as compared with that between parent and child, indicating the possible existence of recessive genetic effects. An elevated familial relative risk probably indicates a genetic component in cancer etiology, although a contribution due to shared environmental exposures within the family is also possible. The contribution of these two factors might be determined by twin studies, although the largest twin study to date has not been informa-

tive due to the lack of concordant twins with kidney cancer.[36]

One of the important genetic alterations identified in familial RCC is the aforementioned VHL syndrome, a rare autosomal dominant condition caused by the point mutations or deletions in *VHL* gene at chromosome 3p25.[37] Individuals with *VHL* alterations have an increased risk of developing benign or malignant tumours of the central nervous system, eye, inner ear and endocrine glands, in addition to the kidney. Furthermore, most sporadic clear cell cancers have somatic *VHL* inactivation. Several genes predisposing to non-clear cell RCC have also been characterised, including mutations in the *MET* oncogene and hereditary type 1 papillary RCC, and mutations in the *BHD* gene causing several histopathological subtypes of RCC.

Identifying rare genetic variants that result in a high risk of renal cancer is important for understanding the etiology of cancer and potentially identifying high risk groups among family members; however, such genes explain very little of the familial risk of renal cancer. It is likely that most of the genetic contribution will be due to multiple low- or moderate-risk variants that act in combination with each other or with environmental risk factors. Such genetic variants will not be detected in studies based on multiple cases in individual families, but instead will require large series of cases and controls and genotyping for hundreds of thousands of genetic variants across the genome. These studies are currently in progress.

Fig. 5.19.5 *Tobacco smoking is a recognised risk factor for kidney cancer*

Avoiding risks

The main known avoidable causes of kidney cancer include cigarette smoking, excess body weight and hypertension, which together are likely to account for up to 60% of all cases of these tumours. Primary prevention by reducing cigarette smoking, obesity and hypertension are, therefore, the clearest strategies for reducing the incidence of the disease. A substantial proportion of cases is also likely to be related to diabetes, although further information on whether this is an independent risk factor is required. It seems unlikely that these exposures can explain the very large disparities in incidence that occur between different populations, and further important causes of renal cancer are likely to exist. Ongoing studies into the genetic epidemiology of kidney cancer might provide new hypotheses for such exposures, and may also help lead to the identification of high-risk subgroups.

REFERENCES

1. Boyle P, Smans M (2008). *IARC Scientific Publications, Number 159, Atlas of cancer mortality in the European Union and the European Economic Area 1993-1997*. Lyon, France: International Agency for Research on Cancer.

2. Eble J, Epstein JI, Sesterhenn IA, et al. (2004). *World Health Organization classification of tumours - Pathology and genetics of tumours of the urinary system and male genital organs*. Lyon, France: International Agency for Research on Cancer.

3. Commission on Cancer / American Cancer Society. *National Cancer Data Base (NCDB)*. Available from: http://www.facs.org/cancer/ncdb Date Accessed: November 11, 2008.

4. Roazzi P, Capocaccia R, Santaquilani M, et al. (2003). Electronic availability of EUROCARE-3 data: a tool for further analysis. *Ann Oncol* 14: S150-S155.

5. Ferlay J, Bray F, Pisani P, et al. (2004). *GLOBOCAN 2002: Cancer Incidence, Mortality and Prevalence Worldwide*. Available from: http://www-dep.iarc.fr/

6. Chow WH, Devesa SS, Warren JL, et al. (1999). Rising incidence of renal cell cancer in the United States. *JAMA* 281: 1628-1631.

7. Parkin DM, Muir CS, Whelan SL, et al. (1992). *IARC Scientific Publications, Number 120, Cancer incidence in five continents, Volume VI*. Lyon, France: International Agency for Research on Cancer.

8. Parkin DM, Whelan SL, Ferlay J, et al. (2002). *IARC Scientific Publications, Number 155, Cancer incidence in five continents, Volume VIII*. Lyon, France: International Agency for Research on Cancer.

9. Hock LM, Lynch J, Balaji KC (2002). Increasing incidence of all stages of kidney cancer in the last 2 decades in the United States: an analysis of surveillance, epidemiology and end results program data. *J Urol* 167: 57-60.

10. Hunt JD, van der Hel OL, McMillan GP, et al. (2005). Renal cell carcinoma in relation to cigarette smoking: meta-analysis of 24 studies. *Int J Cancer* 114: 101-108.

11. IARC (2004). *IARC monographs on the evaluation of carcinogenic risks to humans, Volume 83, Tobacco smoke and involuntary smoking*. Lyon, France: International Agency for Research on Cancer.

12. McLaughlin JK, Lindblad P, Mellemgaard A, et al. (1995). International renal cell cancer study. I. Tobacco use. *Int J Cancer* 60: 194-198.

13. Yuan JM, Castelao JE, Gago-Dominguez M, et al. (1998). Tobacco use in relation to renal cell carcinoma. *Cancer Epidemiol Biomarkers Prev* 7: 429-433.

14. IARC. (2002). *IARC Handbooks of Cancer Prevention, Volume 6, Weight control and physical activity*. Lyon, France: International Agency for Research on Cancer.

15. Bergstrom A, Pisani P, Tenet V, et al. (2001). Overweight as an avoidable cause of cancer in Europe. *Int J Cancer* 91: 421-430.

16. Bergstrom A, Hsieh CC, Lindblad P, et al. (2001). Obesity and renal cell cancer–a quantitative review. *Br J Cancer* 85: 984-990.

17. Chow WH, Gridley G, Fraumeni JF, Jr., et al. (2000). Obesity, hypertension, and the risk of kidney cancer in men. *N Engl J Med* 343: 1305-1311.

18. Flaherty KT, Fuchs CS, Colditz GA, et al. (2005). A prospective study of body mass index, hypertension, and smoking and the risk of renal cell carcinoma (United States). *Cancer Causes Control* 16: 1099-1106.

19. Grossman E, Messerli FH, Boyko V, et al. (2002). Is there an association between hypertension and cancer mortality? *Am J Med* 112: 479-486.

20. Lindgren AM, Nissinen AM, Tuomilehto JO, et al. (2005). Cancer pattern among hypertensive patients in North Karelia, Finland. *J Hum Hypertens* 19: 373-379.

21. McLaughlin JK, Chow WH, Mandel JS, et al. (1995). International renal cell cancer study. VIII. Role of diuretics, other anti-hypertensive medications and hypertension. *Int J Cancer* 63: 216-221.

22. Yuan JM, Castelao JE, Gago-Dominguez M, et al. (1998). Hypertension, obesity and their medications in relation to renal cell carcinoma. *Br J Cancer* 77: 1508-1513.

23. Benichou J, Chow WH, McLaughlin JK, et al. (1998). Population attributable risk of renal cell cancer in Minnesota. *Am J Epidemiol* 148: 424-430.

24. Lindblad P, Chow WH, Chan J, et al. (1999). The role of diabetes mellitus in the aetiology of renal cell cancer. *Diabetologia* 42: 107-112.

25. Wideroff L, Gridley G, Mellemkjaer L, et al. (1997). Cancer incidence in a population-based cohort of patients hospitalized with diabetes mellitus in Denmark. *J Natl Cancer Inst* 89: 1360-1365.

26. Lindblad P, Adami HO (2002). Kidney cancer. In: Adami HO, Hunter D, Trichopoulos D, eds., *Textbook of cancer epidemiology*. New York: Oxford University Press 467-485.

27. IARC (2003). *IARC Handbooks of Cancer Prevention, Volume 8, Fruit and vegetables*. Lyon, France: International Agency for Research on Cancer.

28. Weikert S, Boeing H, Pischon T, et al. (2006). Fruits and vegetables and renal cell carcinoma: findings from the European prospective investigation into cancer and nutrition (EPIC). *Int J Cancer* 118: 3133-3139.

29. Wolk A, Gridley G, Niwa S, et al. (1996). International renal cell cancer study. VII. Role of diet. *Int J Cancer* 65: 67-73.

30. World Cancer Research Fund / American Institute for Cancer Research (1997). *Food, Nutrition and the Prevention of Cancer: a Global Perspective*. Washington, DC: AICR.

31. Siemiatycki J, Richardson L, Straif K, et al. (2004). Listing occupational carcinogens. *Environ Health Perspect* 112: 1447-1459.

32. Sali D and Boffetta P (2000). Kidney cancer and occupational exposure to asbestos: a meta-analysis of occupational cohort studies. *Cancer Causes Control* 11: 37-47.

33. Brauch H, Weirich G, Hornauer MA, et al. (1999). Trichloroethylene exposure and specific somatic mutations in patients with renal cell carcinoma. *J Natl Cancer Inst* 91: 854-861.

34. Amundadottir LT, Thorvaldsson S, Gudbjartsson DF, et al. (2004). Cancer as a complex phenotype: pattern of cancer distribution within and beyond the nuclear family. *PLoS Med* 1: e65 DOI:10.1371/journal.pmed.0010065.

35. Risch N (2001). The genetic epidemiology of cancer: interpreting family and twin studies and their implications for molecular genetic approaches. *Cancer Epidemiol Biomarkers Prev* 10: 733-741.

36. Lichtenstein P, Holm NV, Verkasalo PK, et al. (2000). Environmental and heritable factors in the causation of cancer--analyses of cohorts of twins from Sweden, Denmark, and Finland. *N Engl J Med* 343: 78-85.

37. Richard S, Graff J, Lindau J, et al. (2004). Von Hippel-Lindau disease. *Lancet* 363: 1231-1234.

5.20 Bladder Cancer

Summary

> Populations with a high incidence of bladder cancer include those of Mediterranean Europe and Egypt

> Survival improves with early age of onset

> Tobacco smoking is the most important risk factor for bladder cancer. Occupational exposure to aromatic amines and infection with *Schistosoma haematobium* are also recognised risk factors

> Gene variants of *GSTM1* and *NAT2* are involved in bladder cancer risk, interacting with smoking status for *NAT2*

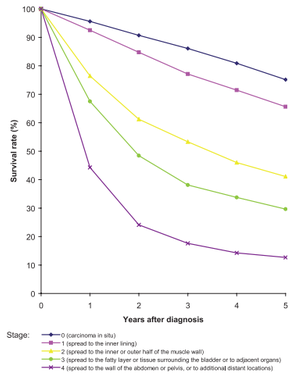


Fig. 5.20.1 *5-year relative survival rates (%) for bladder cancer cases diagnosed in 1990–94, in selected countries and by age at diagnosis (source: Eurocare-3 study). Relative survival rates were based on 104 000 bladder cancer cases diagnosed in Europe in 1990–94. The prognosis of patients with bladder cancer improved at younger ages of diagnosis, with the 5-year relative survival rates falling from 90% for patients diagnosed at 15–44 years old to 61% for patients diagnosed at 75 years or older. On average, Austria showed the highest survival rates, whereas Czech Republic had the lowest rates, with little difference between countries however*

Histological types

The most common type of bladder cancer is urothelial carcinoma, also called transitional cell epithelium[2], although the proportion of this histological type among all cases of bladder cancer varies between countries. For example, 92–99% of bladder cancer cases with available histology in North America, Europe and Australia are urothelial carcinoma, whereas the proportion is around 70–80% in Southeast Asia and substantially less than 50% in parts of Africa [3-7]. In general, urothelial carcinoma constitutes a slightly higher proportion of bladder cancer cases in males than in females. Other types of bladder carcinoma include squamous-cell carcinoma and adenocarcinoma. In Africa, squamous-cell carcinoma is the most common type of bladder cancer, resulting from *schistosoma hematobium* infection. Non-invasive urothelial tumours are often considered as bladder cancer in cancer registries. Non-invasive papillary carcinoma has a tendency to recur and to develop into invasive bladder carcinoma [2]. The variable degree to which such tumours are reported might substantially influence available descriptive data [8].

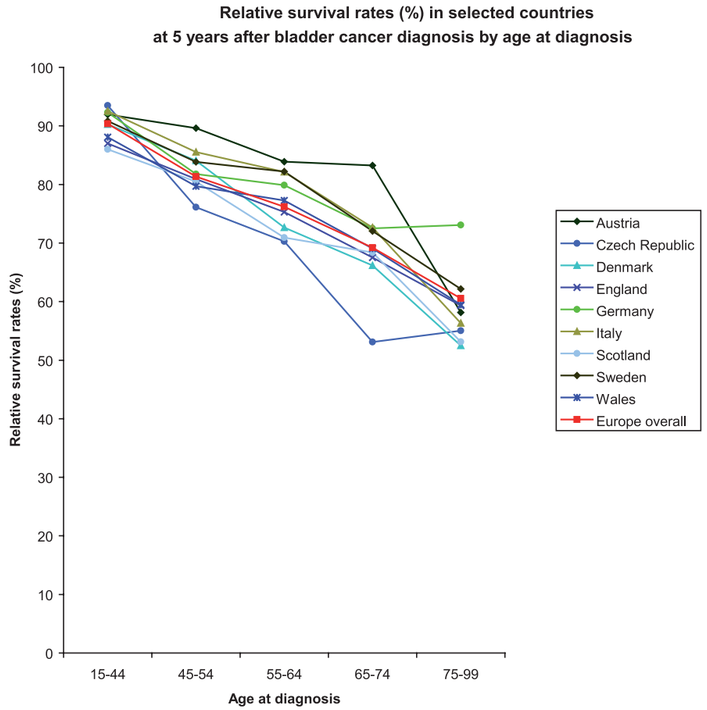


Fig. 5.20.2 *Observed survival rates (%) for bladder cancer cases diagnosed in 1998 in the USA (source: National Cancer DataBase).Important differences were found between the survival rates for different stages at diagnosis.*

Stage of diagnosis

Comprehensive data on stage of diagnosis include the US National Cancer Database (NCDB) and the Eindhoven cancer registry. In 2003, 47% of bladder cancer cases diagnosed in the USA were at stage 0, 22% at stage 1, 11% at stage 2, 5% at stage 3, and 6% at stage 4; for 8% the stage was not reported [9]. Bladder cancer data from the Eindhoven cancer registry showed a considerable shift towards lower stage at diagnosis between 1975 and 1989, mainly in favor of stage 0 [10]. This trend was less evident when invasive tumours were considered separately.

Relative survival rates compare the observed survival over a period of time to the expected survival based on background mortality rates. Figure 5.20.1 shows 5-year relative survival rates after bladder diagnosis for nine different European countries and by age at diagnosis, using data from the third version of the Eurocare study based on 104 000 bladder cancer cases diagnosed between 1990 and 1994 [11]. Overall, the 5-year relative survival rate after bladder cancer diagnosis was 72% in males and 67% in females. On average,

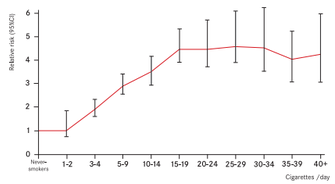
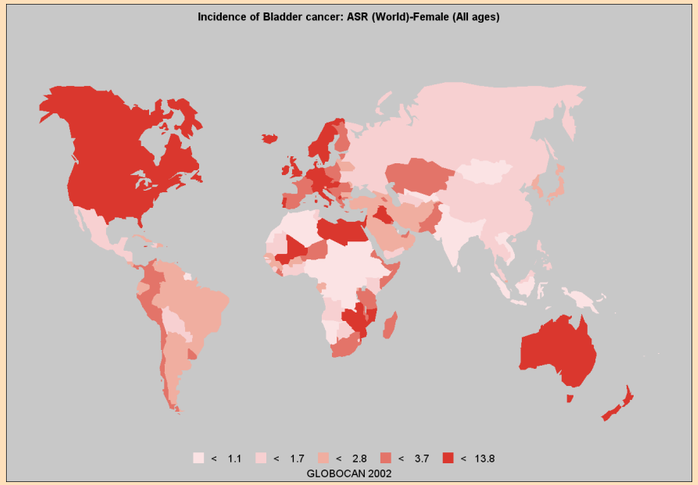
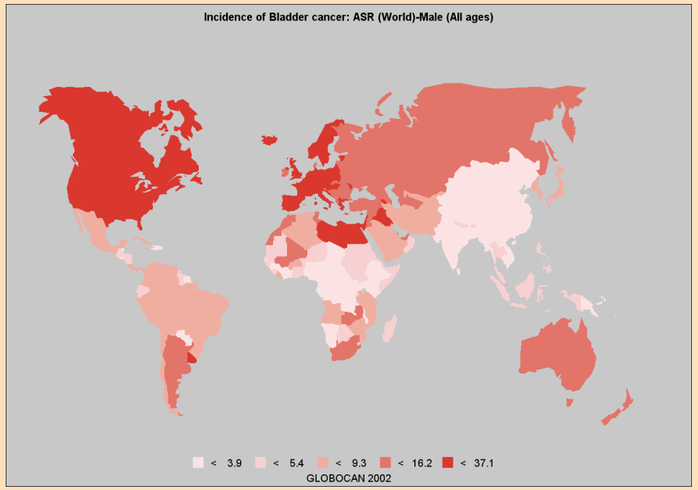


Fig. 5.19.3 *Risk of bladder cancer among men who smoke relative to never-smokers, according to daily cigarette consumption*



World Map 5.20.1



World Map 5.20.2

Austria showed the highest survival rates, whereas Wales had the lowest survival rates for bladder cancer.

In men, the highest rates of bladder cancer were found in Egypt (37.1/100 000), Spain (33.0/100 000), the Netherlands (32.6/100 000), and Italy (29.8/100 000). In women, the pattern is different: The highest rates were found in Zambia (13.8/100 000) and Mozambique (13.0/100 000), although these results were based on frequency data and might therefore not be reliable.

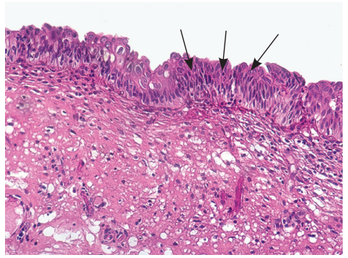


Fig. 5.19.4 *Carcinoma in situ of the bladder; the normal transitional epithelium has been replaced by a disorganized, poorly-differentiated cell layer (arrows)*

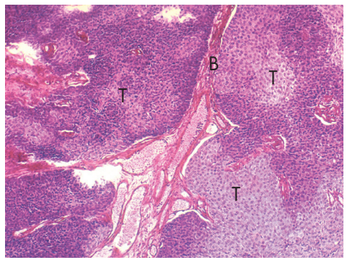
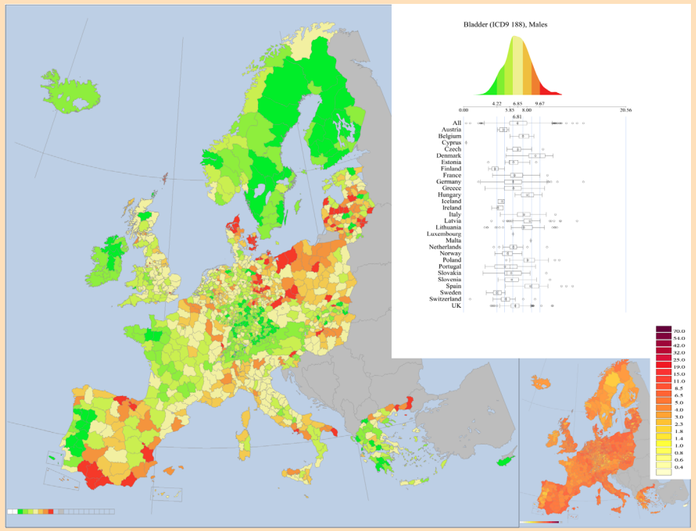


Fig. 5.19.5 *Transitional cell carcinoma of the bladder, moderately differentiated, with a papillary architecture. B = blood vessel, T = Tumour*



European Map 5.20.1 *An intriguing feature of the geographic map of bladder cancer in men is the high rates in coastal areas of Spain and parts of the Mediterranean coastlines of France (including Corsica) and Italy (including Sardinia and Sicily). There were high rates in other regions of Spain, northern Italy and northern Greece. Rates were high in Denmark and in the northern part of the former East Germany and Poland, and in Lithuania and Latvia. There were low rates throughout the Nordic Countries (other than Denmark), Ireland, the south of Germany, Austria and Switzerland.[1]*

Risk factors for bladder cancer

Tobacco use. The most important risk factor for bladder cancer is cigarette smoking, which is thought to account for approximately 66% of new cases in men and 30% of cases in women in industrialized populations [12,13]. Irrespective of the study design, most of the epidemiological studies found relative risks of 1.5–3.0 in smokers compared to non-smokers, as well as dose-response relationships considering both number of cigarettes smoked and duration of cigarette smoking [12,13]. Cigarette smoking seems to have the same effect in males and females, and in different races/ethnicities. A pooled analysis which combined nontransitional cell bladder cancer data from a number of studies found the same associations as for transitional cell carcinomas [14]. It is likely that smokers of black (air-cured) tobacco are at a higher risk than smokers of blond (flue-cured) tobacco [12], and this likely explains much of the higher incidence rates observed in Spain, Italy and Uruguay, where smoking of black tobacco was common in the past.

An immediate decrease in risk (around 40%) of bladder cancer is observed among both men and women who give up smoking, implying a late stage effect in the carcinogenic process, and the decrease in risk continues with time since cessation.

Much of the risk associated with smoking is likely to be due to aromatic amines present in cigarette smoke, including benzidine, 4-aminobiphenyl, naphthylamine and 4-chloro-o-toluidine.

Occupational risks. A high risk of bladder cancer has been reported among workers in industries that involve exposure to aromatic amines, in particular 2-naphthylamine, 4-aminobiphenyl and benzidine, including the rubber and dyestuff industries [15]. Working in aluminum production, auramine manufacture, coal gasification and magenta manufacture also significantly increases the risk of developing bladder cancer. Other occupations that might increase the risk of bladder cancer include leather workers, painters, hairdressers and barbers, coke production workers, and petroleum refining workers, possibly because of exposure to a variety of chemicals including polycyclic aromatic hydrocarbons, polychlorinated biphenyls, formaldehyde and solvents. The uncertainty surrounding these occupations is partly due to the difficulty of measuring past exposure to specific chemical agents.

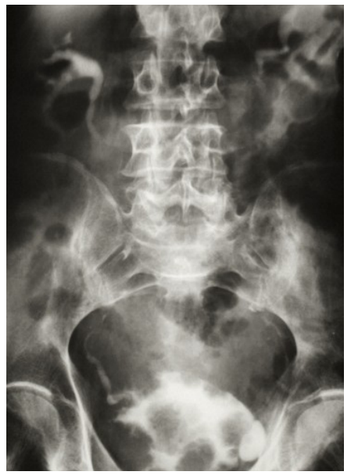
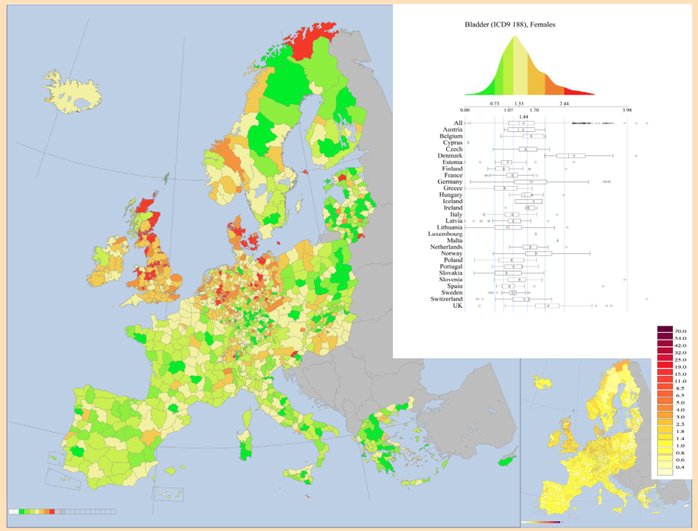


Fig. 5.19.6 *Bladder tumour*



European Map 5.20.2 *In women, rates were high in Denmark and northern Germany (as in males) but were also high in parts of the United Kingdom (especially Scotland) and The Netherlands. There were areas of low rates in the north of Europe except Norway: Sweden, Finland, the Baltic Countries and much of Poland; and in most of southern Europe: Portugal, Spain, France, Italy and Greece.*
In terms of explaining the geographic pattern in Europe, the high rates in men in Spain could well be associated with the prevalent habit of smoking black tobacco, which carries an excess risk of bladder cancer over Virginia cured tobacco. The high rates in Denmark are a reflection of the high incidence rates which have persisted there for decades. The pattern of high risk areas in men–but not women–in areas around the Mediterranean coast is interesting and may be related to differences in smoking habits between the sexes [1]

Dietary factors. Investigations into dietary factors have provided evidence of decreased risks associated with consumption of fruits but not with vegetables [16]. No consistent association has emerged between intake of related micronutrients and reduced risk of bladder cancer [17].

Concerning fluid consumption, an increased risk has been associated with high intake of tap water possibly due to exposure to the by-products of disinfection and arsenic [18]. Consumption of tea and alcohol are probably not associated with bladder cancer, although an increased risk with coffee consumption has been reported in some studies [19].

Familial history and genetic risk factors. First-degree relatives of bladder cancer patients have a 50–100% increased risk of developing the disease compared to the general population [17]. This relative risk is likely to interact with smoking habits, as the risk is elevated fivefold in smoking probands compared with nonsmokers [20].

The enzyme N-acetyl transferase 2 (NAT2) is involved in the detoxification of various bladder carcinogens including arylamines. The gene encoding NAT2 includes a dominant mutation

that results in slow metabolisation of arylamines and is associated with an increased risk of bladder cancer of around 40% [21]. This increased risk of developing bladder cancer appeared to be stronger in cigarette smokers (particularly black tobacco smokers) than non-smokers, and a joint effect between NAT2 slow acetylators and heavy smokers was observed, translating to a much higher risk of developing bladder cancer than exists in nonsmokers that do not possess the *NAT2* mutation. The GSTM1 null genotype also increases the risk of bladder cancer, although it has no interaction with smoking status [21].

Pharmacological-related risk factors

A consistent relationship has been observed between use of phenacetin-containing drugs and bladder cancer, with relative risks varying from 2.4-fold to over 6-fold [22]. Cyclophosphamide, an alkylating agent which has been used to treat both malignant and non-malignant diseases, has also been linked to bladder cancer. Studies based on cohorts of cancer patients indicate an approximately 5-fold increase in risk associated with cyclophosphamide therapy, with higher risks among heavily exposed subjects.

Infection

Infection with *Schistosoma haematobium* is prevalent throughout Africa and is associated with an increased risk of bladder cancer of approximately 2 to 4-fold [23,24]. Infection occurs via contact with water contaminated by the cercarial form (Figure 4). Eggs are eliminated with feces or urine and, under optimal conditions, the eggs hatch and release miracidia, which swim and penetrate specific snail intermediate hosts. The stages in the snail include two generations of sporocysts and the production of cercariae. Upon release from the snail, the infective cercariae swim, penetrate the skin of the human host and shed their forked tail, becoming schistosomulae. The schistosomulae migrate through several tissues and stages to their residence in the veins. Adult worms in humans reside in the mesenteric venules in various locations, which may be specific for each species. *S. haematobium* infection most often occurs in the venous plexus of the bladder, but it can also be found in the rectal venules. The females (7–20mm in length; males slightly smaller) deposit eggs in the small venules of the portal and perivesical systems. The eggs are moved progressively toward the lumen of the intestine (*S. mansoni* and *S. japonicum*) and of the bladder and ureter (*S. haematobium*), and are eliminated with feces or urine, completing the life cycle.

Bladder cancers associated with Schistosoma infection are mainly of the squamous cell type. The infection is responsible for an estimated 50% of bladder cancer cases in some parts of Africa, and about 3% of cases overall [25].

Avoiding risks

Regarding prevention, past changes in industrial processes have undoubtedly led to a decrease in some occupational exposures. Currently, avoidance of cigarette smoking is the most effective public health measure against bladder cancer. Approximately 60% of bladder cancer cases are due to smoking, at least half of which could be prevented by smoking cessation among current smokers. Prevention of Schistosoma infection through avoidance of contaminated water is important in endemic areas. No effective screening approach is available for bladder cancer.

REFERENCES

1. Boyle P, Smans M (2008). *IARC Scientific Publications, Number 159, Atlas of cancer mortality in the European Union and the European Economic Area 1993-1997*. Lyon, France: International Agency for Research on Cancer.

2. Eble J, Epstein JI, Sesterhenn IA, et al. (2004). *World Health Organization classification of tumours. Pathology and genetics of tumours of the urinary system and male genital organs*. Lyon, France: International Agency for Research on Cancer.

3. el-Mawla NG, el-Bolkainy MN, Khaled HM (2001). Bladder cancer in Africa: update. *Semin Oncol* 28: 174-178.

4. Groeneveld AE, Marszalek WW, Heyns CF (1996). Bladder cancer in various population groups in the greater Durban area of KwaZulu-Natal, South Africa. *Br J Urol* 78: 205-208.

5. Ochicha O, Alhassan S, Mohammed AZ, et al. (2003). Bladder cancer in Kano--a histopathological review. *West Afr J Med* 22: 202-204.

6. Parkin DM, Whelan SL, Ferlay J, et al. (2005). *Cancer incidence in five continents, Volumes I to VIII, IARC CancerBase Number 7*. Lyon, France: International Agency for Research on Cancer.

7. Sow M, Nkegoum B, Oyono JL, et al. (2006). [Epidemiological and histological features of urogenital tumours in Cameroon]. *Prog Urol* 16: 36-39.

8. Kogevinas M, Trichopoulos D (2002). Urinary bladder cancer. In: Adami HO, Hunter D, Trichopoulos D, eds., *Textbook of cancer epidemiology*. New York: Oxford University Press 446-466.

9. Commission on Cancer / American Cancer Society. *National Cancer Data Base (NCDB)*. Available from: http://www.facs.org/cancer/ncdb Date Accessed: November 11, 2008.

10. Kiemeney LA, Coebergh JW, Koper NP, et al. (1994). Bladder cancer incidence and survival in the south-eastern part of The Netherlands, 1975-1989. *Eur J Cancer* 30A: 1134-1137.

11. Roazzi P, Capocaccia R, Santaquilani M, et al. (2003). Electronic availability of EUROCARE-3 data: a tool for further analysis. *Ann Oncol* 14 Suppl 5: v150-v155.

12. Brennan P, Bogillot O, Cordier S, et al. (2000). Cigarette smoking and bladder cancer in men: a pooled analysis of 11 case-control studies. *Int J Cancer* 86: 289-294.

13. Brennan P, Bogillot O, Greiser E, et al. (2001). The contribution of cigarette smoking to bladder cancer in women (pooled European data). *Cancer Causes Control* 12: 411-417.

14. Fortuny J, Kogevinas M, Chang-Claude J, et al. (1999). Tobacco, occupation and non-transitional-cell carcinoma of the bladder: an international case-control study. *Int J Cancer* 80: 44-46.

15. Siemiatycki J, Richardson L, Straif K, et al. (2004). Listing occupational carcinogens. *Environ Health Perspect* 112: 1447-1459.

16. Riboli E and Norat T (2003). Epidemiologic evidence of the protective effect of fruit and vegetables on cancer risk. *Am J Clin Nutr* 78: 559S-569S.

17. Pelucchi C, Bosetti C, Negri E, et al. (2006). Mechanisms of disease: The epidemiology of bladder cancer. *Nat Clin Pract Urol* 3: 327-340.

18. Villanueva CM, Cantor KP, King WD, et al. (2006). Total and specific fluid consumption as determinants of bladder cancer risk. *Int J Cancer* 118: 2040-2047.

19. World Cancer Research Fund / American Institute for Cancer Research (1997). *Food, Nutrition and the Prevention of Cancer: a Global Perspective*. Washington, DC: AICR.

20. Lin J, Spitz MR, Dinney CP, et al. (2006). Bladder cancer risk as modified by family history and smoking. *Cancer* 107: 705-711.

21. Garcia-Closas M, Malats N, Silverman D, et al. (2005). NAT2 slow acetylation, GSTM1 null genotype, and risk of bladder cancer: results from the Spanish Bladder Cancer Study and meta-analyses. *Lancet* 366: 649-659.

22. IARC (1987). *IARC monographs on the evaluation of the carcinogenic risks to humans, Supplement 7, Overall evaluations of carcinogenicity: an updating of IARC monographs Volumes 1 to 42*. Lyon, France: International Agency for Research on Cancer.

23. Bedwani R, Renganathan E, El KF, et al. (1998). Schistosomiasis and the risk of bladder cancer in Alexandria, Egypt. *Br J Cancer* 77: 1186-1189.

24. IARC (1994). *IARC monographs on the evaluation of carcinogenic risks to humans, Volume 61, Schistosomes, liver flukes and helicobacter pylori*. Lyon, France: International Agency for Research on Cancer.

25. Parkin DM (2006). The global health burden of infection-associated cancers in the year 2002. *Int J Cancer* 118: 3030-3044.

5.21 Prostate Cancer

Summary

> Prostate cancer is very common, and while the incident rate is rising quickly, in many countries the mortality rate has started to fall

> While aggressive testing with Prostate specific antigen (PSA) has contributed to this decline in mortality, it does not explain all the effect

> The etiology of prostate cancer remains obscure. Tobacco smoking and alcohol consumption are not associated with prostate cancer risk. There is weak evidence of an association with certain dietary practices although the attributable fraction is small

> Chemoprevention studies have been conducted using finasteride, and a major randomised trial of Selenium and Vitamin E is on-going

> Despite many large prostate cancer families, with cases spreading over many generations, there has not been a major gene found for this disease

Urological cancers comprise approximately one third of all cancers diagnosed in men worldwide, and prostate cancer is the commonest of these. The global burden of prostate cancer rose from 200 000 new cases each year in 1975 to reach an estimated 700 000 new cases in 2002. In Europe, it was estimated that in 2006 Prostate Cancer was the fourth commonest form of cancer diagnosed in men, with 345 900 new cases in 2006 and 87 400 deaths recorded [2].

Figure 5.21.1 presents the 20 highest and lowest age-standardised prostate cancer incidence rates (all ages) for the period 1998–2002 among registries with the highest quality data and over one million person-years of observation (to ensure stability of the rates) [3]. The highest rates are from populations in the United States, especially among black population groups, Canada, Switzerland and Austria. The lowest rates are recorded from a variety of populations in Italy and Spain, and Korea, China and India (Figure 5.21.1).

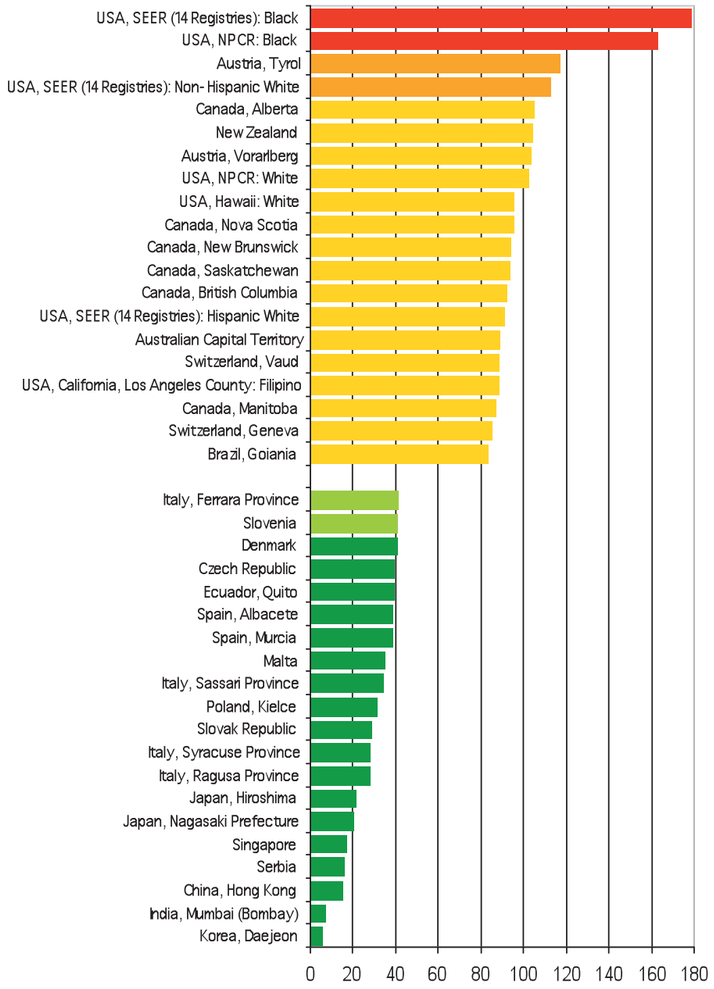


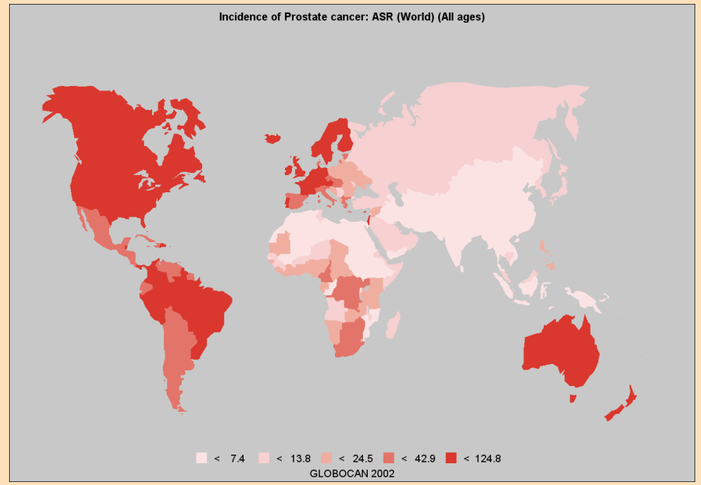
Fig. 5.21.1 *The 20 highest and lowest age-standardised incidence rates (all ages) for the period 1998–2002, for prostate cancer among registries with the highest quality data and over one million person-years of observation (to ensure stability of the rates)*

Long-term series confirm that the (all-ages) mortality rate from prostate cancer has been rising steadily in Ireland (1926–2004) (Figure 5.21.2) and Scotland (1911–2004) (Figure 5.21.3). It is notable that the increased mortality rate is much less in men in middle age (35–64) in Scotland.

Comparisons between trends in incidence and mortality in countries where both are available demonstrate a tendency for large increases in incidence accompanied by little change, and perhaps subsequent declines in mortality rates (Figure 5.21.4).

The Nordic countries (Denmark, Finland, Sweden and Norway) provide some important clues to explain this situation. Incidence rates were increasing and similar in the Nordic countries during the 1980s. Around 1990, a more rapid incidence increase began in all Nordic countries except Denmark, where an increase was seen 5 years later. In 2001, incidence rates in Denmark were half of those seen in the other Nordic countries, but mortality rates varied only marginally among countries. Mean annual declines in prostate cancer mortality of 1.9% and 1.8% were observed from 1996 to 2004 in Finland and Norway, respectively. During the same period, mortality rates levelled off in Iceland and Sweden but continued to increase in Denmark [4].

The rapid increase in incidence during the early 1990s coincided with the introduction of the prostate specific antigen (PSA) test and conveys little information about the occurrence of potentially lethal disease. Mortality rates, however, have recently stabilised or declined in countries where PSA testing and curative treatment have been commonly practiced since the late 1980s. Although other explanatory factors may be in operation, these trends are consistent with a moderate effect of increased curative treatment of early diagnosed prostate cancer and improved treatment of more advanced disease [4].



World Map 5.21.1

In order to quantify the plausible contribution of PSA screening to the nearly 30% decline in the United States prostate cancer mortality rate observed during the 1990s, two mathematical modelling teams independently projected disease mortality in the absence and presence of PSA screening using the same data source, the Surveillance, Epidemiology and End Results (SEER) registry [5]. The teams projected similar mortality increases in the absence of screening and decreases in the presence of screening after 1985. By 2000, the models projected that 45% (Fred Hutchinson Cancer Research Center) to 70% (University of Michigan) of the observed decline in prostate cancer mortality could be plausibly attributed to the stage shift induced by screening. While PSA screening may account for much, but not all, of the observed drop in prostate cancer mortality, other factors, such as changing treatment practices, may also have played a role in improving prostate cancer outcomes [5].

Etiology and genetics

The etiology of prostate cancer remains shrouded in mystery [6]. An IARC Monograph Working Group found no association with Tobacco Smoking [7], and this was confirmed subsequently [8]. Another IARC Monograph Working Group found no association with Alcohol Consumption [9], and this too was confirmed subsequently [10].

There appears to be little association with macronutrient intake and prostate cancer risk. Dietary fat and meat as potential risk factors for prostate cancer have been the focus of many

epidemiologic investigations, and findings from recent studies in particular have been inconsistent. Analysis of the information in the Multiethnic Cohort Study found that intake of different types of fat (total, saturated, monounsaturated or polyunsaturated), n-6 fatty acid, cholesterol, various meats and fats from meat showed no association with overall prostate cancer risk or with non-localised or high-grade prostate cancer. There was little evidence of any relation of fat and meat intake with prostate cancer risk within any of the 4 racial/ethnic groups (African Americans, Japanese Americans, Latinos and whites). The overall findings from this large cohort study of ethnically diverse populations gives no indication that intake of fat and meat substantially affects prostate cancer risk [11].

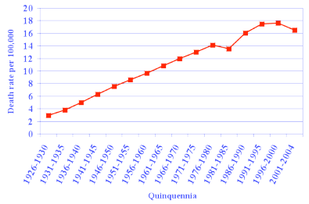


Fig. 5.21.2 *Cancer of the Prostate in Men in Ireland, 1926–2004*
Annual, average age-standardised death rates per 100 000 All-ages, age-standardised mortality rate from prostate cancer per 100 000 in Ireland (1926–2004)

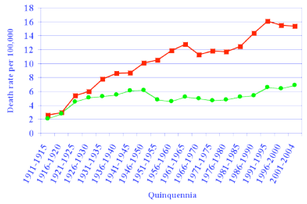
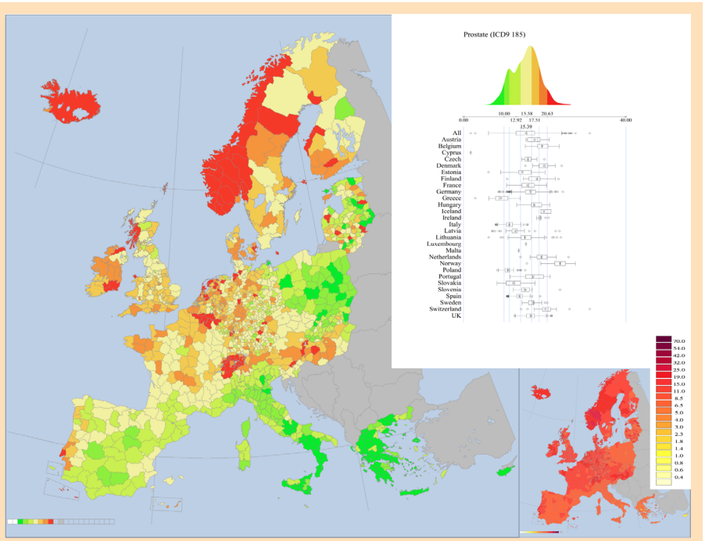


Fig. 5.21.3 *Cancer of the Prostate in Men in Scotland, 1911–2004*
Annual, average age-standardised death rates per 100 000 All-ages, age-standardised mortality rate, and truncated (35–64) rate, from Prostate Cancer per 100 000 in Scotland (1911–2004)



European Map 5.21.1 *High mortality rates from prostate cancer are apparent in Iceland, Norway, much of Sweden, southern Finland and Denmark; there were also higher-than-average rates in The Netherlands, Belgium and northern France, and Ireland.*
There was also a band of high rates from Switzerland eastwards into Austria and western Hungary. Low rates are notable throughout Poland, Greece and Italy, and much of Spain.[1]

Omega-3 fatty acids are purported to reduce the risk of cancer although studies have reported mixed results. A meta-analysis of 38 articles from prospective epidemiological studies investigated the risk of cancer with intake of omega-3 fatty acids. For prostate cancer, there was no evidence of association. Dietary supplementation with omega-3 fatty acids is unlikely to prevent cancer [12].

There are some potential relationships which still need to be clarified. Inverse associations with prostate cancer have been observed for allium vegetable consumption and weak inverse associations for palmitoleic acid, fatty acid, 20:5 n-6 and for oleic acid [13]. Diets rich in olive oil (a source of oleic acid) and allium vegetables might reduce the risk of prostate cancer; this is consistent with low rates in many parts of southern Italy (Figure 5.21.2).

Calcium and dairy foods in relation to prostate cancer were examined in the National Institutes of Health (NIH)-AARP (formerly known as the American Association of Retired Persons) Diet and Health Study (1995/1996–2001) [14]. During up to 6 years of follow-up (n=293 888), the authors identified 10 180 total prostate cancer cases (8754 non-advanced, 1426 advanced and 178 fatal cases). Total and supplemental calcium were unrelated to total and non-advanced prostate cancer. These findings do not provide consistent support for the hypothesis that calcium and dairy foods increase prostate cancer risk.

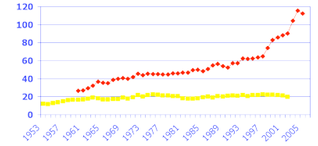
Several studies have reported an inverse association between tomato and/or lycopene intake and the risk of some types of cancer, prompting two petitions to the US Food and Drug Administration (FDA) for qualified health claims regarding tomatoes, lycopene, and the risk reduction for some forms of cancer, notably prostate cancer. The FDA review found no credible evidence to support an association between lycopene intake and a reduced risk of prostate, lung, colorectal, gastric, breast, ovarian, endometrial or pancreatic cancer. The FDA also found no credible evidence for an association between tomato consumption and a reduced risk of lung, colorectal, breast, cervical or endometrial cancer. The FDA found very limited evidence to support an association between tomato consumption and reduced risks of prostate, ovarian, gastric and pancreatic cancers [15].

Statins are commonly used cholesterol-lowering drugs that have proapoptotic and antimetastatic activities that could affect cancer risk or progression. Results from previous epidemiologic studies of the association between statin use and cancer have been inconsistent. Platz and co-workers (2006) investigated the association of statin use with total and advanced prostate cancer, the latter being the most important endpoint to prevent in an ongoing prospective cohort study of 34 989 US male health professionals. Use of statin drugs was not associated with risk of prostate cancer overall but was associated with a reduced risk of advanced (especially metastatic or fatal) prostate cancer [16].

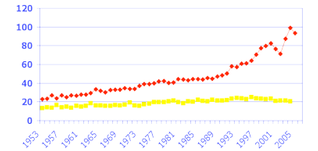
Some recent epidemiologic studies have failed to confirm positive associations between insulin-like growth factor-I (IGF-I) and the risk of prostate cancer observed in earlier studies, but have reported suggestive evidence for a positive association between IGF-binding protein-3 (IGFBP-3) and prostate cancer risk, a result contradicting the earlier assumption that high levels of IGFBP-3 would be protective against prostate cancer. The association between IGF-I and IGFBP-3 and prostate cancer risk was determined by measuring the two peptides in plasma samples collected at baseline in a prospective cohort study of 17 049 men. The risk of prostate cancer was not associated with baseline levels of IGF-I or the molar ratio IGF-I/IGFBP-3 (all odds ratios 0.82–1.08; P(trend) ≥0.2), whereas the risk increased with baseline levels of IGFBP-3 (P(trend) = 0.008), the hazard ratio (HR) associated with a doubling of the concentration of IGFBP-3 being 1.70 (95% CI 1.15–2.52). The HR for quartile 4 relative to quartile 1 of IGFBP-3 was 1.49 (95% CI 1.11–2.00). The HRs did not differ by tumour aggressiveness or age at onset (all Ps ≥0.4). High levels of IGFBP-3 but not IGF-I were associated with an increased risk of prostate cancer [17].

Attention has recently focussed on the metabolic syndrome, characterised by insulin insensitivity, central obesity dyslipidemia and hypertension, on the risk of prostate cancer. It is recognised as a risk factor for cardiovascular disease in men; by the time metabolic syndrome is diagnosed, however, most men already have entrenched cardiovascular disease [18]. One third of men with type 2 diabetes mellitus are now recognised as testosterone deficient. Emerging evidence suggests that testosterone therapy may be able to reverse some aspects of metabolic syndrome [18], although the impact of such a strategy on prostate cancer risk remains an open question.

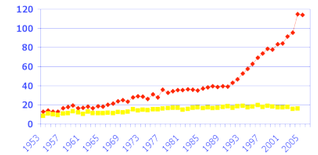
Endogenous androgens have long been suspected as being involved in the etiology of prostate cancer, although epidemiologic studies have failed to support the hypothesis that circulating androgens are positively associated with prostate cancer risk. Some recent studies have even suggested that high testosterone levels might be protective particularly against aggressive cancer. In a large Australian study, high levels of testosterone and adrenal androgens have been associated with reduced risk of aggressive prostate cancer but not with non-aggressive disease [19].



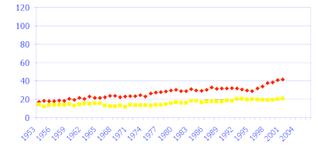
Incidence and Mortality from Prostate Cancer in Sweden, 1953-



Incidence and Mortality from Prostate Cancer in Finland, 1953-



Incidence and Mortality from Prostate Cancer in Norway, 1953-



Incidence and Mortality from Prostate Cancer in Denmark, 1953-

Fig. 5.21.4 *Trends in incidence and mortality in Norway, Denmark, Sweden, Finland and Scotland from mid 1950s to present*

Despite the large number of families with prostate cancer in brothers and across multiple generations, there is no gene which has been identified for prostate cancer with similar significance to those genes (BRCA1 and BRCA2) discovered some years ago for breast cancer. However, the search goes on and there have been some very interesting developments reported recently [20-22].

Prevention of prostate cancer

The dramatic international variation in prostate cancer incidence and mortality rates suggests that changeable environmental factors exert an influence [23]. This has prompted a search for ways to prevent the disease. Epidemiologic studies have reported variations in the strength and consistency of the evidence that dietary factors such as the carotenoid lycopene, selenium, vitamin E and high intake of fat have roles in prostate cancer risk. Impairment of androgen synthesis lowers the risk of prostate cancer. 5-alpha-reductase inhibitors have been shown to decrease prostate size by decreasing androgenic stimulation to the prostate. Other promising but less developed interventions include vitamin D supplements and modification of diet. Any manipulation to decrease one's risk of prostate cancer will by necessity have to be given to a large proportion of men who would never develop prostate cancer even without the intervention. To be acceptable, a successful preventive intervention should have few or no side effects; some additional benefits would be useful. All potential preventive interventions will need to be rigorously evaluated before they can be advocated for prostate cancer prevention [23].

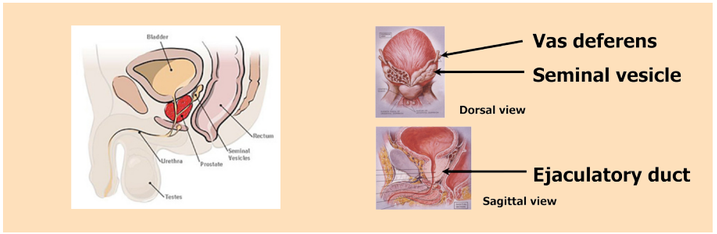


Fig. 5.21.5 *Male Urological Anatomy*

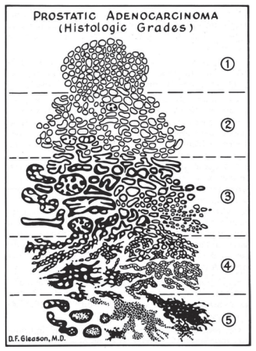


Fig. 5.21.6 *Dr. Donald F Gleason has provided a conceptual diagram (oversimplified) to show the continuum of deteriorating cancer cell architecture, and the four dividing lines along this continuum which he discovered are able to identify patients with significantly different prognosis derived from a study which included 2900 patients. http://www.phoenix5.org/Infolink/GleasonGrading.html*

Prevention of prostate cancer would have a major impact on disease-associated cost, morbidity and mortality for a large segment of the population. A major advance in prevention of prostate cancer came in 2003 with the publication of the Prostate Cancer Prevention Trial [24] which demonstrated that use of finasteride is associated with a 25% reduction in the 7-year period prevalence of prostate cancer in men over age 55 years with normal digital rectal exam and initial prostate specific antigen <3.0 ng/ml. Use of finasteride was associated with a slightly higher risk of Gleason sum 7–10 tumours, some sexual side effects, and fewer urinary symptoms.

A substantial body of new molecular evidence supports the existing body of clinical and epidemiological data leading to testing of vitamin E and selenium as preventative agents in men at risk for prostate cancer [25]. A large chemoprevention trial has been organised. SELECT is a randomised, prospective, double-blind study designed to determine if selenium and vitamin E can reduce the risk of prostate cancer among healthy men. Preclinical, epidemiologic and Phase III data suggest that both selenium and vitamin E have potential efficacy in prostate cancer prevention [26]. The experience of the Prostate Cancer Prevention Trial and the rapid accrual of SELECT during its first year demonstrate the interest and dedication of healthy men to long-term studies of cancer prevention. A total of 32 400 men are planned to be randomised in SELECT; enrolment began in 2001 with final results anticipated in 2013 [26].

REFERENCES

1. Boyle P, Smans M (2008). *IARC Scientific Publications, Number 159, Atlas of cancer mortality in the European Union and the European Economic Area 1993-1997*. Lyon, France: International Agency for Research on Cancer.

2. Ferlay J, Autier P, Boniol M, et al. (2007). Estimates of the cancer incidence and mortality in Europe in 2006. *Ann Oncol* 18: 581-592.

3. Curado MP, Edwards B, Shin HR, et al. (2007). *IARC Scientific Publications, Number 160, Cancer incidence in five continents, Vol. IX*. Lyon, France: International Agency for Research on Cancer.

4. Kvale R, Auvinen A, Adami HO, et al. (2007). Interpreting trends in prostate cancer incidence and mortality in the five Nordic countries. *J Natl Cancer Inst* 99: 1881-1887.

5. Etzioni R, Tsodikov A, Mariotto A, et al. (2008). Quantifying the role of PSA screening in the US prostate cancer mortality decline. *Cancer Causes Control* 19: 175-181.

6. Boyle P, Severi G, Giles GG (2003). The epidemiology of prostate cancer. *Urol Clin North Am* 30: 209-217.

7. IARC (2004). *IARC monographs on the evaluation of carcinogenic risks to humans, Volume 83, Tobacco smoke and involuntary smoking*. Lyon, France: International Agency for Research on Cancer.

8. Giles GG, Severi G, McCredie MR, et al. (2001). Smoking and prostate cancer: findings from an Australian case-control study. *Ann Oncol* 12: 761-765.

9. Baan R, Straif K, Grosse Y, et al. (2007). Carcinogenicity of alcoholic beverages. *Lancet Oncol* 8: 292-293.

10. Baglietto L, Severi G, English DR, et al. (2006). Alcohol consumption and prostate cancer risk: results from the Melbourne collaborative cohort study. *Int J Cancer* 119: 1501-1504.

11. Park SY, Murphy SP, Wilkens LR, et al. (2007). Fat and meat intake and prostate cancer risk: the multiethnic cohort study. *Int J Cancer* 121: 1339-1345.

12. MacLean CH, Newberry SJ, Mojica WA, et al. (2006). Effects of omega-3 fatty acids on cancer risk: a systematic review. *JAMA* 295: 403-415.

13. Hodge AM, English DR, McCredie MR, et al. (2004). Foods, nutrients and prostate cancer. *Cancer Causes Control* 15: 11-20.

14. Park Y, Mitrou PN, Kipnis V, et al. (2007). Calcium, dairy foods, and risk of incident and fatal prostate cancer: the NIH-AARP Diet and Health Study. *Am J Epidemiol* 166: 1270-1279.

15. Kavanaugh CJ, Trumbo PR, Ellwood KC (2007). The U.S. Food and Drug Administration's evidence-based review for qualified health claims: tomatoes, lycopene, and cancer. *J Natl Cancer Inst* 99: 1074-1085.

16. Platz EA, Leitzmann MF, Visvanathan K, et al. (2006). Statin drugs and risk of advanced prostate cancer. *J Natl Cancer Inst* 98: 1819-1825.

17. Severi G, Morris HA, MacInnis RJ, et al. (2006). Circulating insulin-like growth factor-I and binding protein-3 and risk of prostate cancer. *Cancer Epidemiol Biomarkers Prev* 15: 1137-1141.

18. Spark RF (2007). Testosterone, diabetes mellitus, and the metabolic syndrome. *Curr Urol Rep* 8: 467-471.

19. Severi G, Morris HA, MacInnis RJ, et al. (2006). Circulating steroid hormones and the risk of prostate cancer. *Cancer Epidemiol Biomarkers Prev* 15: 86-91.

20. Camp NJ, Cannon-Albright LA, Farnham JM, et al. (2007). Compelling evidence for a prostate cancer gene at 22q12.3 by the International Consortium for Prostate Cancer Genetics. *Hum Mol Genet* 16: 1271-1278.

21. Schaid DJ, McDonnell SK, Zarfas KE, et al. (2006). Pooled genome linkage scan of aggressive prostate cancer: results from the International Consortium for Prostate Cancer Genetics. *Hum Genet* 120: 471-485.

22. Zheng SL, Sun J, Cheng Y, et al. (2007). Association between two unlinked loci at 8q24 and prostate cancer risk among European Americans. *J Natl Cancer Inst* 99: 1525-1533.

23. Brawley OW (2002). The potential for prostate cancer chemoprevention. *Rev Urol* 4 Suppl 5: S11-S17.

24. Thompson IM, Goodman PJ, Tangen CM, et al. (2003). The influence of finasteride on the development of prostate cancer. *N Engl J Med* 349: 215-224.

25. Klein EA and Thompson IM (2004). Update on chemoprevention of prostate cancer. *Curr Opin Urol* 14: 143-149.

26. Klein EA, Thompson IM, Lippman SM, et al. (2003). SELECT: the selenium and vitamin E cancer prevention trial. *Urol Oncol* 21: 59-65.

5.22 Thyroid Cancer

Summary

> Ionizing radiation and history of benign thyroid diseases are the best-established risk factors for thyroid cancer

> Iodine deficiency has been associated with follicular thyroid cancer

> A strong genetic component has been shown for medullary carcinoma, alone or as a part of multiple endocrine neoplasia (MEN) syndrome. The APC gene has been associated with papillary carcinoma

Fig. 5.22.1 *Composite artwork illustrating the controlling role of the tyroid gland in the body*

In most areas of the world, the incidence of thyroid cancer among women is in the range 2–5/100 000; that in men is 1–2/100 000. High-risk areas (incidence >5/100 000 in women) include Central America, Japan and the Pacific islands. International comparisons, however, are complicated by possible differences in diagnostic procedures. The most common thyroid neoplasm (50–80% of the total) is papillary carcinoma, followed by follicular carcinoma (10–40%) and medullary carcinoma (5–15%).

Survival from thyroid cancer is very good (over 85% five-year survival rate in Europe and North America), resulting in low mortality rates (below 1.2/100 000 in women and 0.6/100 000 in men in most areas of the world).

In most countries, incidence rates have been stable or have been slowly increasing (<1%/year) during the last decades; mortality rates have steadily declined, likely because of improved treatment.

Ionizing radiation is the main established risk factor for thyroid cancer [2]. The carcinogenic effect seems greater for exposure before age 5 than subsequently. The pooled analysis of studies of individuals irradiated in childhood for medical conditions and atomic bomb survivors resulted in a summary excess relative risk of 7.7 (95% CI 2.1–29) per Gy, and an excess absolute risk of 4.4 (95% CI 1.9–10) per 10 000 person-years Gy. Several studies have been published on adults exposed to ^{131}I for medical purposes. Although those studies suggest an increased risk, their interpretation is made complex by the fact that these patients were treated because of thyroid diseases. ^{131}I was the main exposure resulting from the accident of the Chernobyl nuclear reactor in 1986; since then, an increased incidence of thyroid cancer has been reported among children living in the contaminated areas of Belarus and Ukraine. Iodine supplementation in the immediate period following the Chernobyl accident has been shown to protect against thyroid cancer [3]. Studies of occupational exposure to low-level ionizing radiation, typically in the nuclear industry, have failed to show an increased in mortality from thyroid cancer.

An association between thyroid cancer and a history of benign thyroid diseases has been observed in most studies, although the strengths of these associations have varied across studies. Because thyroid cancer incidence rates in women are consistently 2–3 times higher than those in men, some studies in various geographic areas have focused on women in an attempt to identify hormonal factors that might explain this excess. However, findings related to menstrual and reproductive factors as well as to exogenous hormone use have been inconsistent, as have findings related to diet and to anthropometric and lifestyle factors.

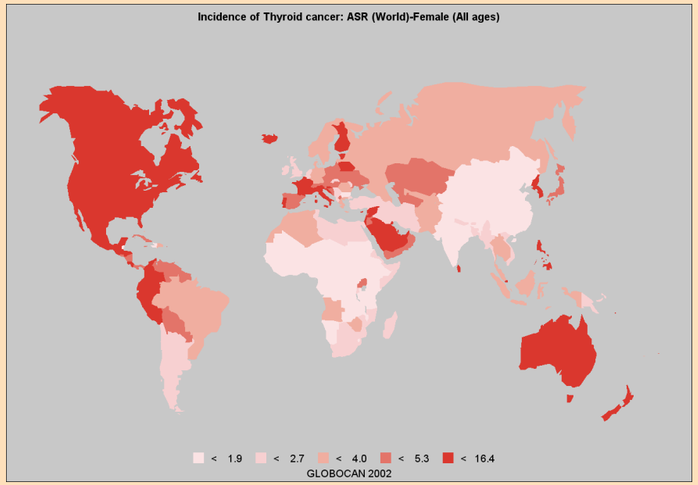
In a pooled analyses, goiter and benign nodules/adenomas were shown to be the strongest risk factors for thyroid cancer apart from radiation in childhood. In women, the pooled odds ratios (OR) were 5.9 for goiter and 38.3 for benign nodules/adenomas. Elevated risks were observed for men and women and in relation to both major histologic types (papillary/follicular). No significant heterogeneity was seen across geographic areas or across studies. The excess risk was greatest within 2–4 years prior to thyroid cancer diagnosis, but an elevated OR was present 10 years or more before cancer. Prior hyperthyroidism was related to a small, statistically non-significant increase that was reduced after allowance for a history of goiter. A history of hypothyroidism was not associated with cancer risk [4].

Elevated levels of thyroid-stimulating hormones are associated with thyroid growth and possibly thyroid cancer. The evidence of an association between iodine deficiency (and presence of endemic goiter) and thyroid cancer is equivocal: studies from central and southern Europe support such an association, which was not confirmed in studies from northern Europe and North America. It is possible that iodine deficiency increases the risk of follicular thyroid cancer, while the papillary type is linked to iodine-rich diet.

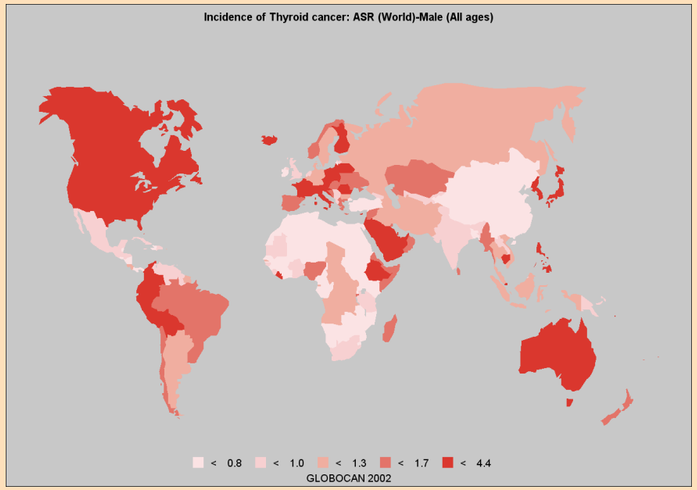
Among other risk factors considered, pooled analyses have focussed only on fish/seafood [5] and cruciferous and other vegetables [6]. Fish was not associated with thyroid cancer risk in all studies combined, but there was a suggestion of reduced risk in endemic goiter areas. It was reassuring to note that high levels of fish consumption did not appreciably increase risk in iodine-rich areas, and fish consumption was inversely related to thyroid cancer risk in endemic goiter areas. Cruciferous vegetables, which contain goitrogenic substances as well as several constituents which can inhibit carcinogenesis, were weakly and non-significantly related to reduced risk of thyroid cancer.

A strong genetic component has been shown for medullary carcinoma: about 20% of these neoplasms are associated with an autosomal dominant gene, with penetrance close to 100% [7]. It can also be associated with other endocrine neoplasms within the multiple endocrine neoplasia syndromes (MEN type 2). These include medullary thyroid carcinoma and hyperparathyroidism (MEN2A), resulting from mutation in the *ret* proto-oncogene, or mucosal neuromas of the lip and gastro intestinal tract (MEN 2B, [2]). Familial factors play a role in papillary carcinoma, too. Among the genes associated with papillary thyroid cancer are the *ret* and the APC gene.

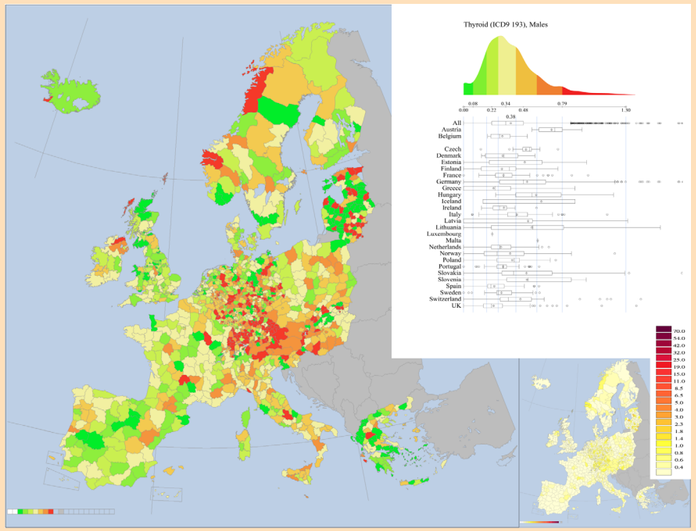
The prospects for prevention of thyroid cancer are made complex by the limited understanding of its etiology, with the exception of relatively rare high-risk conditions, such as childhood exposure to ionizing radiation and high-risk families.



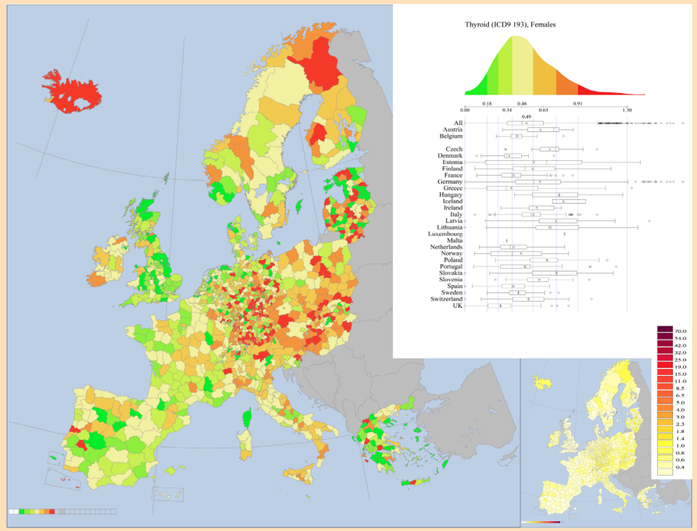
World Map 5.22.1



World Map 5.22.2



European Map 5.22.1 *In men, there appears to be an aggregation of high rates in the centre of Europe - the neighbouring countries of Austria, central and southern Germany, Switzerland and the west of the Czech Republic. There were generally low rates in the United Kingdom, Spain, Portugal, France and Greece [1].*



European Map 5.22.2 *In females, there was the same pattern of generally higher rates in Austria and adjacent countries, and mostly lower-than-average rates in much of western Europe. However, it must be kept in mind that all these mortality rates were very low in absolute terms [1].*

REFERENCES

1. Boyle P, Smans M (2008). *IARC Scientific Publications, Number 159, Atlas of cancer mortality in the European Union and the European Economic Area 1993-1997.* Lyon, France: International Agency for Research on Cancer.

2. Ron E, Schneider A (2006). Thyroid Cancer. In: Schottenfeld D, Fraumeni JF, eds., *Cancer epidemiology and prevention.* New York: Oxford University Press 975-994.

3. Cardis E, Kesminiene A, Ivanov V, et al. (2005). Risk of thyroid cancer after exposure to 131I in childhood. *J Natl Cancer Inst* 97: 724-732.

4. Franceschi S, Preston-Martin S, Dal Maso L, et al. (1999). A pooled analysis of case-control studies of thyroid cancer. IV. Benign thyroid diseases. *Cancer Causes Control* 10: 583-595.

5. Bosetti C, Kolonel L, Negri E, et al. (2001). A pooled analysis of case-control studies of thyroid cancer. VI. Fish and shellfish consumption. *Cancer Causes Control* 12: 375-382.

6. Bosetti C, Negri E, Kolonel L, et al. (2002). A pooled analysis of case-control studies of thyroid cancer. VII. Cruciferous and other vegetables (International). *Cancer Causes Control* 13: 765-775.

7. Negri E, Ron E, Franceschi S, et al. (2002). Risk factors for medullary thyroid carcinoma: a pooled analysis. *Cancer Causes Control* 13: 365-372.

5.23 Tumours of the Nervous System

Summary

> Tumours of the nervous system account for less than 2% of all malignancies (about 175 000 cases per year worldwide); the incidence does not vary markedly between regions or populations

> The incidence of these tumours tended to increase in most cancer registration areas over the last few decades, most probably because of better reporting by cancer registries and improvement in non-invasive imaging technologies

> Etiology is largely unknown; the only unequivocal cause is therapeutic irradiation, but occurrence in these circumstances is very rare

> The nervous system is frequently involved in inherited tumour syndromes, including neurofibromatosis (NF1/NF2 germline mutations), von Hippel-Lindau disease (VHL), tuberous sclerosis (TSC1/TSC2) and Li-Fraumeni syndrome (p53)

> Glioblastomas are the most common brain tumours and mainly affect adults. These tumours are surgically incurable and largely resistant to radiation and chemotherapy; only 3% of patients survive longer than 3 years

> Embryonal tumours, including cerebellar medulloblastomas, retinoblastomas and peripheral neuroblastoma, predominantly afflict children, ranking second after leukaemia as the most common types of paediatric cancer

Over 90% of nervous system tumours arise from the brain, the cranial nerves and the cranial meninges. On clinical grounds, benign tumours may be as dangerous as malignant tumours when they grow in the cranium or, in the base of the skull, or in the vertebrae and compress the surrounding nervous tissues.

Gliomas arise from the glial cells and are classified pathologically as astrocytomas (low-grade) and glioblastomas (high-grade). They represent 40–60% of primary tumours of the brain, are predominantly malignant, and are more common in men. Meningiomas arise from the cranial meninges and represent 20–35% of brain neoplasms, while schwannomas (or neurilemomas) arise from the Schwann cells of the nerve sheath (mainly of the eighth cranial (acoustic) nerve) and represent 5–10% of all brain neoplasms. These two latter types are mainly benign. Rare types of nervous system neoplasms include pituitary adenomas, childhood primary neuroectodermal tumours (also called medulloblastoma) and tumours of the spine and the peripheral nerves.

Although not very frequent, brain tumours contribute significantly to morbidity, often affect children and overall have a poor prognosis. Due to marked resistance to radiation and chemotherapy, the prognosis for patients with glioblastomas is very poor. The majority of patients die within 9–12 months, and fewer than 3% survive more than 3 years.

Epidemiology

Data on the descriptive epidemiology of nervous system tumours are difficult to interpret, because many studies include both benign and malignant tumours.

The age distribution of brain tumours is bimodal, with a peak incidence in children and a second larger peak in adults aged 45–70. In most developed countries, brain tumours are the 12th most frequent cause of cancer-related mortality in men.

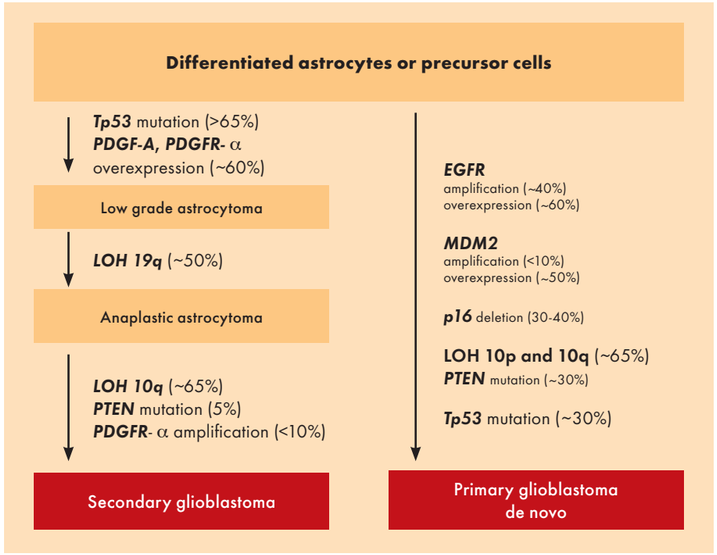


Fig. 5.23.1 *Genetic pathways in the evolution of primary and secondary glioblastoma*

The incidence of brain tumours is slightly higher in men than in women; the male:female ratio is approximately 1.3 for gliomas and 0.6 for meningiomas. There is a geographical variability in the incidence of brain neoplasms: rates in men are 6 to 8/100 000 in most countries from the Americas, Europe and Oceania, and in the range of 2 to 3/100 000 in Africa and Asia. In the USA, rates of gliomas are 30–50% higher in Whites than in other ethnic groups, while rates of meningiomas are slightly higher in Blacks.

During the last decades, incidence and mortality from brain tumours have increased in most developed countries, mainly in the older age groups [2]. The increase in the incidence was confined to the late 1970s and early 1980s and coincided with the introduction of improved diagnostic methods [3]. After 1983 and more recently during the period of increasing prevalence of mobile phone users, the incidence has remained relatively stable for both men and women. Analysis of temporary trends in introduction of medical technologies and improved diagnosis of brain tumours shows that most if not all of the increase is attributable to (i) the introduction of high-resolution neuroimaging (e.g. CT Scan, Magnetic Resonance Imaging, PET Scan) in the last decades; (ii) variations in diagnostic and reporting procedures; and (iii) the brain as a frequent site of metastases, principally from breast and lung cancer, because with more primitive imaging modalities, brain metastases may have been misclassified as primary brain

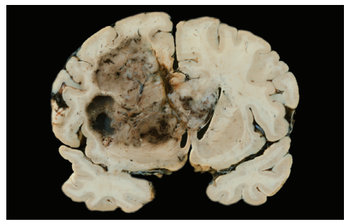
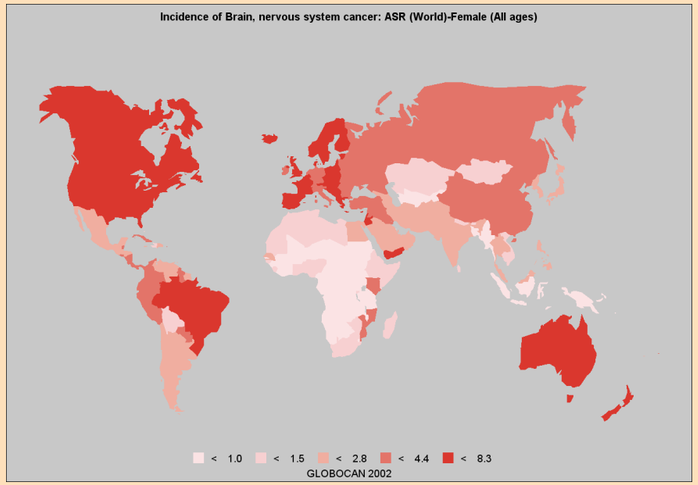
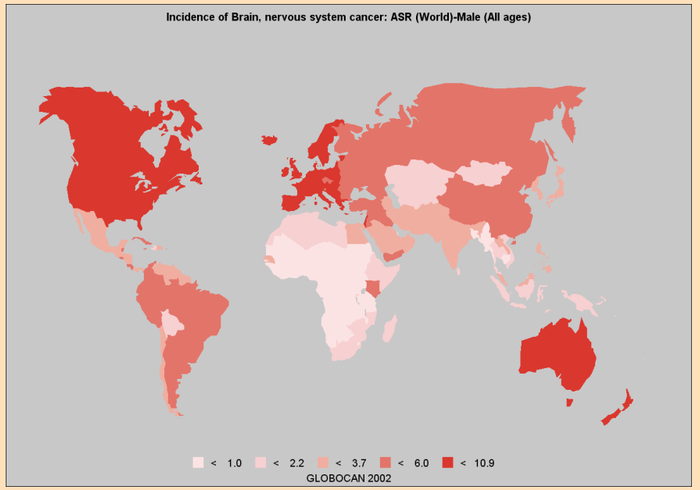


Fig. 5.23.2 *A large glioblastoma multiforme in the left frontal lobe, extending into the corpus callosum and the contralateral white matter*



World Map 5.23.1

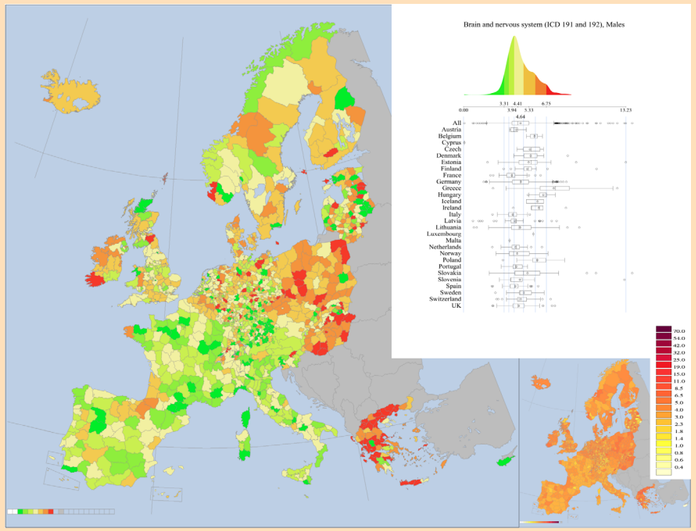


World Map 5.23.2

tumours. The likelihood for these three reasons being at the source of the recent increase in brain tumours incidence is reinforced by stable or even slight decreases in mortality from brain tumours (e.g. in the USA, [4]), which underlines that a large proportion of additional brain tumours found thanks to new imaging technologies are not as deadly and are probably more curable than brain tumours diagnosed in the past.

Geographical variation in incidence is less than for most other human neoplasms, but incidence tends to be higher in more developed countries.

The incidence of gliomas tends to be higher among people from high socioeconomic groups. Association of higher socioeconomic status with central nervous system tumours and greater access to imaging technologies in more affluent economic strata partly explain why the incidence of these tumours is greater in high than in medium- and low-resource countries, and within countries is also greater in upper socio-economic classes.



European Map 5.23.1 *In men, mortality rates from cancers of the brain and central nervous system were generally low in the south and west of Europe, including Portugal, Spain, France, Italy, Switzerland, Austria and southern Germany. Rates were noticeably higher-than-average in most of Greece, Hungary, the Czech Republic, Slovakia and Poland, and in parts of northern Germany and Belgium [1].*

Tumour (WHO Grade)	Typical location	Age at clinical manifestation (% of cases)			Five-year survival (% of patients)	Genetic alterations
		0–20 yrs	20–45 yrs	>45 yrs		
Pilocytic astrocytoma (Grade I)	Cerebellum, optic nerve	74	20	6	>85	*NF1* (neurofibromatosis cases)
Low grade diffuse astrocytoma (Grade II)	Cerebral hemispheres	10	61	29	>50	*p53* mutation
Glioblastoma (Grade IV)	Cerebral hemispheres	3	25	72	<3	*EGFR* amplification, *PTEN* mutation, p16 deletion, LOH chromosome10
Oligodendroglioma (Grade II/III)	Cerebral hemispheres	8	46	46	>50	LOH 1p, 19q
Ependymoma (Grade II)	Ventricles, spinal cord	37	38	25	<30	*NF1* (spinal tumours)
Medulloblastoma (Grade IV)	Cerebellum	74	23	3	>50	Isochromosome 17, *MYC* amplification, *PTCH*, beta-catenin
Neuroblastoma (Grade IV)	Abdomen	>95			>90 (<1 yr old) 20-50 (>1 yr)	LOH 1p, 11q, *MYCN* amplification, trisomy 17q

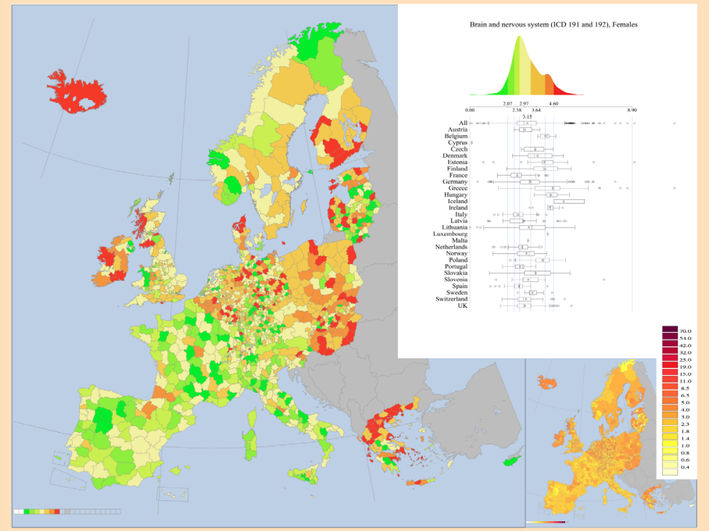
Table 5.23.1 *Summary of epidemiological data on intracranial tumours*

Etiology

During the last few decades, incidence and mortality from brain tumours have increased in most developed countries. However, differences in the descriptive epidemiology of brain cancer, including time trends, can be partially due to variations in diagnostic and reporting procedures.

Ionizing radiation is the only established non-genetic risk factor for brain tumours [2]. It causes all three major types of central nervous system tumours, but the association is stronger for meningioma and schwannoma than for glioma. The evidence comes mainly from studies of atomic bomb survivors and of patients given X-ray therapy in the head and neck region. Head trauma has been suggested as a risk factor for meningioma, and acoustic trauma (as in the case of jobs with exposure to loud noise) as a risk factor for acoustic schwannoma. N-nitroso compounds, in particular nitrosoureas, are potent experimental brain carcinogens, and are part of tobacco smoke. The evidence of an etiological role of tobacco smoking, either active or passive (i.e. childhood exposure to tobacco smoke) in humans is inconclusive [5]. Several other lifestyle, environmental (e.g. occupational exposures, use of pesticides) and medical (e.g. allergic conditions) factors have been suggested to play an etiological role in brain cancer, but the evidence is not sufficient to draw a conclusion.

Some studies have suggested an increased incidence of central nervous system tumours associated with certain occupations, including farming, fire-fighting, metalworking and the rubber and petrochemical industries, and with those who work as anatomists, pathologists and embalmers, but most of these reports have not been confirmed and causative agents have not been identified. Suggestions that radio-frequency radiation generated by mobile phones and microwave telecommunications may play a role in the etiology of malignant gliomas remain to be substantiated.



European Map 5.23.2 *The map for women shows both that the between- and within-country variability in the rates were very closely similar to those in males [1]*

The very limited knowledge about the etiology of tumours of the central nervous system offers scarce resources for an effective preventive strategy.

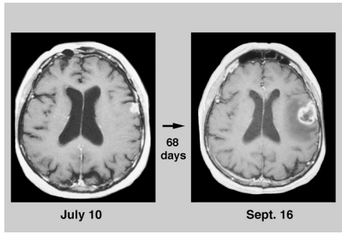


Fig. 5.23.3 *An MRI scan of a primary glioblastoma in a 79-year-old patient. A small cortical lesion rapidly developed into a full-blown glioblastoma with perifocal oedema and central necrosis*

Pathology and genetics

The WHO classification of tumours of the nervous system contains more than 50 clinico-pathological entities with a great variation in

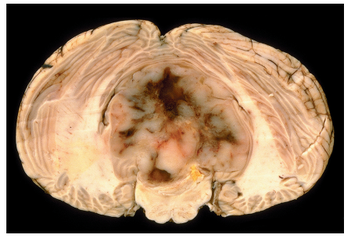


Fig. 5.23.4 *Macroscopic image of a medulloblastoma of the cerebellar vermis, compressing the brainstem*

Syndrome	Gene	Chromosome	Nervous system	Skin	Other tissues
Neurofibromatosis 1	*NF1*	17q11	Neurofibromas, MPNST, optic nerve gliomas, astrocytomas	Café-au-lait spots axillary freckling,	Iris hamartomas, osseous lesions, phaeochromocytoma, leukaemia
Neurofibromatosis 2	*NF2*	22q12	Bilateral vestibular schwannomas, peripheral schwannomas, meningiomas, meningioangiomatosis, spinal ependymomas, astrocytomas, micro-hamartomas, cerebral calcifications	-	Posterior lens opacities, retinal hamartoma
von Hippel-Lindau	*VHL*	3p25	Haemangioblastomas	-	Retinal haemangioblastomas renal cell carcinoma,
Tuberous sclerosis	*TSC1 TSC2*	9q34 16p13	Subependymal giant cell astrocytoma, cortical tubers	Cutaneous angiofibroma ("adenoma sebaceum") peau de chagrin, subungual fibromas	Cardiac rhabdomyomas, adenomatous polyps of the duodenum and the small intestine, cysts of the lung and kidney, lymphangioleiomyomatosis, renal, angiomyolipoma
Li-Fraumeni	*p53*	17p13	Astrocytomas, glioblastomas, medulloblastomas	-	Breast carcinoma, bone and soft tissue sarcomas, adrenocortical carcinoma, leukaemia
Cowden	*PTEN (MMAC1)*	10q23	Dysplastic gangliocytoma of the cerebellum (Lhermitte-Duclos), megalencephaly	Multiple trichilemmomas, fibromas	Hamartomatous polyps of the colon, thyroid neoplasms, breast carcinoma
Turcot	*APC*	5q21	Medulloblastoma	-	Colorectal cancer
	hMLH1	3p21	Glioblastoma	Café-au-lait spots	Colorectal cancer
	hPSM2	7p22			
Naevoid basal cell carcinoma syndrome (Gorlin)	*PTCH*	9q31	Medulloblastoma	Multiple basal palmar and plantar pits	Jaw cysts, ovarian fibromas, skeletal abnormalities

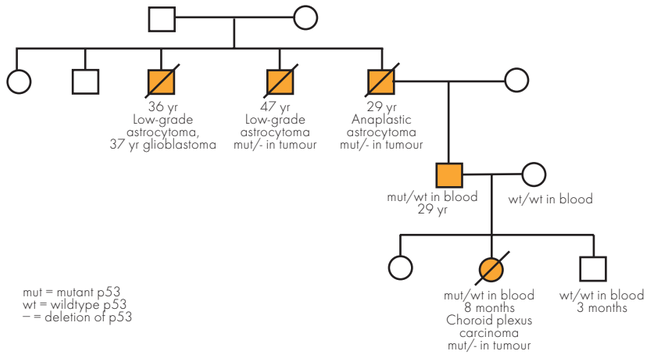
Table 5.23.2 *Major familial tumour syndromes involving the nervous system*

biological behaviour, response to therapy and clinical out-come [6]. The most frequent ones are listed in Table 5.23.1

Many genetic alterations involved in the development of nervous tissue tumours have been identified and are summarised in Table 5.23.2. Precise knowledge of these genetic lesions and may lead to novel therapeutic approaches, including gene therapy.

Cancer of the eye

Neoplasms of the eye are rare; the incidence is below 1/100 000 in all regions of the world, with the exception of Central and Southern Africa. The main histological types are squamous cell cancer arising from the conjunctiva; retinoblastoma, which arises in children and is relatively common in Africa; and uveal melanoma, which is the main adult type outside of Africa. Solar radiation and solar elastosis are causes of conjunctiva carcinoma [7]; the role of sun exposure in uveal melanoma is controversial. For instance, in populations where a sustained increase in cutaneous melanoma incidence is observed since several decades, the incidence of uveal melanoma remains quite constant. About 50% of cases of retinoblastoma are caused by an inherited mutation in the Rb gene.



Orange shading = carrier of CGG>TGG mutation in the p53 gene (resulting in a change of amino acid from arginine to tryptophan).

Fig. 5.23.5 *Pedigree of a family with Li-Fraumeni syndrome, caused by a germline mutation in codon 248 of the p53 tumour suppressor gene. Blood samples of affected family members have a mutation in one allele. In tumours, the second allele is usually deleted. This family shows a remarkable clustering of brain tumours*

REFERENCES

1. Boyle P, Smans M (2008). *IARC Scientific Publications, Number 159, Atlas of cancer mortality in the European Union and the European Economic Area 1993-1997*. Lyon, France: International Agency for Research on Cancer.

2. Fisher JL, Schwartzbaum JA, Wrensch M, et al. (2007). Epidemiology of brain tumors. *Neurol Clin* 25: 867-90, vii.

3. Lonn S, Klaeboe L, Hall P, et al. (2004). Incidence trends of adult primary intracerebral tumors in four Nordic countries. *Int J Cancer* 108: 450-455.

4. Jemal A, Siegel R, Ward E, et al. (2007). Cancer statistics, 2007. *CA Cancer J Clin* 57: 43-66.

5. Filippini G, Maisonneuve P, McCredie M, et al. (2002). Relation of childhood brain tumors to exposure of parents and children to tobacco smoke: the SEARCH international case-control study. Surveillance of Environmental Aspects Related to Cancer in Humans. *Int J Cancer* 100: 206-213.

6. Louis DN, Ohgaki H, Wiestler OD, et al. (2007). *World Health Organization classification of tumours of the central nervous system*. Lyon, France: International Agency for Research on Cancer.

7. Tulvatana W, Bhattarakosol P, Sansopha L, et al. (2003). Risk factors for conjunctival squamous cell neoplasia: a matched case-control study. *Br J Ophthalmol* 87: 396-398.

CANCER INSTITUTE PROFILE:
Centro Nacional de Investigaciones Oncologicas
(Spanish National Cancer Research Centre)

The Centro Nacional de Investigaciones Oncologicas (CNIO), located in Madrid, Spain, is fully dedicated to basic, translational and applied cancer research. Basic cancer research focuses on the molecular mechanisms of how genetic (oncogenes and tumour suppressors) and epigenetic events contribute to malignant transformation with special emphasis in the areas of genetic stability and proliferative signalling. Translational research is represented by the Molecular Pathology Programme that focuses primarily on lymphoma, lung, pancreas, bladder and melanoma, and the Human Cancer Genetics programme dedicated to studying inherited breast and endocrine tumours as well as the genetic epidemiology of bladder cancer. Bioinformatics and structural biology are also actively represented at the CNIO. Finally, we have seven research groups (four in biology and three in medicinal chemistry) fully dedicated to target-based drug discovery. A new programme on Cancer Cell Biology will be implemented during 2008. The CNIO also has eleven support units covering a wide range of technologies as well as a large barrier facility to house one of the largest collections in Europe of genetically engineered strains of mice. Scientific productivity at the CNIO for 2006–07 consists of 300 publications, of which 166 were generated at the CNIO and 134 were collaborations with other institutes. The average impact factor of these publications was 7.78 implying a total impact factor of 2335 (1397 for the publications generated at the CNIO).

website: www.cnio.es

5.24 Lymphoma

Summary

> Hodgkin lymphoma occurs mainly in young adulthood and then at old age. The main known cause of this disease is infection with Epstein-Barr virus.

> Non-Hodgkin lymphomas are a heterogeneous group of neoplasms with different causes and clinical behaviour. Their incidence has risen in recent decades but the increase has stopped since 2000: the causes of this trend are not known.

> Severe immunodeficiency, such as that occurring in AIDS patients, leads to non-Hodgkin lymphoma. Less severe forms of the immunological function alteration are likely to contribute to the burden of this disease.

> Several environmental factors, such as pesticides, have been suspected to cause lymphoma, but a causal link has not been confirmed.

The term lymphoma encompasses a diverse group of neoplasms which originate from the cells of the lymphopoietic system. Traditionally, two main groups of lymphomas have been distinguished including Hodgkin lymphoma (HL), characterised by large polynuclear cells named after Reed and Sternberg, and a diverse group of other neoplasms, defined as non-Hodgkin lymphoma (NHL). The complexity of lymphomas is reflected by the various classifications that have been used to separate different subtypes. The most recent World Health Organisation classification system [2] represents an effort to reach a consensus to allocate all lymphoma cases into clear categories. Neoplasms are divided between B and T cell lymphocytes, with over 20 different clinicopathological entities. Importantly, this classification incorporates all lymphoproliferative diseases, including multiple myeloma, B-cell acute lymphoblastic leukaemia, Burkitt lymphoma and HL.

Hodgkin lymphoma

The incidence of HL varies from low-incidence populations, with rates lower than 1/100 000, including areas of Southern and Eastern Asia and of Sub-Saharan Africa, to high-incidence populations, with rates in the order of 3/100 000 found in the USA and some European countries, as well as in Israeli Jews [3]. The incidence in men is consistently higher than in women, with a ratio of between 1.5 and 2. The incidence has been relatively stable over time and may even be declining. The age of onset of HL shows a bimodal distribution in high-resource populations, with a first peak between age 15 and 35 and a second peak after the age of 60. In low-resource countries the first peak tends to be observed during childhood. This bimodal distribution suggests that the HL includes at least two different entities.

Viral infections play an important role in the etiology of HL [4]. Its onset may be related to decreased or delayed exposure to infectious agents during childhood, as indicated by its association with having fewer siblings, living in single-family houses, and early birth order.

Infection with Epstein-Barr virus (EBV) is associated with the majority of HL cases. EBV is ubiquitous throughout the world, with 80–100% of individuals being infected by age 30 [5]. In low-resource countries infection occurs earlier in life, whereas in high-resource countries infection is often delayed until adolescence. The EBV genome is present in about 50% of the lymphoma cells of cases, and another EBV-related condition, infectious mononucleosis, is associated with a moderately elevated risk of development of HL. Sero-epidemiological studies indicate that patients with HL can be distinguished by an altered antibody profile to EBV.

A type 2 immune environment (predominance of Th2 cytokines and chemokines, and in particular of interleukin 13) is present in HL, but its etiological role is unclear. Patients suffering from immunodeficiences or autoimmune diseases are at increased risk of HL. A link between HL and lifestyle and environmental (e.g. occupation) factors has not been established. HL patients have an increased familial risk of HL and NHL, but this evidence is not supported by the identification of genetic variants at increased risk.

Non-Hodgkin lymphoma

The incidence of NHL is higher than the incidence of HL. Rates of over 10/100 000 are reported from the USA, Australia, Western Europe, and from Israel and the West Asia, while low rates of less than 5/100 000 are reported in Southern and Eastern Asia and parts of Africa [3]. Men have a 1.5–2 fold higher incidence than women. There is a strong geographical variation for some lymphoma subgroups. For example, Burkitt lymphoma is common among children in eastern Africa, and rates of adult T-cell leukaemia/lymphoma are increased in southern Japan and parts of Africa. The trend by age of NHL, on the other hand, shows a steady increase with age in most populations. Exceptions are the populations in which a specific type of lymphoma predominates, such as Burkitt lymphoma in children.

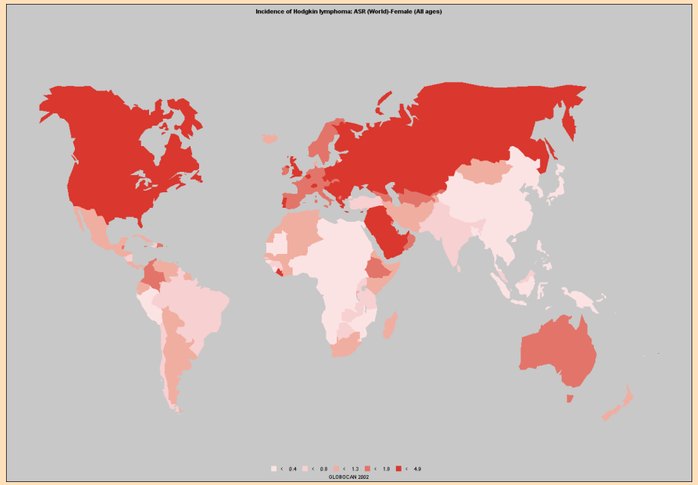
An increase in the incidence of NHL was observed in most high-resource countries until the end of the 20th century. The rate of increase was approximately 4% per year in most populations. In the last few years, however, this increase has levelled off. The reasons for the increase in NHL incidence have been widely discussed, and it is possible that improvement in diagnostic procedures during the 1980s and 1990s explains part of it, in particular in the elderly. However, it is now accepted that the trend also reflected a real increase in the number of cases, the causes of which are not known.

Fig. 5.24.1 *Classical Hodgkin lymphoma. Spleen*

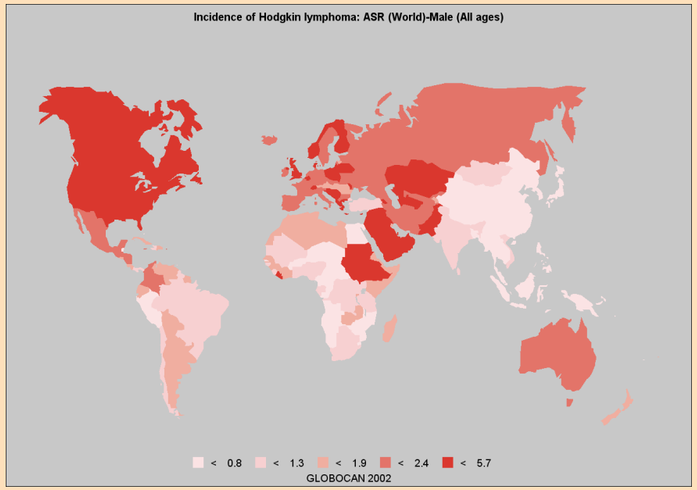
The current knowledge of potential risk factors for NHL is limited [6]. However, there is strong evidence that altered immunological function, either immunostimulation or immuno-suppression, entails an increased risk of NHL. For example, immunosuppressed renal transplant patients have a risk 30 times higher for developing NHL compared to the general population. Lymphomas that develop in immunosuppressed patients share common characteristics. They are generally high-grade B-cell lymphomas and are more likely to be extranodal and of worse prognosis. Lymphomas have also been reported for a variety of other conditions which are either auto-immune in nature, or require immunosuppressive treatment, including Sjögren syndrome and systemic lupus erithematosous.

Infectious agents associated with lymphoma include HIVuman T-cell lymphotropic virus 1 EBV and HCV. Human T-cell lymphotropic virus-2 and human herpes viruses 6 and 8 have also been linked to the development of NHL. In addition, infection with *Helicobacter pylori* is a risk factor for gastric lymphoma.

EBV is particularly prominent in lymphomas developing in immunosuppressed patients, and also in Burkitt lymphomas. The relationship with other forms of lymphoma is, however, unclear. Regarding HIV, NHL is 60 times more frequent among patients with AIDS than in the general population[7]. About 3% of patients with AIDS developed NHL, which represents a small contribution to the overall incidence of NHL, except in populations with a high HIV prevalence such as regions of sub-Saharan Africa. AIDS-related lymphomas tend to be high-grade B-cell lymphomas.



World Map 5.24.1



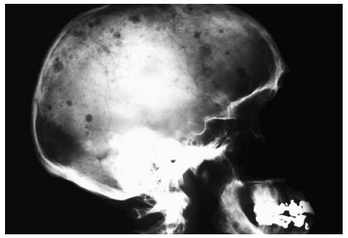
World Map 5.24.2

Human T-cell lymphotropic virus-1, and possibly human T-cell lymphotropic virus-2, appear to be associated with the rare adult T-cell leukaemia/lymphoma, a disease entity with strong geographical clustering in Japan, the Caribbean and parts of Africa. Transmission of the human T-cell lymphotropic virus is similar to that of HIV, involving vertical (mother-to-child) transmission, sexual contact or blood transfusion.

A familial aggregation is present for lymphoma: the risk of the disease among first-degree relatives of cases has been reported in the order of 1.5–4. However, the risk seems higher for siblings of the same sex, suggesting a role of shared environmental factors rather than genetics. Highly penetrant genetic predisposition to lymphomas is not very common but includes ataxia telangiectasia, Wiskott-Aldrich syndrome and hypogammaglobulinemia. Approximately 25% of the patients with rare forms of genetic immunodeficiency will develop a lymphoma.

The increasing recreational exposure to ultraviolet radiation in some populations and the decrease in the atmospheric ozone layer have been related to the observed increase in the incidence of NHL, but this hypothesis has not been supported by analytical studies, which, if anything, showed a decreased risk of lymphoma for high UV exposure [8].

Exposure to pesticides has been associated with NHL risk in studies conducted both on manufacturing workers and applicators in agriculture [9]. The results, however, are not very compelling, with the possible exception of phenoxy herbicides and chlorophenols. This effect might be due to contamination with dioxin. Farming as an occupation has also been weakly associated with lymphoma risk. Organic solvents represent another group of chemicals whose association with lymphoma risk has been widely investigated, without conclusive findings.



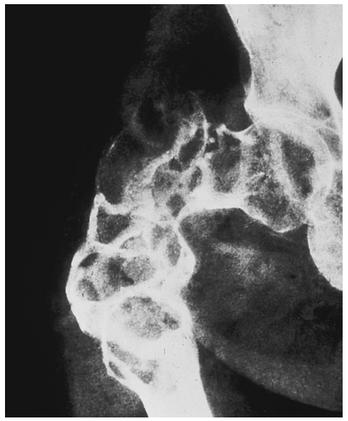
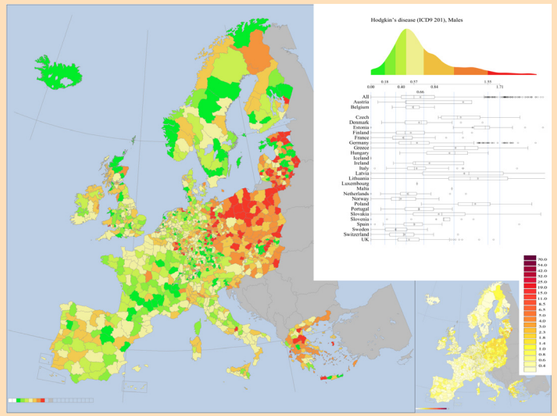
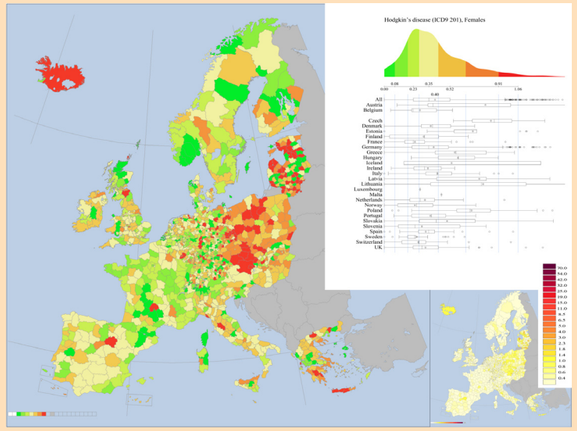


Fig. 5.24.2 *Radiographs of (A) skull and (B) femoral head demonstrate multiple lytic bone lesions*



European Map 5.24.1 *In men, the highest national mortality rates from Hodgkin Lymphoma were in Lithuania (1.4), Poland (1.4), Estonia (1.3), Latvia (1.2), Austria (1.2), the Czech Republic (1.2) and Greece (1.1). The lowest national rates were recorded in Sweden (0.3), Norway (0.4), France (0.4) and Switzerland (0.4). No deaths were recorded from this cause among males in Iceland during this period [1].*



European Map 5.24.2 *In females, the highest mortality rates from Hodgkin Lymphoma were in the Czech Republic (0.8), Austria (0.8), Lithuania (0.8), Latvia (0.8), Estonia (0.7) and Poland (0.7). Rates in most of the other countries were 0.2 to 0.4 per 100 000 [1].*

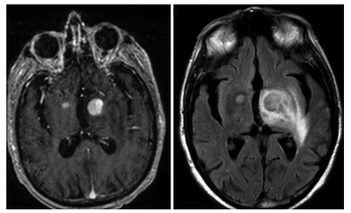
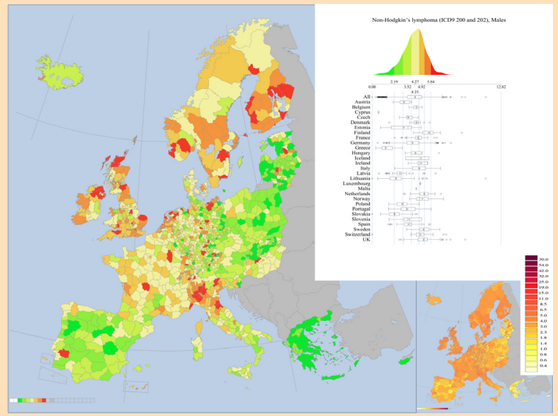
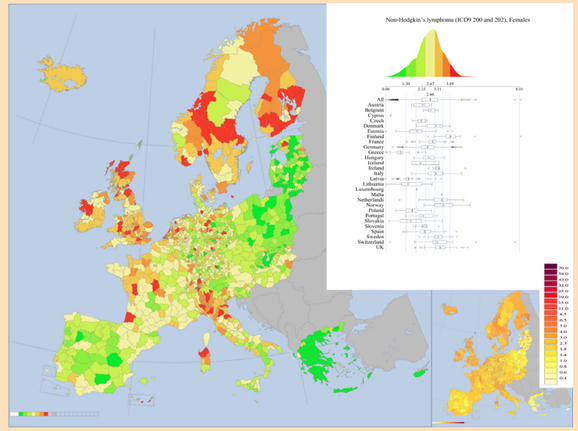


Fig. 5.24.3 *Nuclear magnetic resonance imaging (MRI) of CNS DLBCL. T1 after gadolinium injection (A) and fluid attenuated inversion recovery (FLAIR) sequences (B). There are two enhancing mass lesions in the basal ganglia.*



European Map 5.24.3 *In men, there were high regional mortality rates from Non-Hodgkin Lymphoma in the south of Norway, Sweden and Finland, in the United Kingdom and in northern Italy. There were aggregations of low rates in the Baltic Countries, much of central Europe including Austria, and southern Italy, Spain, Portugal and Greece [1].*



European Map 5.24.4 *The broad geographical pattern of the variability in mortality rates from Non-Hodgkin Lymphoma in women was very closely similar to that for men, with high regional rates in parts of Norway, Sweden and Finland, in the United Kingdom, and northern, but not southern, Italy. There were aggregations of low rates in central and southern Europe [1].*

PRECURSOR LYMPHOID NEOPLASMS	
B lymphoblastic leukaemia/lymphoma	
B lymphoblastic leukaemia/lymphoma, NOS	9811/3
B lymphoblastic leukaemia/lymphoma with recurrent genetic abnormalities	
B lymphoblastic leukaemia/lymphoma with t(9;22)(q34;q11.2); *BCR-ABL1*	9812/3
B lymphoblastic leukaemia/lymphoma with t(v;11q23); *MLL* rearranged	9813/3
B lymphoblastic leukaemia/lymphoma with t(12;21)(p13;q22); *TEL-AML1(ETV6-RUNX1)*	9814/3
B lymphoblastic leukaemia/lymphoma with hyperdiploidy	9815/3
B lymphoblastic leukaemia/lymphoma with hypodiploidy (hypodiploid ALL)	9816/3
B lymphoblastic leukaemia/lymphoma with t(5;14)(q31;q32); *IL3-IGH*	9817/3
B lymphoblastic leukaemia/lymphoma with t(1;19)(q23;p13.3); *E2A-PBX1(TCF3-PBX1)*	9818/3
T lymphoblastic leukaemia/lymphoma	9837/3
MATURE B-CELL NEOPLASMS – The most important types are:	
Chronic lymphocytic leukaemia/ small lymphocytic lymphoma	9823/3
Hairy cell leukaemia	9940/3
Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)	9699/3
Nodal marginal zone lymphoma	9699/3
Follicular lymphoma	9690/3
Mantle cell lymphoma	9673/3
Diffuse large B-cell lymphoma (DLBCL), NOS	9680/3
Burkitt lymphoma	9687/3
MATURE T-CELL AND NK-CELL NEOPLASMS	
T-cell prolymphocytic leukaemia	9834/3
T-cell large granular lymphocytic leukaemia	9831/3
Chronic lymphoproliferative disorder of NK-cells	9831/3
Aggressive NK cell leukaemia	9948/3
Systemic EBV positive T-cell lymphoproliferative disease of childhood	9724/3
Hydroa vacciniforme-like lymphoma	9725/3
Adult T-cell leukaemia/lymphoma	9827/3
Extranodal NK/T cell lymphoma, nasal type	9719/3
Enteropathy-associated T-cell lymphoma	9717/3
Hepatosplenic T-cell lymphoma	9716/3
Subcutaneous panniculitis-like	
T-cell lymphoma	9708/3
Mycosis fungoides	9700/3
Sézary syndrome	9701/3
Primary cutaneous CD30 positive T-cell lymphoproliferative disorders	
Lymphomatoid papulosis	9718/1
Primary cutaneous anaplastic large cell lymphoma	9718/3
Primary cutaneous gamma-delta T-cell lymphoma	9726/3
Primary cutaneous CD8 positive aggressive epidermotropic cytotoxic T-cell lymphoma	9709/3
Primary cutaneous CD4 positive small/medium T-cell lymphoma	9709/3
Peripheral T-cell lymphoma, NOS	9702/3
Angioimmunoblastic T-cell lymphoma	9705/3
Anaplastic large cell lymphoma, *ALK* positive	9714/3
Anaplastic large cell lymphoma, ALK negative	9702/3
HODGKIN LYMPHOMA	
Nodular sclerosis classical	
Hodgkin lymphoma	9663/3
Lymphocyte-rich classical	
Hodgkin lymphoma	9651/3
Mixed cellularity classical	
Hodgkin lymphoma	9652/3
Lymphocyte-depleted classical	
Hodgkin lymphoma	9653/3

Table 5.24.1 *WHO Classification of Tumours*

REFERENCES

1. Boyle P, Smans M (2008). *IARC Scientific Publications, Number 159, Atlas of cancer mortality in the European Union and the European Economic Area 1993-1997*. Lyon, France: International Agency for Research on Cancer.

2. Jaffe ES, Harris NL, Stein H, et al. (2001). *World Health Organization classification of tumours. Pathology and genetics of tumours of haematopoietic and lymphoid tissues*. Lyon, France: International Agency for Research on Cancer.

3. Parkin DM, Whelan SL, Ferlay J, et al. (2002). *IARC Scientific Publications, Number 155, Cancer incidence in five continents, Volume VIII*. Lyon, France: International Agency for Research on Cancer.

4. Mueller NE, Grufferman S (2006). Hodgkin's lymphoma. In: Schottenfeld D, Fraumeni JF, eds., *Cancer epidemiology and prevention*. New York: Oxford University Press 872-897.

5. IARC (1997). *IARC monographs on the evaluation of carcinogenic risks to humans, Volume 70, Epstein-barr virus and kaposi's sarcoma herpesvirus/human herpesvirus 8*. Lyon, France: International Agency for Research on Cancer.

6. Hartge P, Bracci PM, Wang SS, et al. (2006). Non Hodgkin's Lymphoma. In: Schottenfeld D, Fraumeni JF, eds., *Cancer epidemiology and prevention*. New York: Oxford University Press. 898-918.

7. IARC (1996). *IARC monographs on the evaluation of carcinogenic risks to humans, Volume 67, Human immunodeficiency viruses and human t-cell lymphotropic viruses*. Lyon, France: International Agency for Research on Cancer.

8. Armstrong BK and Kricker A (2007). Sun exposure and non-Hodgkin lymphoma. *Cancer Epidemiol Biomarkers Prev* 16: 396-400.

9. Boffetta P and de Vocht F (2007). Occupation and the risk of non-Hodgkin lymphoma. *Cancer Epidemiol Biomarkers Prev* 16: 369-372.

5.25 Leukaemias

Summary

> Recognised risk factors for leukaemias are ionizing radiation, alkylating agents used in chemotherapy, and occupational benzene exposure. However, the etiology of most leukaemias is not known. Familial clustering is seen in 5% of cases of chronic lymphoblastic leukaemia

> Chronic myeloid leukaemia was one of the first cancers to be linked to an acquired genetic abnormality, translocation (9;22), known as the Philadelphia chromosome

> Due to differing access to treatment, there is considerable global variation in survival. Among men in the USA and Western Europe, 5-year survival is at 43%; in Eastern Europe, 29%; Japan, 25%; India, 19%; South America, 24%; Thailand, 15%; and in sub-Saharan Africa, 14%

> In recent decades, there has been considerable progress in the development of treatments for leukaemia. In areas with good access to these treatments, 5-year survival in children has reached 80%

Leukaemias arise in one of the types of white blood cells. They may arise in lymphoblasts, which are lymphoid cells in the early stage of development, resulting in a rapid-onset illness termed acute lymphoblastic leukaemia. Alternatively, when the neoplasm involves mature cells, it is termed chronic lymphocytic leukaemia and is usually more indolent. In the WHO classification, chronic lymphocytic leukaemia is part of NHL [2]. Leukaemias may also be granulocytic in origin, occurring in either young myeloblastic cells resulting in acute myeloid leukaemia, or in the mature granulocytes resulting in chronic myeloid leukaemia. There also exist several rarer varieties including monocytic and hairy cell leukaemias.

Epidemiology

Acute lymphoblastic leukaemia is the most common childhood cancer, while over 80% of lymphoid leukaemias occurring in adulthood are chronic lymphocytic leukaemia. Incidence rates for chronic lymphocytic leukaemia are difficult to interpret because it is often diagnosed incidentally or in the course of evaluating other conditions. Differences in medical care may therefore substantially bias incidence data. Bearing this possible ascertainment bias in mind, the highest rates of lymphoid leukaemias are observed in areas of Canada, the USA, Western Europe and Oceania, and the lowest are in South America, the Caribbean, Asia and Africa. Rates tend to be lower in females although the ratio is usually less than 2. Some increases in leukaemia over time have been reported, although the extent to which these represent real increases in incidence is unclear. Some increasing incidence trends have been reported for both chronic and acute myeloid leukaemia, although these are not consistent and may simply reflect changes in clinical practice.

Etiology

Although the cause of most leukaemias is not known, there is consistent evidence for three factors, namely ionizing radiation, alkylating agents used in chemotherapy, and occupational benzene exposure [3]. Leukaemia was the first cancer to be linked to ionizing radiation after the atomic bombings in Hiroshima and Nagasaki. Excess incidences have been observed for acute lymphoblastic leukaemia, acute myeloid leukaemia and chronic myeloid leukaemia, but not for chronic lymphocytic leukaemia. Cohorts of patients who have received radiotherapy for both malignant and non-malignant conditions have also been found to be at an increased risk of leukaemia, usually myeloid. Whether there is any increased risk of leukaemia from other sources, including low-level diagnostic radiation, occupational exposure in the nuclear industry for workers and their offspring, or nuclear test explosions, is more contentious. Part of the problem lies in extrapolating from high acute doses experienced in particular circumstances like atomic bombing, to small or chronic exposures in other instances. There is no consistent evidence that exposure to electromagnetic fields is associated with leukaemia risk (see Chapter 2.12).

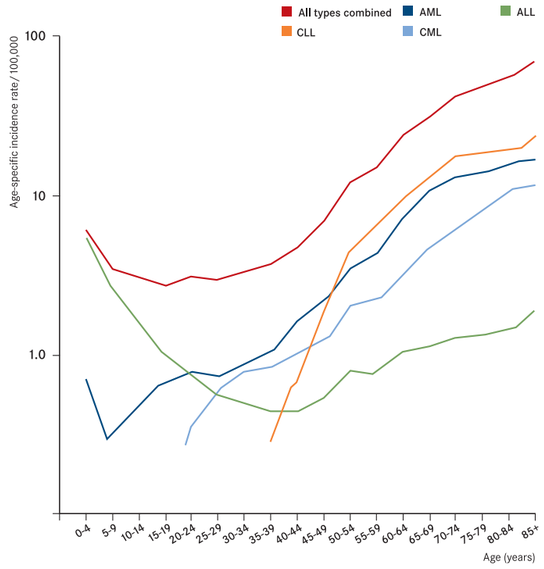
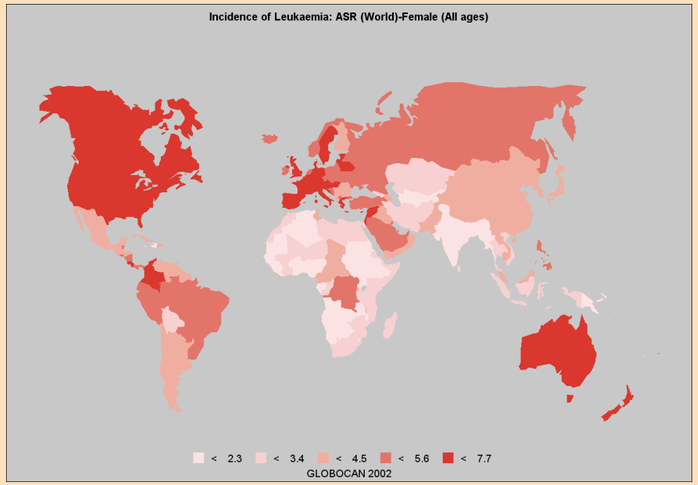


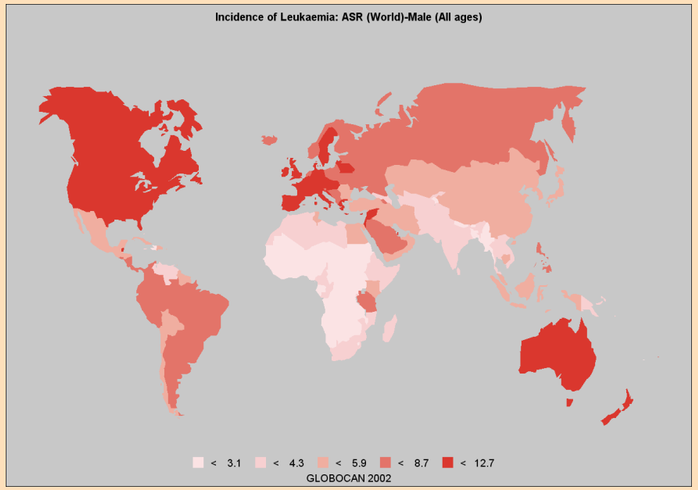
Fig. 5.25.1 *Age-specific incidence rates in the USA of leukaemia overall and of different subtypes. AML = acute myeloid leukaemia, ALL = acute lymphoblastic leukaemia, CLL = chronic lymphocytic leukaemia, CML = chronic myelogenous leukaemia. Note the high incidence of ALL in children*

Some leukaemias are also related to, or induced by therapy for a prior malignancy, most notably Hodgkin Lymphoma. Such patients have a 20–40 fold increased risk of leukaemia, most of which are acute myeloid leukaemia. The risk appears to be related to chemotherapy including alkylating agents (the majority being combination therapy with MOPP (mustargen, oncovin (vincristine), procarbazine, prednisone)). The effect is greater when patients are treated with both chemotherapy and radiotherapy, although whether an independent effect exists for radiotherapy is unclear. Other chemotherapy regimes which appear to be associated with acute myeloid leukaemia are those which contain the epipodophyllotoxin drugs teniposide and etoposide.

Occupational benzene exposure is also a recognized cause of leukaemia, in particular for acute myeloid leukaemia. An increased risk of between 3- and 5-fold has been observed in several occupational cohorts of workers following exposure to high levels of benzene, as has occurred in the past in shoe manufacturing, rubber manufacturing and printing. This type of leukaemia is fre-



World Map 5.25.1



World Map 5.25.2

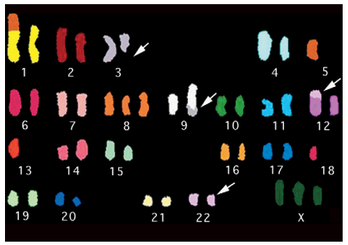


Fig. 5.25.2 *Spectral karyotyping of a chronic myeloid leukaemia case reveals a variant Philadelphia chromosome involving translocations between chromosomes 3, 9, 12 and 22. Secondary changes involving chromosomes 1, 5, 8, 18 and X are also seen, indicating advanced disease*

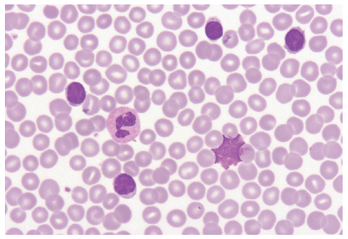
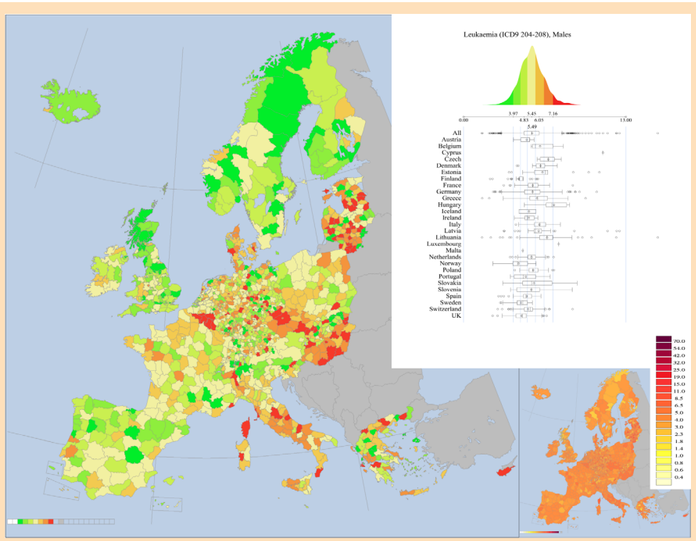


Fig. 5.25.3 *CLL in the peripheral blood. The CLL lymphocytes are small, round, with distinct clumped chromatin. Smudge cells are commonly seen*



European Map 5.25.1 *In men, the features of the geographic distribution of leukaemia mortality are the generally low rates in the Nordic countries and most of the United Kingdom and Ireland, and the areas of above-average rates in parts of the Baltic countries (particularly Lithuania), the Czech Republic and Hungary, southern Belgium and Luxembourg, and central and northern Italy [1].*

quently preceded by aplastic anemia. The role of low-dose exposure remains unclear. Tobacco smoking is a cause of acute myeloid leukaemia, possibly because of the relatively high levels of benzene present in the smoke.

Detection

Myelogenous leukaemias are characterised by an increase in the number of myeloid cells in bone marrow and blood, with resulting anemia, leukopenia and thrombocytopenia. At presentation, fatigue, night sweats, weight loss, and splenomegaly may be seen in both chronic and acute myeloid leukaemia. Patients with acute disease may also present with bruising or hemorrhage and have an increased risk of infection, with spleen and liver enlargement seen more rarely.

In high-resource settings, the majority of patients with chronic lymphoblastic leukaemia are diagnosed incidentally when a complete blood count obtained for other purposes is found to contain an elevated absolute lymphocyte count (>5000/μl). If not diagnosed incidentally, the most common symptoms are lymph node swelling with recurring infections; other abnormalities include enlarged spleen or liver, anaemia or thrombocytopenia, severe night sweats, and weight loss [4]. Patients with acute lymphoblastic leukaemia experience more rapid onset of these symptoms and may also exhibit bruising, bleeding or fever. Other possible symptoms seen in acute lymphoblastic leukaemia are bone pain, particularly in children, and central nervous system involvement.

Pathology and genetics

Nearly all chronic myeloid leukaemia arises from an acquired genetic abnormality, translocation t(9;22), in a bone marrow stem cell, known as the Philadelphia chromosome. This translocation results when the *ABL* gene from chromosome 9 merges with the *BCR* gene on chromosome 22, resulting in a *BCR-ABL* fusion gene on 22q11 that encodes for uncontrolled tyrosine kinase activity. The Philadelphia chromosome is additionally seen in one fourth of adult acute lymphoblastic leukaemia.

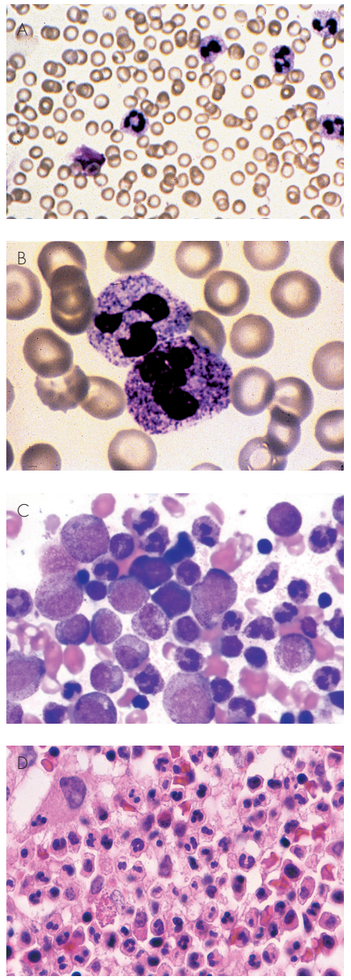
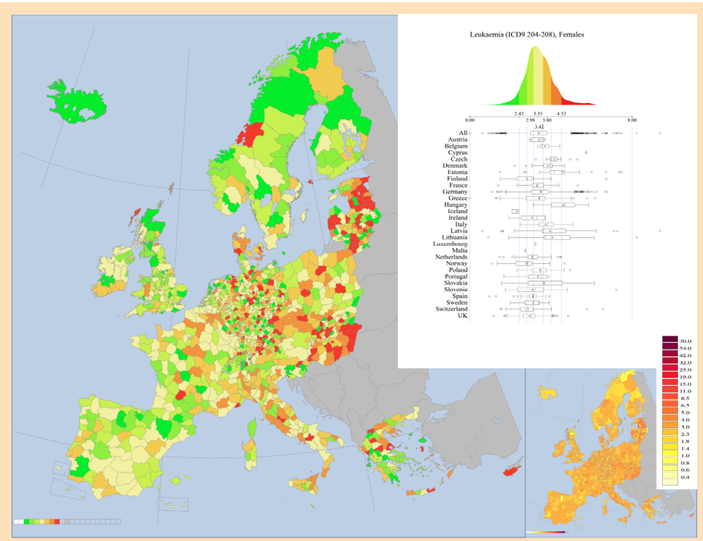


Fig. 5.25.4 *Chronic neutrophilic leukaemia. A The neutrophilia characteristic of the peripheral blood in CNL. B The toxic granulation commonly observed. C The bone marrow aspirate smear demonstrates neutrophil proliferation from myelocytes to segmented forms with toxic granulation, but no other significant abnormalities. D The bone marrow biopsy specimen is hypercellular, showing a markedly elevated myeloid: erythroid ratio with increased numbers of neutrophils, particularly mature segmented forms*



European Map 5.25.2 *The patterns in the variability in the rates of leukaemia mortality in women were closely similar to those in men: generally low rates in the Nordic countries (except Denmark) and the United Kingdom, and areas of high rates in the Baltic countries, the Czech Republic and Hungary [1].*

Acute myeloid leukaemia is a heterogeneous disease with regards to chromosome aberrations and clinical features. Broadly, this malignancy can be differentiated into three groups based on cytogenetics: the first group, comprising <15% of cases, includes generally younger patients who have more favourable chromosome abnormalities including inv(16), t(8;21), t(15;17) and t(16;16). These individuals respond well to specific chemotherapy regimens. The next group, comprising a nearly a third of patients, many of whom are older, have unfavourable cytogenetic profiles including deletions of the long arms of chromosomes 5 and 7 or complex karyotypes. The remaining intermediate prognosis group is comprised of persons with all other aberrations [5].

Chronic lymphocytic leukaemia is characterised by a proliferation of CD5 surface antigen-expressing B cells, and has been associated with a precursor condition, monoclonal B-cell lymphocytosis. Although specific susceptibility genes have yet to be identified for chronic lymphocytic leukaemia, familial aggregation is found among approximately 5% of cases [6]. Chromosomal abnormalities are common in CLL, with the most frequently documented being an interstitial deletion in 13q14 (>50% of cases), which is associated with a more favourable prognosis [7]. Aberrations associated with intermediate survival are trisomy 12 (15-20% of cases), while poorer survival is seen with del(11q), involving *ATM* (15-30%), and del(17p), involving P53 (10–20%) [7,8].

The importance of mutations in *IgVH* as a prognostic indicator has been recently recognised, with the presence of unmutated genes signifying a poorer cytogenetic profile and more advanced disease [8].

Acute lymphoblastic leukaemia is characterised by clonal expansion of lymphoblasts, either B-cell (80%) or T-cell phenotype. B-cell immunophenotypic subtypes exhibit a variety of genetic abnormalities. Multiple molecular pathways are involved in pathogenesis. Common genetic alterations include hyperdiploidy and translocations *(BCR-ABL, E2A-PBX1, TCR)* [9]. Among T-cell acute lymphoblastic leukaemia patients, half have a normal karyotype, while recurrent translocations are seen in one third of patients.

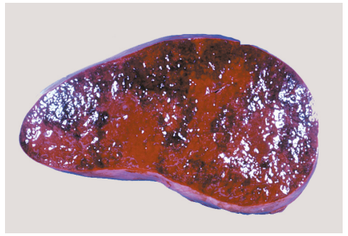


Fig. 5.25.5 *Splenomegaly in CML. The gross appearance of the spleen is solid and uniformly deep red, although areas of infarct may appear as lighter coloured regions*

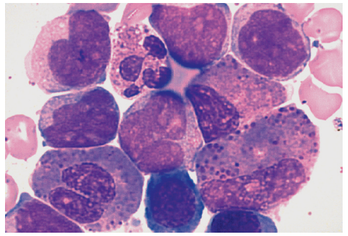


Fig. 5.25.6 *Acute myeloid leukaemia with associated inv(16)(p13.1q22). Abnormal eosinophils, one with large basophilic coloured granules, are present*

Management

In the last 50 years, marked improvements in the management of leukaemia have resulted in increasing survival among patients with leukaemia. Advances in treatment have contributed to 5-year survival reaching 80% among children [10]. The treatment process involves a cytogenetic workup, as this are used to select the treatment course. Supportive care is often required to manage the sequelae of myelosuppression and of severe, life-threatening infections.

For acute leukaemias, treatment strategy should include control both of systemic disease (bone marrow, liver) and central nervous system-directed therapy. Treatment choice and intensity is guided by risk stratification, which is determined by age and specific clinical and biologic markers. Current therapeutic regimens involve induction of remission using specific chemotherapy regimens, followed by consolidation or intensification of treatment, and with acute lymphoblastic leukaemia, are then followed by maintenance therapy. For ALL, induction therapy includes a glucocorticoid, vincristine, an anthracycline and possibly PEG-asparaginase [11]. Postremission therapies consist of chemotherapy and, if indicated, hematopoietic stem cell transplantation [12]. Minimal residual disease burden should be determined after initial treatment to assess treatment response.

Treatment of chronic leukaemias ranges from palliative care to a variety of therapies. Chronic lymphocytic leukaemia usually occurs in elderly patients and is not curable, and consequently is frequently treated conservatively. With the exception of patients with p53 mutations, treatment is not indicated for early-stage asymptomatic chronic lymphocytic leukaemia, as there is no evidence that treatment improves survival [13]. With advanced chronic lymphocytic leukaemia, the recommended first-line treatment is fludarabine in combination with cyclophosphamide [14]. At the present time, alemtuzumab, rituximab and autologous stem cell transplant are among the second-line treatments which appear promising [15]. The tyrosine kinase inhibitor Gleevec (imatinib mesylate) is the first-line therapy for chronic myeloid leukaemia. If resistance is seen, clinical strategies may involve imatinib dose escalation, interferon-α or several emerging therapies [16].

Given differing access to treatment due to cost, survival rates vary considerably between developed and developing countries. Survival rates for all leukaemias in the USA and Western Europe (43% among men and 45% among women) are the highest, while rates lag considerably in Eastern Europe (29% among both men and women), Japan (25% men, 29% women), India (19% among both), South America (24% among both), Thailand (15% among both) and sub-Saharan Africa (14% men, 17% women) [17]. Rates differ by condition. In the USA, 5-year survival rates in adults are 60% for acute lymphoblastic leukaemia and 75% for chronic lymphocytic leukaemia; lower survival rates are seen with acute myeloid leukaemia (17%) and chronic myeloid leukaemia (40%) [18].

WHO Classification of tumours of haematopoietic and lymphoid tissues

MYELOPROLIFERATIVE NEOPLASMS

- Chronic myelogenous leukaemia, *BCR-ABL1* positive
- Chronic neutrophilic leukaemia
- Polycythaemia vera
- Primary myelofibrosis
- Essential thrombocythaemia
- Chronic eosinophilic leukaemia, NOS
- Mastocytosis :
  - Cutaneous mastocytosis
  - Systemic mastocytosis
  - Mast cell leukaemia
  - Mast cell sarcoma
  - Extracutaneous mastocytoma
- Myeloproliferative neoplasm, unclassifiable

MYELOID AND LYMPHOID NEOPLASMS WITH EOSINOPHILIA AND ABNORMALITIES OF *PDGFRA, PDGFRB* OR *FGFR1*

- Myeloid and lymphoid neoplasms with *PDGFRA* rearrangement
- Myeloid neoplasms with *PDGFRB* rearrangement
- Myeloid and lymphoid neoplasms with *FGFR1* abnormalities

MYELODYSPLASTIC/MYELOPROLIFERATIVE NEOPLASMS

- Chronic myelomonocytic leukaemia
- Atypical chronic myeloid leukaemia, *BCR-ABL1* negative
- Juvenile myelomonocytic leukaemia
- Myelodysplastic/myeloproliferative neoplasm, unclassifiable
- *Refractory anaemia with ring sideroblasts associated with marked thrombocytosis*

MYELODYSPLASTIC SYNDROMES

- Refractory cytopenia with unilineage dyplasia
  - Refractory anaemia
  - Refractory neutropenia
  - Refractory thrombocytopenia
- Refractory anaemia with ring sideroblasts
- Refractory cytopenia with multilineage dysplasia
- Refractory anaemia with excess blasts
- Myelodysplastic syndrome associated with isolated del(5q)
- Myelodysplastic syndrome, unclassifiable
- Childhood myelodysplastic syndrome
- *Refractory cytopenia of childhood*

ACUTE MYELOID LEUKAEMIA (AML) AND RELATED PRECURSOR NEOPLASMS

- **AML with recurrent genetic abnormalities**
- AML with t(8;21)(q22;q22); *RUNX1-RUNX1T1*
- AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*
- Acute promyelocytic leukaemia with t(15;17)(q22;q12); *PML-RARA*
- AML with t(9;11)(p22;q23); *MLLT3-MLL*
- AML with t(6;9)(p23;q34); *DEK-NUP214*
- AML with inv(3)(q21q26.2) or t(3;3)(q21;q26.2); *RPN1-EVI1*
- AML (megakaryoblastic) with t(1;22)(p13;q13); *RBM15-MKL1*
- AML *with mutated NPM1*
- AML *with mutated CEBPA*
- **AML with myelodysplasia-related changes**
- **Therapy-related myeloid neoplasms**
- **Acute myeloid leukaemia, NOS**
- AML with minimal differentiation
- AML without maturation
- AML with maturation
- Acute myelomonocytic leukaemia
- Acute monoblastic and monocytic leukaemia
- Acute erythroid leukaemia
- Acute megakaryoblastic leukaemia
- Acute basophilic leukaemia
- Acute panmyelosis with myelofibrosis
- **Myeloid sarcoma**
- **Myeloid proliferations related to Down syndrome**
- Transient abnormal myelopoiesis
- Myeloid leukaemia associated with Down syndrome
- **Blastic plasmacytoid dendritic cell neoplasm**

ACUTE LEUKAEMIAS OF AMBIGUOUS LINEAGE

- Acute undifferentiated leukaemia
- Mixed phenotype acute leukaemia with t(9;22)(q34;q11.2); *BCR-ABL1*
- Mixed phenotype acute leukaemia with t(v;11q23); *MLL* rearranged
- Mixed phenotype acute leukaemia, B/myeloid, NOS
- Mixed phenotype acute leukaemia, T/myeloid, NOS
- *Natural killer (NK) cell lymphoblastic leukaemia/lymphoma*

PRECURSOR LYMPHOID NEOPLASMS

- **B lymphoblastic leukaemia/lymphoma**
- B lymphoblastic leukaemia/lymphoma, NOS
- B lymphoblastic leukaemia/lymphoma with recurrent genetic abnormalities
- B lymphoblastic leukaemia/lymphoma with t(9;22)(q34;q11.2); *BCR-ABL1*
- B lymphoblastic leukaemia/lymphoma with t(v;11q23); *MLL rearranged*
- B lymphoblastic leukaemia/lymphoma with t(12;21)(p13;q22); *TEL-AML1 (ETV6-RUNX1)*
- B lymphoblastic leukaemia/lymphoma with hyperdiploidy
- B lymphoblastic leukaemia/lymphoma with hypodiploidy (hypodiploid ALL)
- B lymphoblastic leukaemia/lymphoma with t(5;14)(q31;q32); *IL3-IGH*
- B lymphoblastic leukaemia/lymphoma with t(1;19)(q23;p13.3); *E2A-PBX1 (TCF3-PBX1)*
- **T lymphoblastic leukaemia/lymphoma**

MATURE B-CELL NEOPLASMS

- Chronic lymphocytic leukaemia/small lymphocytic lymphoma
- B-cell prolymphocytic leukaemia
- Splenic marginal zone lymphoma
- Hairy cell leukaemia
- *Splenic B-cell lymphoma/leukaemia, unclassifiable*
- *Splenic diffuse red pulp small B-cell lymphoma*
- *Hairy cell leukaemia-variant*
- Lymphoplasmacytic lymphoma
- Waldenström macroglobulinemia
- Heavy chain diseases
- Alpha heavy chain disease
- Gamma heavy chain disease
- Mu heavy chain disease
- Plasma cell myeloma
- Solitary plasmacytoma of bone
- Extraosseous plasmacytoma
- Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
- Nodal marginal zone lymphoma
- *Paediatric nodal marginal zone lymphoma*
- Follicular lymphoma
- *Paediatric follicular lymphoma*
- Primary cutaneous follicle centre lymphoma
- Mantle cell lymphoma
- Diffuse large B-cell lymphoma (DLBCL), NOS
- T-cell/histiocyte rich large B-cell lymphoma
- Primary DLBCL of the CNS
- Primary cutaneous DLBCL, leg type
- *EBV positive DLBCL of the elderly*
- DLBCL associated with chronic inflammation
- Lymphomatoid granulomatosis
- Primary mediastinal (thymic) large B-cell lymphoma
- Intravascular large B-cell lymphoma
- ALK positive large B-cell lymphoma
- Plasmablastic lymphoma
- Large B-cell lymphoma arising in HHV8-associated multicentric Castleman disease
- Primary effusion lymphoma
- Burkitt lymphoma
- B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma
- B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma

MATURE T-CELL AND NK-CELL NEOPLASMS

- T-cell prolymphocytic leukaemia
- T-cell large granular lymphocytic leukaemia
- *Chronic lymphoproliferative disorder of NK-cells*
- Aggressive NK cell leukaemia
- Systemic EBV positive T-cell lymphoproliferative disease of childhood
- Hydroa vacciniforme-like lymphoma
- Adult T-cell leukaemia/lymphoma
- Extranodal NK/T cell lymphoma, nasal type
- Enteropathy-associated T-cell lymphoma
- Hepatosplenic T-cell lymphoma
- Subcutaneous panniculitis-like T-cell lymphoma
- Mycosis fungoides
- Sézary syndrome
- Primary cutaneous CD30 positive T-cell lymphoproliferative disorders
- Lymphomatoid papulosis
- Primary cutaneous anaplastic large cell lymphoma
- Primary cutaneous gamma-delta T-cell lymphoma
- *Primary cutaneous CD8 positive aggressive epidermotropic cytotoxic T-cell lymphoma*
- *Primary cutaneous CD4 positive small/medium T-cell lymphoma*
- Peripheral T-cell lymphoma, NOS
- Angioimmunoblastic T-cell lymphoma
- Anaplastic large cell lymphoma, ALK positive
- *Anaplastic large cell lymphoma, ALK negative*

HODGKIN LYMPHOMA

- Nodular lymphocyte predominant Hodgkin lymphoma
- Classical Hodgkin lymphoma
- Nodular sclerosis classical Hodgkin lymphoma
- Lymphocyte-rich classical Hodgkin lymphoma
- Mixed cellularity classical Hodgkin lymphoma
- Lymphocyte-depleted classical Hodgkin lymphoma

Table 5.25.1 *WHO Classification of tumours of haematopoietic and lymphoid tissues*

WHO Classification of tumours of haematopoietic and lymphoid tissues

HISTIOCYTIC AND DENDRITIC CELL NEOPLASMS	
• Histiocytic sarcoma • Langerhans cell histiocytosis • Langerhans cell sarcoma • Interdigitating dendritic cell sarcoma	• Follicular dendritic cell sarcoma • Fibroblastic reticular cell tumour • Indeterminate dendritic cell tumour • Disseminated juvenile xanthogranuloma

POST-TRANSPLANT LYMPHOPROLIFERATIVE DISORDERS (PTLD)	
• Early lesions – Plasmacytic hyperplasia – Infectious mononucleosis-like PTLD • Polymorphic PTLD	• Monomorphic PTLD (B- and T/NK-cell types) • Classical Hodgkin lymphoma type PTLD

Table 5.25.1 *(cont.)*

REFERENCES

1. Boyle P, Smans M (2008). *IARC Scientific Publications, Number 159, Atlas of cancer mortality in the European Union and the European Economic Area 1993-1997*. Lyon, France: International Agency for Research on Cancer.

2. Swerdlow SH, Campo E, Lee Harris N, et al. (2008). *World Health Organization classification of tumours. Pathology and genetics of tumours of haematopoietic and lymphoid tissues*. Lyon, France: International Agency for Research on Cancer.

3. Linet MS, Schubauer-Berigan MK, Weisenburger DD, et al. (2007). Chronic lymphocytic leukaemia: an overview of aetiology in light of recent developments in classification and pathogenesis. *Br J Haematol* 139: 672-686.

4. Abbott BL (2006). Chronic lymphocytic leukemia: recent advances in diagnosis and treatment. *Oncologist* 11: 21-30.

5. Ferrara F, Palmieri S, Leoni F (2008). Clinically useful prognostic factors in acute myeloid leukemia. *Crit Rev Oncol Hematol* 66: 181-193.

6. Goldin LR and Slager SL (2007). Familial CLL: Genes and Environment. *Hematology Am Soc Hematol Educ Program* 2007: 339-345.

7. Caporaso N, Goldin L, Plass C, et al. (2007). Chronic lymphocytic leukaemia genetics overview. *Br J Haematol* 139: 630-634.

8. Montserrat E (2006). New prognostic markers in CLL. *Hematology Am Soc Hematol Educ Program* 279-284.

9. Jabbour EJ, Faderl S, Kantarjian HM (2005). Adult acute lymphoblastic leukemia. *Mayo Clin Proc* 80: 1517-1527.

10. Ries LAG, Smith MA, Gurney JG, et al. (1999). *Cancer Incidence and Survival among Children and Adolescents: United States SEER Program 1975-1995*. Bethesda, MD: National Cancer Institute, SEER Program.

11. Pui CH and Jeha S (2007). New therapeutic strategies for the treatment of acute lymphoblastic leukaemia. *Nat Rev Drug Discov* 6: 149-165.

12. Estey E and Dohner H (2006). Acute myeloid leukaemia. *Lancet* 368: 1894-1907.

13. Chemotherapeutic options in chronic lymphocytic leukemia: a meta-analysis of the randomized trials. CLL Trialists' Collaborative Group (1999). *J Natl Cancer Inst* 91: 861-868.

14. Flinn IW, Neuberg DS, Grever MR, et al. (2007). Phase III trial of fludarabine plus cyclophosphamide compared with fludarabine for patients with previously untreated chronic lymphocytic leukemia: US Intergroup Trial E2997. *J Clin Oncol* 25: 793-798.

15. Auer RL, Gribben J, Cotter FE (2007). Emerging therapy for chronic lymphocytic leukaemia. *Br J Haematol* 139: 635-644.

16. Jabbour E, Cortes JE, Giles FJ, et al. (2007). Current and emerging treatment options in chronic myeloid leukemia. *Cancer* 109: 2171-2181.

17. Parkin DM, Bray F, Ferlay J, et al. (2005). Global cancer statistics, 2002. *CA Cancer J Clin* 55: 74-108.

18. Ries LAG, Young JL, Keel GE, et al. (2007). *SEER Survival Monograph: Cancer Survival Among Adults: U.S. SEER Program, 1988-2001, Patient and Tumor Characteristics*. Bethesda, MD: National Cancer Institute, SEER Program.

5.26 Cancer in Children

Summary

- Cancer in children is rare and specific in its occurrence, pathology, detection, treatment and outcome
- Most common cancers in childhood comprise leukaemia, lymphoma and brain tumours, with varying ranks across different populations
- Little is known about the etiology of childhood cancers, and the few established causal associations only explain a small proportion of cases
- Good long-term survival is achieved in the most developed countries, while in many developing countries it is considerably poorer
- Current priorities for childhood cancer management aim at improvement of quality of life of the growing number of childhood cancer survivors

The term childhood cancer usually comprises all cancers arising in individuals before the age of 15 years. These tumours are rare, but present specific ethical, psychological and societal concerns. Histologically, childhood tumours are very variable and are classified into twelve major groups (Figure 5.26.1), further divided into 47 diagnostic subgroups according to the International Classification of Childhood Cancer [2].

Occurrence

In childhood populations of Europe, North America and other developed regions of the world, cancer incidence rates are around 140 per million [3]. Cancer incidence in the developing countries is less well known, because there have been too few efficient population-based cancer registries. Overall incidence rates for the most recent period evaluated systematically among the world populations are shown in Figure 5.26.2. In some developing countries, where the children comprise 40–50% of the population, the proportion of childhood cancers represents 3–10% of the total, whereas in the developed countries, it is less than 1%. Mortality patterns also differ. Cancer accounts for some 4–5% of childhood deaths in developed countries, (where it is the second-leading cause of death among children aged 1–14), and less than 1% in developing countries, where deaths from infectious diseases are much more prominent. Globally, some 160 000 new cases and 90 000 deaths of cancer in children under 15 years of age are estimated to occur each year [4].

The proportion and rank of various cancers varies between childhood populations around the world, as shown in Figure 5.26.2. The sample of the world populations was selected to illustrate the geographical variability and the pattern is not necessarily the same in the neighbouring countries. Overall, the most common cancer groups are leukaemia, lymphomas and central nervous system (CNS) tumours. Acute leukaemia is the most common form of cancer in most countries, especially in early childhood. Only in tropical Africa, lymphomas seem to be more common. In the developed countries, brain tumours generally account for one fifth to one quarter of childhood cancers. Their rarer registration in developing countries is at least partly due to under-diagnosis. Wilms tumour is very rare in Asian children, as is Ewing sarcoma of bone. Retinoblastoma appears to be rather more common in African children than elsewhere, while neuroblastoma appears to be very rare in central Africa. Black children are more prone than others to development of Wilms tumour and osteosarcoma. Generally very rare Burkitt lymphoma is one of the most commonly registered tumours in some countries of sub-tropical Africa [3].

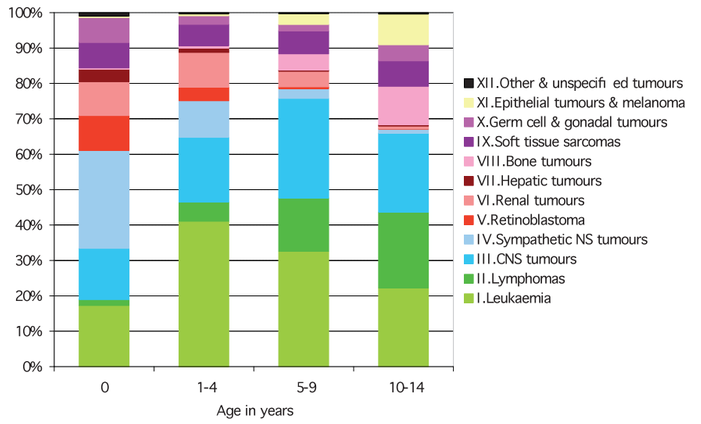


Fig. 5.26.1 *Composition of tumour types across childhood age groups. Based on the 51 395 cases of cancer registered in the European cancer registries in the 1970s–1990s and assembled in the ACCIS study [1] . NS, nervous system; CNS, central nervous system*

Pathology and genetics

Childhood cancers share a number of common characteristics which distinguish them from the tumours arising later in life. Typical tumours of childhood resemble embryonal tissues arrested at different stages of maturation (retinoblastoma, hepatoblastoma, Wilms tumour). The unique morphologic features of some childhood malignancies (clear cell sarcoma of kidney, malignant rhabdoid tumour, melanotic neuroectodermal tumour) are not generally encountered in those occurring in adults. Cancer in childhood is also typical by the frequent occurrence of the undifferentiated tumours, commonly referred to as "small round cell tumours" such as the Ewing family tumours, Burkitt lymphoma and several acute leukaemia types. Finally, childhood neoplasms are rarely preceded by precursor lesions [5].

Table 5.26.1 summarises selected identified genetic syndromes associated with childhood cancer, according to the review by Stiller in 2004 [6]. However, these genetic syndromes account for a very small proportion of the childhood cancer cases. Numerical chromosome abnormalities are also associated with childhood cancer. For example, Down syndrome (trisomy 21) appreciably increases the risk of acute lymphoblastic leukaemia (ALL) and acute myeloid leukaemia (AML) [6]. Recently, epigenetic alterations were implicated in the development of childhood neoplasms. An example is the loss of imprinting of IGF2, shown to be involved in the carcinogenesis of Wilms tumour [7].

Etiology

In general, little is known about etiological factors of childhood cancer, as most studies are limited in statistical power due to its rarity. Because of its onset early in life, exposure to environmental factors either *in utero* or after birth may be less determining than for cancers developing in adults. Only a few exposures, mostly exceptional, have been shown to cause cancer in children. For example, thyroid cancer has increased dramatically in the population of children living in the three countries surrounding Chernobyl, due to the radioactive fallout from the accident there [8]. A causal association has been shown between increased risk of cancer of the vagina in the female offspring of women who used a medication called diethylstilbestrol during their pregnancies to alleviate morning sickness in the 1970s [9]. In-utero diagnostic radiotherapy was associated with risk of childhood leukemia [10], but due to the substantially reduced doses used nowadays, the impact on incidence is undetectable.

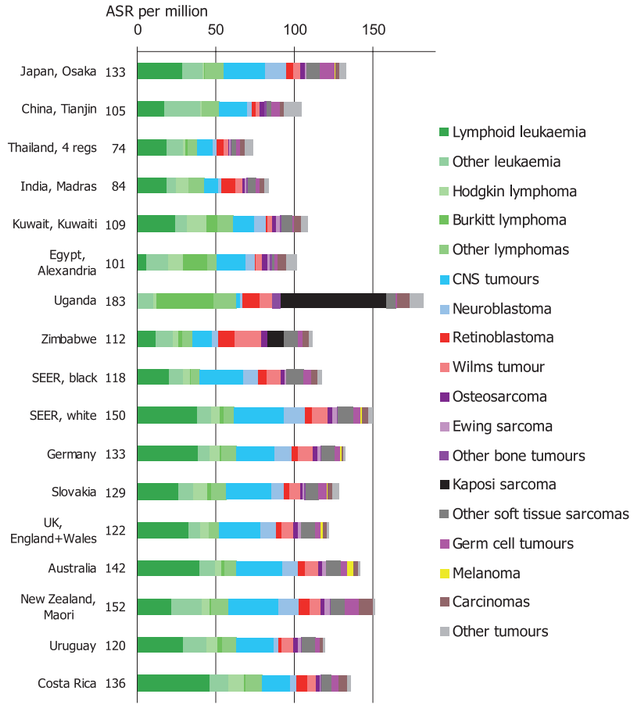


Fig. 5.26.2 *Cancer incidence rates in children aged 0–14 years in the countries shown in the 1980s and assembled in an international comparative study [3]. ASR, age-standardised incidence rate (world standard). CNS, central nervous system*

Syndrome	Locus	Gene	Childhood cancer
Some familial neoplastic syndromes			
Familial retinoblastoma	13q14	RB1	Retinoblastoma, osteosarcoma
Familial Wilms tumour	17q12-21	FWT1	Wilms tumour
Familial Wilms tumour 2	19q13	FWT2	Wilms tumour
Li-Fraumeni syndrome	17q13	TP53	Adrenocortical carcinoma,
	22q12	CHK2	Soft tissue sarcoma,
	22q11	SNF5	Osteosarcoma, central nervous system (CNS) tumours
Hereditary non-polyposis colon cancer	2p22-21	MSH2	Glioma
	3p21	MLH1	
	7p22	PMS2	
Familial adenomatous polyposis	5q21	APC	Medulloblastoma, hepatoblastoma
Gorlin syndrome	9q31	PTCH	Medulloblastoma, basal cell carcinoma
Neurofibromatosis type 1	17q11	NF1	Astrocytoma, juvenile myelomonocytic leukaemia (JMML), acute lymphoblastic leukaemia (ALL), rhabdomyosarcoma, malignant peripheral nerve sheath tumors (MPNST)
Neurofibromatosis type 2	22q12	NF2	Meningioma
Some inherited immunodeficiency and bone marrow failure syndromes			
Ataxia telangiectasia	11q22	ATM	Lymphoma, leukemia
Wiskott-Aldrich syndrome	Xp11	WAS	Non-Hodgkin lymphoma
Bloom syndome	15q26	BLM	Non-Hodgkin lymphoma, Wilms tumour, osteosarcoma
Nijmegen breakage syndrome	8q21	NBS1	Non-Hodgkin lymphoma
Fanconi anaemia	16q24	FANCA	Acute myeloid leukaemia (AML), hepatoma
Some other genetic syndromes			
Rothmund-Thomson syndrome	8p24	RECQL4	Osteosarcoma
WAGR syndrome	11p13	WT1	Wilms tumour
Denys-Drash syndrome	11p13	WT1	Wilms tumour
Beckwith-Wiedemann syndrome	11p15	Multiple genes	Wilms tumour, hepatoblastoma, neuroblastoma, pancreatoblastoma
Tuberous sclerosis	9q34	TSC1	Subependymal giant cell astrocytoma
	16p13	TSC2	

Table 5.26.1 *Genetic syndromes associated with childhood cancer [6]*

Pathogenesis of some childhood cancers involves both genetic changes and exogeneous risk factors. For example, the African type Burkitt lymphoma is associated with both the Epstein-Barr virus (EBV) and a chromosomal translocation deregulating expression of the c-myc oncogene [11]. Other co-factors, which must operate to activate the carcinogenic action of such a common infection as is the EBV might be the immuno-suppression caused by malaria, human immunodeficiency virus (HIV) infection or other conditions. In immuno-compromised children EBV is probably implicated also in Hodgkin disease, non-Hodgkin lymphomas, nasopharyngeal carcinoma and others.

Other risk factors have been studied, less conclusively. Childhood leukemia seems to be associated with high socioeconomic status, which might be a marker of yet-unidentified (cluster of) risk factors. Infection is suspected to play a role in the etiology of common childhood leukaemia, which may occur as an unusual response to a common infectious agent, as yet unidentified [12,13]. Additional hypotheses, concerning the timing of infections, or the presence of important co-factors, would be required to clarify the causal relationship.

A number of other risk factors have been studied to reveal their part in the causation of various childhood neoplasms, but the evidence is not decisive. The suspected exposures include non-ionising radiation, maternal smoking, alcohol consumption and diet, paternal occupation, exposure to various chemicals such as benzene, nitrosamines, pesticides, hair dyes and some medications, etc, and have been reviewed in several publications [6,14,15].

Detection

Many paediatric malignancies are seen predominantly in pre-school children, while others, such as non-Hodgkin lymphomas, most cases of Hodgkin disease, bone tumours and different epithelial tumours occur in older children and adolescents [Figure 5.26.1]. Cancer usually develops over a short time with no pre-cancerous stage, and it is often disseminated at diagnosis. Therefore, there is little room for implementation of screening practices. Screening for neuroblastoma, conducted nationally in Japan, and on population samples in Germany, France and the UK, did not reduce the mortality rate from this neoplasm. The increase in incidence in the screened population was thus due to over-diagnosis of non-symptomatic cases not necessarily requiring a treatment [16].

Being rare, detection of cancer in children often depends on the preparedness of primary health providers. In the poorest countries many cancers may remain undetected in children, due to the lack of training or experience of health professionals and paediatricians who are used to dealing primarily with infectious diseases. Other factors contributing to under-detection may be a preferential choice of a traditional healer and other traditional beliefs. In cancer registration data such prejudgments are reflected in a relative lack of infants among registered cases or excess registrations among boys as compared to girls [3].

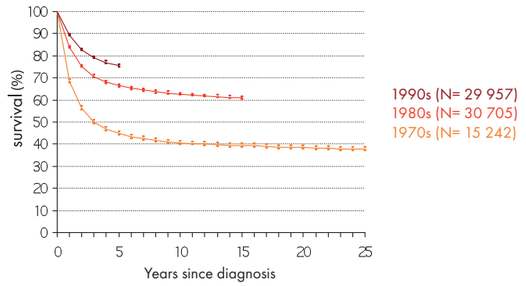


Fig. 5.26.3 *Survival of childhood cancer patients registered (age 0–14 years) during the periods shown in Western Europe and analysed in the ACCIS study [1]. 95% confidence intervals are represented by the dots around the yearly survival estimates. N, numbers of cases diagnosed in the period shown and followed up for 25, 15 and 5 years, respectively*

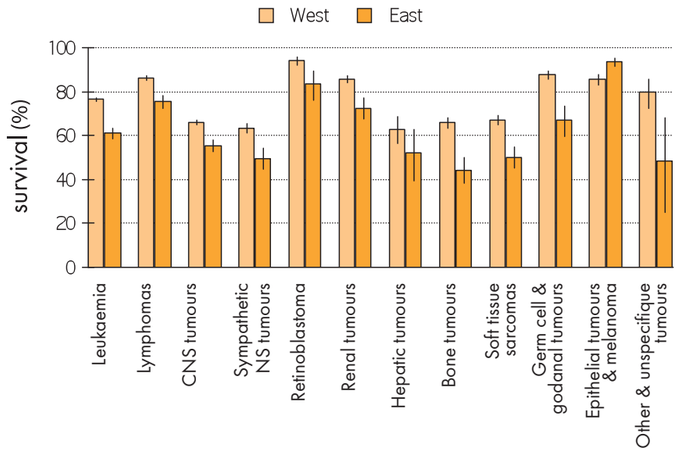


Fig. 5.26.4 *Five-year in survival from cancer in children aged 0–14 years registered during the 1990s in Europe and followed up for five years, according to the place of residence at diagnosis and the tumour type, as analysed in the ACCIS study [1]. CNS, central nervous system; NS, nervous system*

Continued development of non-invasive diagnostic methods, such as computerised tomography (CT), magnetic resonance imaging (MRI) and nuclear medicine scans increase the accessibility, the timeliness and the precision of diagnosis [17]. These advances probably explain at least in part the rapid increase in the incidence of CNS tumours observed in the USA and Europe in recent decades [18,19], as well as their low incidence rates in developing countries [3].

Management

Survival of childhood cancer patients is good, at least in developed countries. Since the 1960s, when most children who were diagnosed with cancer died, the treatment has improved remarkably (Figure 5.26.3), such that nowadays 75% of children survive 5 years from diagnosis or more [1, 20, 21, 22]. The prognosis differs by tumour type, with highest survival for retinoblastoma, thyroid carcinoma, Hodgkin lymphoma, etc. Lowest survival is observed for some CNS tumours, certain leukaemias and some sarcomas of bone and soft tissues (Figure 5.26.4). To a variable degree the outcome also depends on the age at diagnosis. Within Europe, differences in survival were observed between countries grouped by the socio-economic level of development (Figure 5.26.4). The less favourable outcome in the countries with lower socio-economic status can be attributed to the longer delays in diagnosis and treatment, insufficient treatment potential, problems with tackling associated morbidity and lesser inclusion of patients in clinical trials [20].

Taking into account the differences observed in Europe and in the absence of data on childhood cancer survival in most of the developing world, it is generally assumed that the survival of these children is dismal. The main reasons are late diagnosis, unavailability of treatment, therapy abandonment, prior undernourishment, inadequate supportive therapy and unsuccessful follow-up. All these factors relate to lack of financial resources to support efficient health care system for childhood cancer patients [23].

The improvement of survival reported from high-resource countries [1,20,21,22] results from increasing use of intensive chemotherapy combined with other modalities of treatment, improved generalised supportive management, application of results of clinical trials and centralisation of care permitting each patient to benefit from the best of the multidisciplinary expertise and technology available for these rare conditions. The current challenge is to optimise treatment to achieve a maximal treatment effect with minimal toxicity. This may be achieved through elucidation of mechanisms of resistance and exploration of the potential of novel therapeutic approaches [17]. The aim is to eliminate or reduce the numerous late effects of treatment and thus improve the quality of life of the growing population of survivors of childhood cancer.

REFERENCES

1. Steliarova-Foucher E, Stiller C, Kaatsch P, et al. (2004). Geographical patterns and time trends of cancer incidence and survival among children and adolescents in Europe since the 1970s (the ACCISproject): an epidemiological study. *Lancet* 364: 2097-2105.

2. Steliarova-Foucher E, Stiller C, Lacour B, et al. (2005). International Classification of Childhood Cancer, third edition. Cancer 103: 1457-1467.

3. Parkin DM, Kramarova E, Draper GJ, et al. (1998). *IARC Scientific Publications, Number 144, International incidence of childhood cancer, Volume II*. Lyon, France: International Agency for Research on Cancer.

4. Ferlay J, Bray F, Pisani P, Parkin DM. (2004). GLOBOCAN 2002: Cancer incidence, mortality and prevalence worldwide. *IARC CancerBase* No. 5 Version 2.0. Lyon: IARCPress.

5. Sayed K, Parham DM (2003). Unique pathologic features of childhood cancer. In: Kufe DW, Holland JF, Frei E, et al., eds., *Cancer medicine* 6. Hamilton, Ontario: B.C. Decker. 2407-2411.

6. Stiller CA (2004). Epidemiology and genetics of childhood cancer. *Oncogene* 23: 6429-6444.

7. Bjornsson HT, Brown LJ, Fallin MD, et al. (2007). Epigenetic specificity of loss of imprinting of the IGF2 gene in Wilms tumors. *J Natl Cancer Inst* 99: 1270-1273.

8. Kazakov VS, Demidchik EP, Astakhova LN (1992). Thyroid cancer after Chernobyl. *Nature* 359: 21.

9. Giusti RM, Iwamoto K, Hatch EE (1995). Diethylstilbestrol revisited: a review of the long-term health effects. *Ann Intern Med* 122: 778-788.

10. Stewart A, Webb J, Hewitt D (1958). A survey of childhood malignancies. *Br Med J* 1: 1495-1508.

11. Kelly GL and Rickinson AB (2007). Burkitt lymphoma: revisiting the pathogenesis of a virus-associated malignancy. *Hematology Am Soc Hematol Educ Prog* 2007: 277-284.

12. Greaves MF (1988). Speculations on the cause of childhood acute lymphoblastic leukemia. *Leukemia* 2: 120-125.

13. Kinlen LJ (1995). Epidemiological evidence for an infective basis in childhood leukaemia. *Br J Cancer* 71: 1-5.

14. Bunin GR (2004). Nongenetic causes of childhood cancers: evidence from international variation, time trends, and risk factor studies. *Toxicol Appl Pharmacol* 199: 91-103.

15. Ross JA, Spector LG (2006). Cancers in children. In: Schottenfeld D, Fraumeni JF, eds., *Cancer epidemiology and prevention*. New York: Oxford University Press 1251-1268.

16. Report of the 1998 Consensus Conference on Neuroblastoma Screening (1999). *Med Pediatr Oncol* 33: 357-359.

17. Reaman GH (2003). Pediatric oncology: principles and practice. In: Kufe DW, Holland JF, Frei E, et al., eds., *Cancer medicine 6*. Hamilton, Ontario: B.C. Decker 2291-2293.

18. Linet MS, Ries LA, Smith MA, et al. (1999). Cancer surveillance series: recent trends in childhood cancer incidence and mortality in the United States. *J Natl Cancer Inst* 91: 1051-1058.

19. Peris-Bonet R, Martinez-Garcia C, Lacour B, et al. (2006). Childhood central nervous system tumours–incidence and survival in Europe (1978-1997): report from Automated Childhood Cancer Information System project. *Eur J Cancer* 42: 2064-2080.

20. Pritchard-Jones K, Kaatsch P, Steliarova-Foucher E, et al. (2006). Cancer in children and adolescents in Europe: developments over 20 years and future challenges. *Eur J Cancer* 42: 2183-2190.

21. Ries LAG, Smith MA, Gurney JG, et al. (1999). *Cancer incidence and survival among children and adolescents: United States SEER Program 1975-1995*. Bethesda, MD: National Cancer Institute, SEER Program.

22.Gatta G, Capocaccia R, Stiller C, Kaatsch P, Berrino F, Terenziani M; EUROCARE Working Group. (2005). Childhood cancer survival trends in Europe: a EUROCARE Working Group study. J Clin Oncol 23: 3742-51.

23. Ribeiro RC, Steliarova-Foucher E, Magrath I, Lemerle J, Eden T, Forget C, Mortara I, Tabah-Fish I, Divino JJ, Howard S, Cavalli F. Baseline status of pediatric oncology in 10 low- or mid-income countries receiving "My Child Matters" support. *Lancet Oncology* 2008; 9:721-729.

5.27 Cancer in Adolescents

Summary

- Cancer occurs rarely in adolescence, though the incidence is roughly twice as high as in children
- Typical cancers of adolescents include lymphomas, bone and soft tissue sarcomas, germ cell tumours, melanoma and carcinomas of thyroid and nasopharynx. Leukaemias and brain tumours are also common. Adolescent cancers are often detected late
- Many tumours occurring in adolescents have characteristic pathological and genetic features, requiring a morphology-based classification
- The risk factors include various infectious agents, exposure to hormones, radiation (ionising and non-ionising) and some life-style factors
- Despite of a large proportion of cancers with a relatively good prognosis, the overall population-based 5-year survival of adolescents with cancer attains about 75% in developed countries. A more focused approach to the management of this group of patients would probably contribute to an improvement

Cancer in adolescents comprises all cases occurring in individuals aged 15 to 19 years. This definition reflects relatively well various biological, societal, statistical and clinical specificities of this life period, although other age-spans may be considered in some sources. The age group 15–19 years is convenient in population-based studies, because of the availability of population and other data for this age group. It coincides relatively well with the period of physical and sexual development, even though the onset of this process tends to occur a bit earlier in girls and has shifted towards younger ages in both sexes over the last few decades.

The range of tumours occurring in adolescents makes the usual classification by tumour site (used to classify cancers in predominantly adult population) unsatisfactory. International Classification for Childhood Cancer (ICCC) [1], reflecting primarily morphological entities, is therefore often used in descriptive studies. This is similar to the classification adapted specifically for adolescents [2].

Occurrence

Adolescence is a period characteristic of physical, sexual, mental and societal maturation. The two first aspects influence the spectrum of cancer types occurring in this age group, which is different from that in childhood and in adulthood. In the populations of Caucasian descent, the most common cancers are lymphomas and carcinomas (Figure 5.27.1). Other frequent cancer groups are CNS tumours, germ cell tumours and sarcomas of bone and soft tissues, with slightly different ranks in males and females (Figure 5.27.1). Worldwide, the rates vary about three-fold in males (90–300 per million) and in females (88–270 per million). In some populations, incidence rates in females are higher than in males, though. Overall incidence rate for large series was 202.2 per million person-years during 1986–1995 in the USA [4], with an estimated increase to 216 in year 2000 [5]. In Europe, the incidence rate was 186.0 per million person-years in the period 1988–1997 (Table 5.27.1) [3]. These variations are illustrated in Figure 5.27.2, which is based on the most recent international data series classified according to tumour site [6].

Adolescence is the age of predominant occurrence of a few specific tumour types. Bone tumours (both osteosarcoma and Ewing tumour) usually present the first age-specific peak in adolescents overall and in males (in females the first peak of the two types of bone tumours occurs in the age group 10–14) [7]. This peak is present in all ethnic groups in the US population, although it is worth noting that Ewing sarcomas are very rare in African Americans (Figure 5.27.3). Ovarian germ cell tumours, including dysgerminomas, malignant teratomas and mixed germ cell tumours, are most common in adolescent girls [8]. In the world regions with intermediate overall incidence rates of the nasopharyngeal carcinoma, the first age peak of this tumour is seen in adolescents [8].

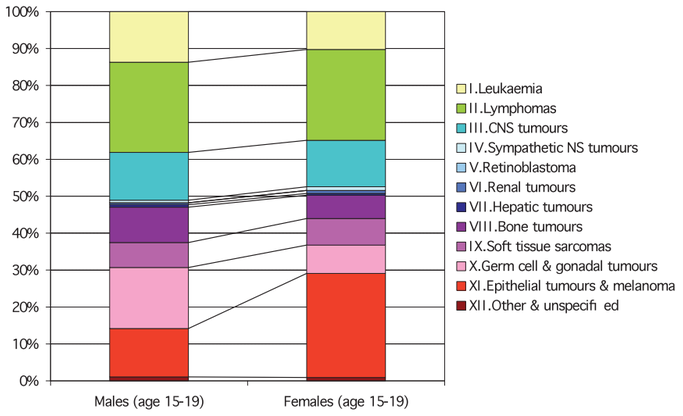


Fig. 5.27.1 *Relative frequency of various cancers in adolescents aged 15–19 years, based on 8272 cases registered in European cancer registries during 1988–1997 and included in the ACCIS study [7]. CNS, central nervous system. NS, nervous system*

The incidence rates were reported to increase in Europe by 2% per year over the period 1978-1997, mainly due to the increase of incidence of lymphoid leukaemia, Hodgkin lymphoma, astrocytoma, gonadal germ cell tumours, thyroid carcinoma and melanoma [8]. In the USA an overall annual increase of 0.7% was reported for the period 1975–2000 [5]. The highest increase was previously reported for the gonadal germ cell tumours in both sexes, acute lymphocytic leukaemia, non-Hodgkin lymphomas and osteosarcoma [4]. Although some of this increase may be related to improvement in diagnosis and reporting, the true rise in incidence of some of these tumour groups cannot be disregarded.

Pathology and genetics

Together with the particular spectrum, cancers in adolescents present special biological characteristics. Thus, acute lymphocytic leukaemia usually bears poorer prognosis in adolescence than in childhood. Astrocytic and glial tumours of the brain are usually diagnosed with higher grades. Common adulthood carcinomas occurring in this early period in life may be more often associated with genetic factors that cause these tumours to arise earlier in life. For example, 20% of breast cancers in women aged less than 30 years may be caused by pathogenic alterations in breast susceptibility genes [9]. Some tumours occur as part of familial syndromes, sometimes as second primary malignancies after a childhood cancer. As reviewed by Birch et al. [10], TP53 mutations were shown specifically in adolescents and young adults with anaplastic astrocytoma, glioblastoma and osteosarcoma, while medulloblastoma diagnosed in older children, adolescents and young adults may be more frequently associated with the APC gene. Ewing sarcoma is also conditioned genetically, as suggested by the variation of its incidence across ethnic groups (Figure 5.27.3) and various chromosomal aberrations, of which t(11;22)(q24;q12) is detectable in a large majority of cases [11]. Chromosomal changes have also been reported for germ cell tumours of testes and ovaries in adolescents with a typical amplification of the 12p chromosome [12]. Melanoma is common in fair-skinned populations, and may occur in a familial form, which indicates genetically underlined etiology [13]. However, inheritance probably explains only a small fraction of cancers in adolescents [5].

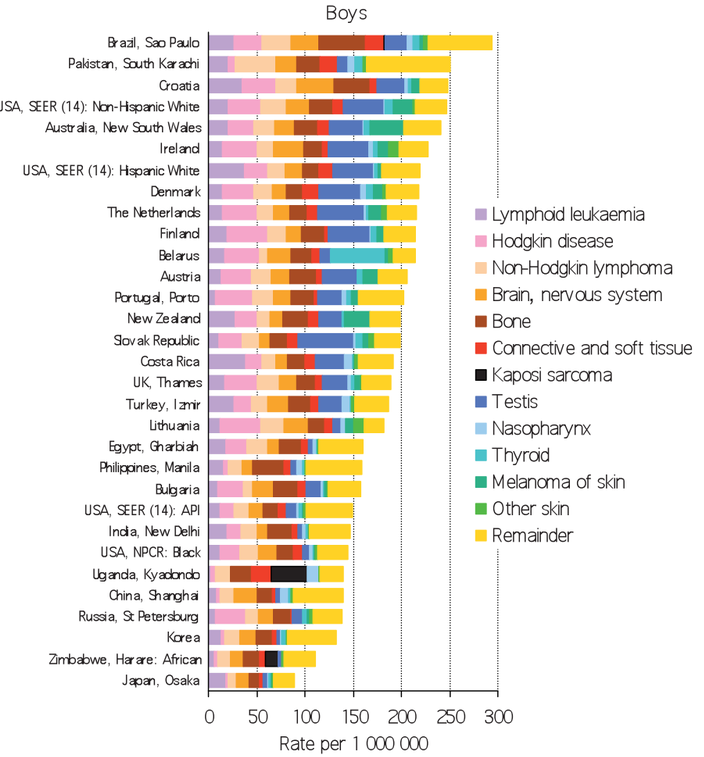


Fig. 5.27.2 *Incidence rates of cancer in adolescents (age 5–19 years) in various population-based cancer registries. Based on a total number of 10 528 cases in boys and 8 777 in girls [6]*

Etiology

Apart from genetic susceptibility, a large proportion of cancers in adolescents may probably be attributed to infection. Infectious etiology is a likely explanation for acute lymphocytic leukaemia (ALL) and lymphomas. While the infectious agent for ALL has not been identified as yet, Epstein-Barr virus (EBV) is implicated in several cancers. In Hodgkin lymphoma, its effect is modified by age, sex, geographical residence, ethnicity and the level of economic development [14]. Non-Hodgkin lymphomas are also linked to EBV, but also to human immunodeficiency virus (HIV) and human T-cell lymphotropic virus type 1 (HTLV-1). EBV is also implicated in nasopharyngeal carcinoma, especially in the areas of the highest incidence (East Asia). *Helicobacter pylori* may play a role in gastric lymphoma, possibly together with other infections [15,16]. Most cases of hepatic carcinoma, occurring with highest frequencies in Hong Kong and sub-Saharan African registries, are due to Hepatitis B and C viruses [17]. HIV infection is behind the spectacular rise in the incidence of the previously endemic form of Kaposi's sarcoma in some African countries (Figure 5.27.2) [17]. Simian-virus (SV40), the contaminant of the polio vaccine in the 1950s, was suspected to cause some brain and bone tumours [18], although the allegation has not been confirmed [19].

Some testicular germ cell tumours are thought to arise in response to hormonal stimulation by oestrogens in utero or oestrogen-like substances in the environment. However, sedentary lifestyle may also contribute to the explanation of the continuous increase of testicular germ cell tumours in western populations (Figure 5.27.2) [20].

The age-sex specific incidence rates for bone tumours further suggest that their occurrence may be associated with the growth spurt, which occurs earlier in girls than in boys (see Rare Tumours Figure 5.28.2 (c,d). A portion of osteosarcomas may also arise as secondary malignancy, often following radiotherapy for other tumours in childhood [21].

Ionising radiation released accidentally in 1986 in Chernobyl explains the record rates of thyroid carcinomas in adolescent girls (and to a lesser extent in boys) in Belarus (Figure 5.27.2) and some other most exposed countries [22]. The extreme incidence rates of melanoma in some white populations (Figure 5.27.2) are due to excessive exposure to UV radiation, entangled with socio-economic factors [23].

Detection

The single most important issue specific to the detection of a range of cancers occurring in adolescents is probably the delay in diagnosis. Diagnosis may be delayed in this age group more than in others due to a combination of specific circumstances, including the invincible attitude, unawareness, insufficient health insurance coverage, change of primary health care provider or inadequate training of attending practitioner [24].

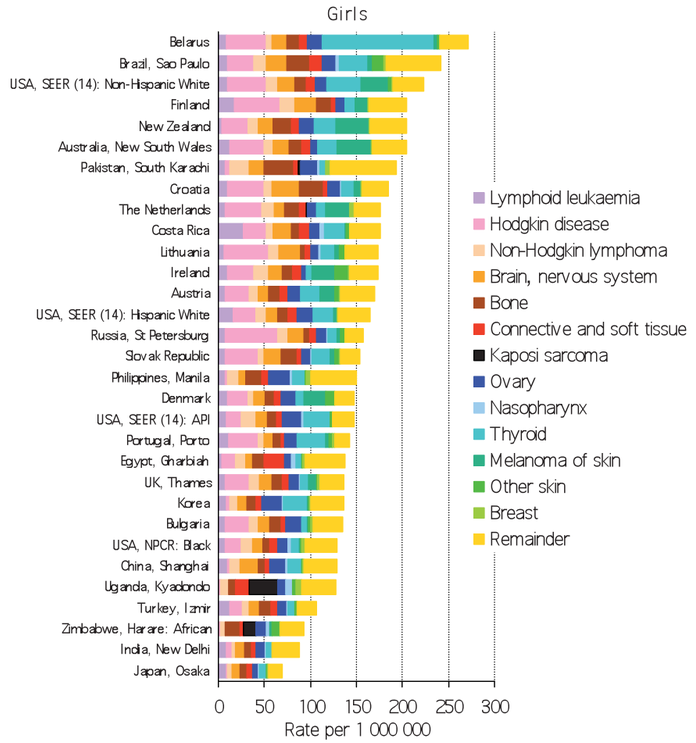


Fig. 5.27.2 *(cont.)*

Management

Compared to other age groups in the USA, adolescents and young adults (ages 15–45) have shown the smallest improvement in survival over the period 1975–1997 [5]. The reasons for this lag may be multiple: delay in diagnosis, lower participation in clinical trials, poor compliance with treatment and psychosocial issues [24]. The referral pattern for the adolescents with cancer is not clearly defined in most countries, although this group has specific needs that differ from those of children and adults. Adapted specialised cancer units for adolescents were established in the UK, although their number is largely insufficient to cover the totality of demand [25]. These units respect all aspects of the management specific for adolescents, including therapy, psychosocial support, palliative treatment and follow-up. The recent debate about the appropriate care for adolescents with cancer [26-28] will hopefully bring about a greater increase in survival for this group of cancer patients.

Overall survival at five years since diagnosis for adolescents diagnosed in the 1990s in Europe was almost 75% (Table 5.27.2), having improved over the last two decades of the 20th century (Figure 5.27.4). Should this trend continue, and specialised approach to the management of adolescents with cancer be adopted widely, the patients diagnosed nowadays may expect outcomes that are better still. Five-year survival of the adolescents diagnosed with cancer in the USA by the end of 1990s reaches 80%, based on SEER data [29]. Leukaemia (especially ANLL), bone tumours and soft-tissue sarcomas are the most challenging diagnoses.

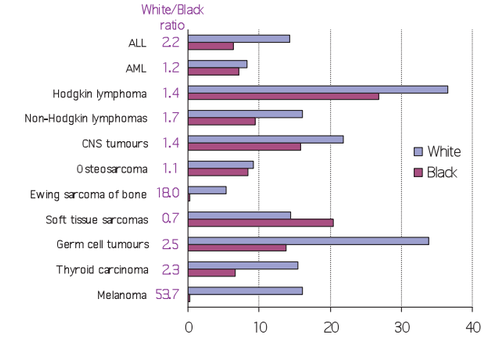


Fig. 5.27.3 *Incidence rates of cancer in adolescents aged 15–19 years (both sexes), based on 9814 cases registered in SEER registries in the USA during 1975–1995 [4]. ALL, acute lymphoblastic leukaemia; AML, acute myeloblastic leukaemia*

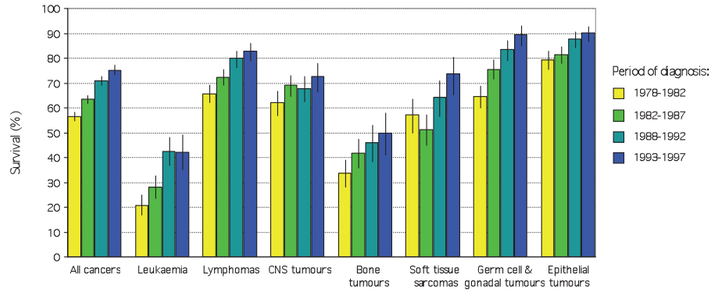


Fig. 5.27.4 *Five-year survival of adolescents aged 15–19 years (both sexes) diagnosed in the calendar periods shown in the European registration areas contributing to the ACCIS study [3]. Line sections represent the 95% confidence intervals of the survival estimate. N, total number of cases included in survival analysis for each tumour group. CNS, central nervous system*

Tumour type		N	B/G	Rate
All cancers		**8272**	**1.2**	**186.0**
Leukaemia		**1006**	**1.7**	**22.6**
	lymphoid	562	2.0	12.6
	acute non-lymphocytic	312	1.3	7.0
Lymphoma		**2027**	**1.2**	**45.6**
	Hodgkin	1319	1.0	29.7
CNS		**1057**	**1.3**	**23.8**
	astrocytoma	459	1.2	10.3
Bone tumours		**672**	**1.9**	**15.1**
	osteosarcoma	372	1.9	8.4
	Ewing sarcoma	185	2.0	4.2
Soft tissue sarcomas		**576**	**1.2**	**13.0**
	rhabdomyosarcoma	131	1.8	2.9
	fibrosarcoma	212	1.0	4.8
Germ cell & gonadal		**1040**	**2.7**	**23.4**
	gonadal germ-cell	773	5.1	17.4
	gonadal carcinoma	117	0.0	2.6
Epithelial		**1640**	**0.6**	**36.9**
	thyroid carcinoma	368	0.3	8.3
	melanoma	571	0.6	12.8
	skin carcinoma	165	0.8	3.7

Table 5.27.1 *Incidence rates of cancer in adolescents aged 15–19 years in 1988–1997 in Europe and included in the ACCIS study [3]. N, number of cases; B/G, boys to girls ratio; Rate, age specific incidence rate per million person-years*

Tumour type		N	OS (95%CI)
All cancers		**6494**	**73 (71,74)**
Leukaemia		**811**	**44 (40,48)**
	lymphoid	450	50 (44,54)
	acute non-lymphocytic	245	35 (29,42)
Lymphomas		**1597**	**81 (79,83)**
	Hodgkin	1045	89 (87,91)
	non-Hodgkin	360	64 (59,69)
	unspecified	137	74 (65,81)
CNS tumours		**866**	**70 (66,73)**
	astrocytoma	348	65 (59,70)
	other glioma	162	75 (67,81)
	unspecified	141	65 (56,73)
Bone tumours		**486**	**48 (43,53)**
	osteosarcoma	271	52 (45,58)
	Ewing sarcoma	144	31 (23,39)
Soft tissue sarcomas		**430**	**67 (62,71)**
	fibrosarcoma	164	81 (74,86)
	other specified	123	74 (64,81)
Germ cell tumours		**839**	**87 (84,89)**
	testicular	520	90 (87,92)
Carcinomas and epithelial neoplasms		**1245**	**88 (86,90)**
	thyroid	285	99 (97,100)
	melanoma	427	88 (84,91)
	skin	150	98 (92,100)
	other	331	79 (74,83)

Table 5.27.2 *Survival of adolescents aged 15–19 years (both sexes) diagnosed with cancer in Europe in 1988–1997 and included in the survival analysis in the ACCIS study [7]. N, numbers of cases included in the analyses; OS, observed 5-year survival; CI, confidence interval of the observed survival; CNS, central nervous system*

REFERENCES

1. Steliarova-Foucher E, Stiller C, Lacour B, et al. (2005). International Classification of Childhood Cancer, third edition. *Cancer* 103: 1457-1467.

2. Birch JM, Alston RD, Kelsey AM, et al. (2002). Classification and incidence of cancers in adolescents and young adults in England 1979-1997. *Br J Cancer* 87: 1267-1274.

3. Stiller CA, Desandes E, Danon SE, et al. (2006). Cancer incidence and survival in European adolescents (1978-1997). Report from the Automated Childhood Cancer Information System project. *Eur J Cancer* 42: 2006-2018.

4. Smith MA, Gurney JG, Ries LA (1999). Cancer among adolescents 15-19 years old. In: Ries LAG, Smith MA, Gurney JG, et al., eds., *Cancer incidence and survival among children and adolescents: United States SEER Program 1975-1995.* Bethesda, MD: National Cancer Institute, SEER Program. 157-164.

5. Bleyer A, Viny A, Barr R (2006). Introduction. In: Bleyer A, O'Leary M, Barr R, et al., eds., *Cancer epidemiology in older adolescents and young adults 15 to 29 years of age, including SEER incidence and survival: 1975-2000.* Bethesda, MD: National Cancer Institute, SEER Program 1-14.

6. Curado MP, Edwards B, Shin HR, et al. (2007). *IARC Scientific Publications, Number 160, Cancer incidence in five continents, Volume IX.* Lyon, France: International Agency for Research on Cancer.

7. Mascarenhas L, Siegel S, Spector L, et al. (2006). Malignant bone tumours. In: Bleyer A, O'Leary M, Barr R, et al., eds., *Cancer epidemiology in older adolescents and young adults 15 to 29 years of age, including SEER incidence and survival: 1975-2000.* Bethesda, MD: National Cancer Institute, SEER Program 97-110.

8. Stiller CA (2007). International patterns of cancer incidence in adolescents. *Cancer Treat Rev* 33: 631-645.

9. Lalloo F, Varley J, Ellis D, et al. (2003). Prediction of pathogenic mutations in patients with early-onset breast cancer by family history. *Lancet* 361: 1101-1102.

10. Birch JM, Alston RD, Quinn M, et al. (2003). Incidence of malignant disease by morphological type, in young persons aged 12-24 years in England, 1979-1997. *Eur J Cancer* 39: 2622-2631.

11. Ushigome S, Machinami R, Sorensen PH (2002). Ewing sarcoma / Primitive neuroectodermal tumour (PNET). In: Fletcher CDM, Unni KK, Mertens F, eds., *World Health Organization classification of tumours. Pathology and genetics of tumours of soft tissue and bone.* Lyon, France: International Agency for Research on Cancer 298-300.

12. Sandberg AA, Meloni AM, Suijkerbuijk RF (1996). Reviews of chromosome studies in urological tumors. III. Cytogenetics and genes in testicular tumors. *J Urol* 155: 1531-1556.

13. Hemminki K, Zhang H, Czene K (2003). Familial and attributable risks in cutaneous melanoma: effects of proband and age. *J Invest Dermatol* 120: 217-223.

14. Glaser SL, Lin RJ, Stewart SL, et al. (1997). Epstein-Barr virus-associated Hodgkin's disease: epidemiologic characteristics in international data. *Int J Cancer* 70: 375-382.

15. Baris D and Zahm SH (2000). Epidemiology of lymphomas. *Curr Opin Oncol* 12: 383-394.

16. Muller AM, Ihorst G, Mertelsmann R, et al. (2005). Epidemiology of non-Hodgkin's lymphoma (NHL): trends, geographic distribution, and etiology. *Ann Hematol* 84: 1-12.

17. Parkin DM (2006). The global health burden of infection-associated cancers in the year 2002. *Int J Cancer* 118: 3030-3044.

18. Fisher SG, Weber L, Carbone M (1999). Cancer risk associated with simian virus 40 contaminated polio vaccine. *Anticancer Res* 19: 2173-2180.

19. Engels EA (2005). Cancer risk associated with receipt of vaccines contaminated with simian virus 40: epidemiologic research. *Expert Rev Vaccines* 4: 197-206.

20. Woodward PJ, Heidenreich A, Looijenga JHJ, et al. (2004). Germ cell tumours. In: Eble J, Epstein JI, Sesterhenn IA, et al., eds., *World Health Organization classification of tumours. Pathology and genetics of tumours of the urinary system and male genital organs.* Lyon, France: International Agency for Research on Cancer 221-249.

21. Koshy M, Paulino AC, Mai WY, et al. (2005). Radiation-induced osteosarcomas in the pediatric population. *Int J Radiat Oncol Biol Phys* 63: 1169-1174.

22. Kazakov VS, Demidchik EP, Astakhova LN (1992). Thyroid cancer after Chernobyl. *Nature* 359: 21.

23. de Vries E, Bray F, Coebergh JW, et al. (2006). Malignant melanoma: Introduction. In: LeBoit P, Burg G, Weedon D, et al., eds., *World Health Organization classification of tumours. Pathology and genetics of skin tumours.* Lyon, France: International Agency for Research on Cancer 52-65.

24. Albritton K and Bleyer WA (2003). The management of cancer in the older adolescent. *Eur J Cancer* 39: 2584-2599.

25. Whelan J (2003). Where should teenagers with cancer be treated? *Eur J Cancer* 39: 2573-2578.

26. Bleyer A, O'Leary M, Barr R, et al. (2006). *Cancer epidemiology in older adolescents and young adults 15 to 29 years of age, including SEER incidence and survival: 1975-2000.* Bethesda, MD: National Cancer Institute, SEER Program.

27. Michelagnoli MP, Pritchard J, Phillips MB (2003). Adolescent oncology–a homeland for the "lost tribe". *Eur J Cancer* 39: 2571-2572.

28. Pavlidis N (2007). Adolescent oncology. *Cancer Treat Rev* 33: 595-664.

29. Bleyer A, Barr R (2006). Highlights and challenges. In: Bleyer A, O'Leary M, Barr R, et al., eds., *Cancer epidemiology in older adolescents and young adults 15 to 29 years of age, including SEER incidence and survival: 1975-2000.* Bethesda, MD: National Cancer Institute, SEER Program 173-189.

5.28 Rare Cancers

Summary

> "Rare cancer" is an arbitrary term, because it is difficult to establish a standard definition

> Rare cancers are common when considered as a group

> Although their rarity is an obstacle to etiology studies, any cluster in unusual setting may quickly lead to identification of an external cause

> Some rare cancers are undoubtedly genetic in origin

> The wide variation in outcome reflects the variety of rare cancers, the diagnostic delay and the level of expertise in the management of a given malignancy

There is no precise definition of a rare cancer, and many cancers may or may not be considered rare, depending on the precision of the criteria employed. For example, a threshold incidence rate of less than 1/50 000 would place breast cancer in men in the rare category, but that is not so in women[1]. Neuroblastoma is rare, but in infants (below 1 year of age) it is the most common malignancy [2]. Even certain lung cancers may be rare, for example carcinoid tumors [3]. Kaposi sarcoma is unusual almost everywhere in the world except equatorial Africa [4]. Rarity may also depend on the time period, as is the case for melanoma, a rare cancer worldwide before its incidence started to rise in 1960s [5]. Finally, with advances in diagnostic techniques, new entities are being recognised, most of them rare.

Occurrence

Table 5.28.1 shows a list of cancers, as defined by the International Classification of Diseases, that may be considered rare because of their low incidence rates. Table 5.28.1 does not include those rare cancers that are described in other chapters of this World Cancer Report, such as gall bladder carcinoma, testicular cancer, thyroid cancer and others.

Figure 5.28.1 shows the combined incidence of 12 rare cancers in men and 13 rare cancers in women and the variability of their occurrence worldwide. Even though the rate for each group of tumours is very low (and much lower still for

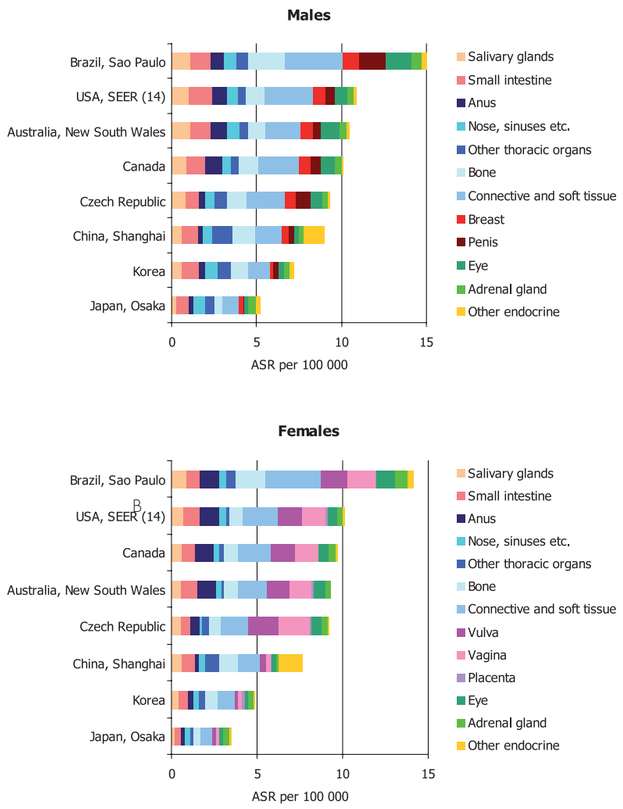


Fig. 5.28.1 *Age-standardised incidence rates (ASR, World standard) of some rare cancers in selected large registries included in Volume IX of Cancer Incidence in Five Continents [7], with cancers defined as in Table 5.28.1 SEER (14) is based on data from 14 registries contributing to the Surveillance, Epidemiology and End Results program . N, total number of cases comprised in the rates calculation.*
Males, comprising 49 381 cases / Females, comprising 53 466 cases

further specific entities), the combined incidence rate for this non-exhaustive list of cancers is comparable to those of common cancers, emphasising the importance of studies of rare cancers.

Schematically, the rare cancers have four main patterns of age distribution (Figure 5.28.2). A continuous increase with age (Figure 5.28.2a) is observed for malignancies of the salivary glands, small intestine, anus and vulva. The J-shaped curve (Figure 5.28.2b), which shows a higher incidence in very young children than in adolescents and young adults and which then rises again with age thereafter is characteristic for cancers of the nose, sinuses, thoracic organs, connective and soft tissue, male breast, vagina and adrenal cortex. Bone tumours and other endocrine neoplasms display a curve with bimodal distribution, with the first peak in adolescence (Figure 5.28.2c and d). A small transitory increase in incidence around adolescence is also seen for soft tissue sarcomas in some populations. Finally, placental cancer reaches its peak in the most common age of procreation, with low rates on both ends of the age-specific curve (inverse U-shape).

Pathology and genetics

Rare cancers comprise a large number of pathologic entities. For example, cancers of the small intestine include carcinoids, adenocarcinomas, lymphomas, sarcomas and others. Their behaviour is modified by their localisation within the small bowel, with carcinoids, lymphomas, and sarcomas occurring in order of decreasing frequency in the ileum, jejunum, and duodenum; the reverse is true for adenocarcinomas [9]. Cancers of the salivary glands vary widely in their histological appearance and molecular characteristics, ranging from low-grade, minimally invasive tumours to highly lethal malignancies [10].

Some rare tumours are found in association with certain familial syndromes. Werner syndrome, an autosomal recessive disorder characterised by premature aging and an increased risk of rare cancers, has been mapped to chromosome 8p. It seems to be more common in Japan than elsewhere. Associated cancers are soft tissue sarcoma, osteosarcoma, myeloid disorders, benign meningioma, adrenocortical carcinoma and others [11,12]. The Lynch Cancer Family Syndrome, characterised by the frequent occurrence of multiple types of common cancers, may also be associated with rare cancers [13]. Familial clustering of rare tumours has also been shown in Li-Fraumeni syndrome [14]. The syndromes associated with some rare cancers may result from both genetic and environmental causes [15] and may be influenced by individual cancer susceptibility [16].

Etiology

The etiology of many rare cancers is unknown, because recruitment of a sufficient number of cases requires very large studies. In addition, there is little comparability between the studies dealing with rare neoplasms due to the lack of standard definition. On the other hand, clusters of rare cancers detected in specific circumstances may lead to identification of some "signal cancers" [17], such as bone sarcoma after the occupational exposure to radium in dial painters [18]. Other occupational exposures have been also implicated in vinyl chloride workers developing liver angiosarcoma [19] or in furniture-makers diagnosed with nasal adenocarci-

Cancer site (ICD-10 codes)	Males		Females	
	N	ASR per 100 000	N	ASR per 100 000
Salivary glands (C07-08)	7507	1.0	5454	0.6
Small intestine (C17)	9691	1.3	8829	1.1
Anus (C21)	5995	0.8	9272	1.1
Nose, sinuses etc. (C30-C31)	4421	0.6	3161	0.4
Other thoracic organs (C37-38)	2800	0.4	1812	0.2
Bone (C40-41)	6323	1.1	5246	0.8
Connective and soft tissue (C47+C49)	18132	2.7	15124	2.0
Breast (C50)	6798	0.9	-	-
Vulva (C51)	-	-	14291	1.5
Vagina (C52)	-	-	4543	0.5
Placenta (C58)	-	-	506	0.1
Penis (C60)	4146	0.6	-	-
Eye (C69)	4871	0.8	4121	0.6
Adrenal gland (C74)	1680	0.3	1758	0.3
Other endocrine (C75)	895	0.2	613	0.1

Table 5.28.1 *Numbers (N) and age-standardised incidence rates (ASR, World standard) of some rare cancers in the National Program of Cancer Registries of the USA [6]. The cancers shown are those occurring with a frequency of around 1 in 50 000 or less in the majority of the world populations, as recorded in Cancer Incidence in Five Continents, Volume IX [7] except those included in other chapters of World Cancer Report 2008. ICD-10, International Classification of Diseases 10th revision [8]*

noma in the early 1960s [20]. The exogenous hormone diethylstilboestrol, used for therapeutic purposes, has caused vaginal carcinoma in the daughters of women using this drug during their pregnancy [21]. Dioxin (2,3,7,8 –TCDD), a toxic pollutant of pesticides, has been declared a human carcinogen [22], based on studies of both common and rare cancers (including soft tissue sarcoma) after exposure to dioxin. Viruses (HPV, HIV) may play a role in the origin of anal cancer [23]. A dose–response relationship was detected between alcohol intake and the risk of male breast cancer [24].

Detection

Rare cancers are often of low clinical and research interest, which may considerably delay their diagnosis and consequently, worsen the prognosis. Their rarity and diversity frequently challenge the diagnostic acumen of the clinician. Novel molecular biology techniques serve to enhance the diagnosis and classification of these tumours and are indispensable for application of tailored therapies [25].

Management

Surgical resection is probably the most commonly used therapy in rare cancers, with chemotherapy and radiation therapy as adjuvants. For rare tumours of the head and neck, new techniques of irradiation (e.g. intensity-modulated radiotherapy or three-dimensional conformal radiotherapy) appear to improve the control of these tumours [26. Radiotherapy has replaced resection as first-line treatment in anal cancer [27]. Progress in molecular biology techniques allows identification of new prognostic factors,

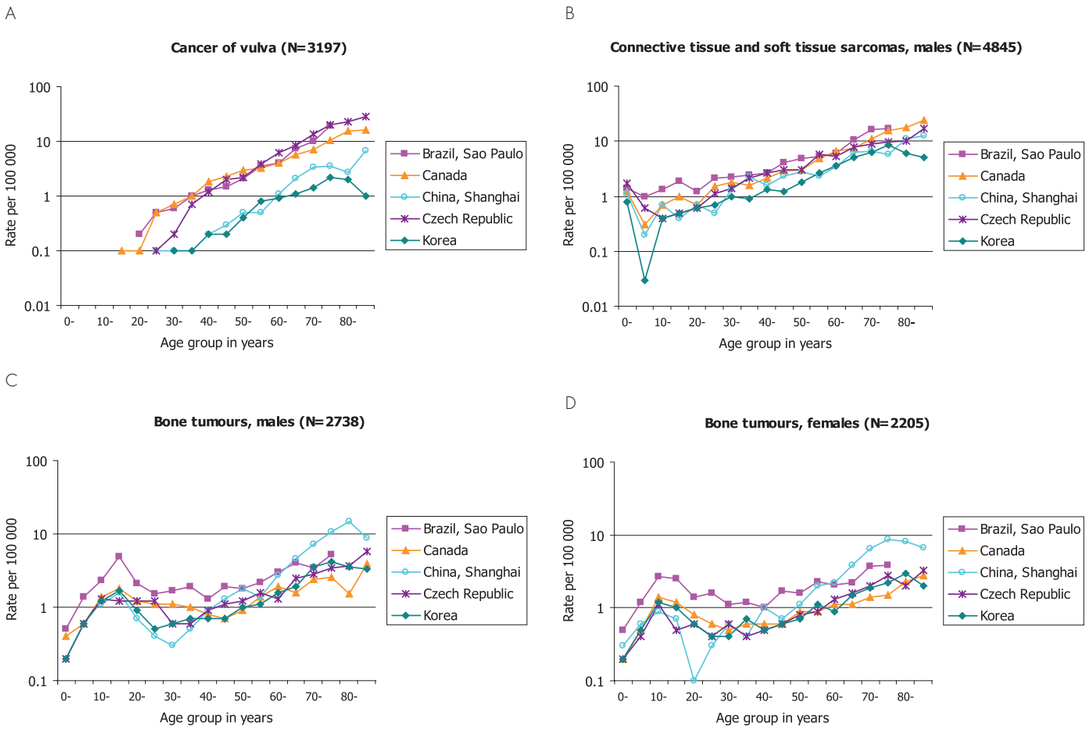


Fig. 5.28.2 *Age-specific incidence rates for some rare cancers in selected populations included in Volume IX of Cancer Incidence in Five Continents [7]. N, total numbers of cases contributing to the statistics in each graph*

and development of molecular-targeted therapies. For cancers with very bad prognosis (e.g. salivary glands, sweat glands), systemic palliative therapy should also be determined in clinical trials [10].

In a large European study, the population-based 5-year relative survival ranged from good to poor for 14 specific tumour types (Figure 5.28.3) [3]. In another population-based study, the 5-year relative survival for small intestine cancer was 54%, but varied with the histological type: 83% for carcinoids, 62% for lymphomas, 45% for sarcomas and 25% for adenocarcinomas [9]. Large clinical series show 5-year relative survival of 86% for patients with parathyroid carcinoma [28]. The relative 5-year survival rates of patients with anal cancer in the population covered by SEER registries is over 70% for women and 60% for men, with much lower rates (less than 30%) among black men. Earlier detection improves the survival of patients with anal cancer [29]. Five-year relative survival rates of vaginal carcinoma patients diagnosed from 1985 through 1989 ranged from 96% for stage 0 (in situ) to 36% for stages III–IV. An even lower five-year relative survival rate of 14% was observed for women with vaginal melanoma [30]. Five-year relative survival rates for vulvar melanoma (N=223) diagnosed between 1985 and 1989 differed by stage, with 77% survivors with stage 0 dropping to 24% for those with stage IV, while recurrent disease was associated with 100% fatality [28].

For some rare cancers, treatment outcome has been particularly successful. Examples include hairy cell leukaemia, chronic myelogeneous leukaemia, seminoma, gastrointestinal stromal tumour, (del)5q myelodysplastic syndrome, acute promyelocytic leukaemia. The reason for this success may be the same as the reason for their rarity, whereby a single molecular genetic aberration needs to be targeted, in contrast to multiple aberrations in the most common cancers [31]. The limited numbers of patients within each tumour type require large international trials to allow identification of prognostic factors or to compare the outcome. Translational research studies and a multidisciplinary approach in specialised centres are vitally important for rare cancers. The Rare Cancer Network, initiated in 1993 to carry out large retrospective studies on rare cancers with the participation of more than 70 institutions from 21 countries, may help in the definition of international standards for management of these tumours [32].

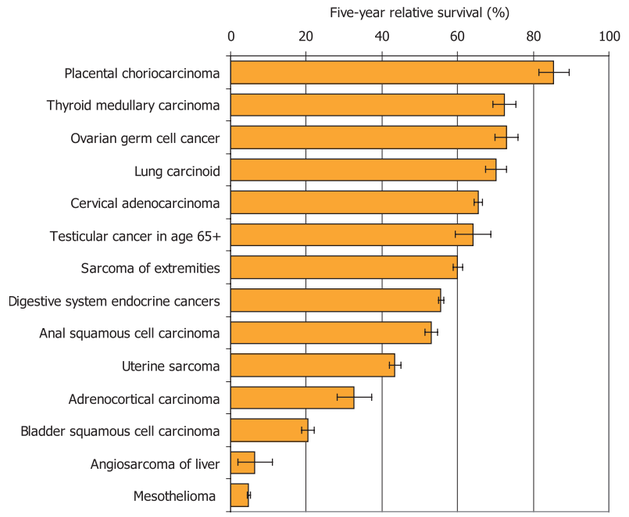


Fig. 5.28.3 *Five-year relative survival from some rare cancers in patients diagnosed during 1983–1994 in Europe, EUROCARE [3]. 95% confidence intervals are shown as line sections*

REFERENCES

1. Ferlay J, Bray F, Pisani P, et al. (2004). GLOBOCAN 2002: Cancer Incidence, Mortality and Prevalence Worldwide. *IARC CancerBase* No. 5 Version 2.0. Lyon: International Agency for Research on Cancer. Available from: http://www-dep.iarc.fr/ Date Accessed: November 12, 2008.

2. Spix C, Pastore G, Sankila R, et al. (2006). Neuroblastoma incidence and survival in European children (1978-1997): report from the Automated Childhood Cancer Information System project. *Eur J Cancer* 42: 2081-2091.

3. Gatta G, Ciccolallo L, Kunkler I, et al. (2006). Survival from rare cancer in adults: a population-based study. *Lancet Oncol* 7: 132-140.

4. Parkin DM, Ferlay J, Hamdi-Cherif M, et al. (2003). *IARC Scientific Publications, Number 153, Cancer in Africa: epidemiology and prevention*. Lyon, France: International Agency for Research on Cancer.

5. Parkin DM, Whelan SL, Ferlay J, Storm HH. Cancer Incidence in Five Continents, Vol. I to VIII IARC CancerBase No. 7, Lyon, 2005.

6. Ahmed F, Cardinez CJ, Jamison PM, et al. (2007). Cancer incidence in the USA, National Program of Cancer Registries (NPCR) 1998-2002. In: Curado MP, Edwards B, Shin HR, et al., eds., *IARC Scientific Publications, Number 160, Cancer incidence in five continents, Volume IX*. Lyon, France: International Agency for Research on Cancer. Available from: http://www-dep.iarc.fr/ Date Accessed: November 12, 2008.

7. Curado MP, Edwards B, Shin HR, Storm H, Ferlay J, Heanue M, Boyle P. (2007). IARC Scientific Publications, Number 160, Cancer incidence in five continents, Volume, IX. Lyon, France: International Agency for Research on Cancer. Available from: http://www-dep.iarc.fr/ Date Accessed: November 12, 2008.

8. WHO. (1992). *International statistical classification of diseases and related health problems : ICD-10*. Geneva: World Health Organization.

9. DiSario JA, Burt RW, Vargas H, et al. (1994). Small bowel cancer: epidemiological and clinical characteristics from a population-based registry. *Am J Gastroenterol* 89: 699-701.

10. Laurie SA and Licitra L (2006). Systemic therapy in the palliative management of advanced salivary gland cancers. *J Clin Oncol* 24: 2673-2678.

11. Goto M, Miller RW, Ishikawa Y, et al. (1996). Excess of rare cancers in Werner syndrome (adult progeria). *Cancer Epidemiol Biomarkers Prev* 5: 239-246.

12. Takazawa R, Ajima J, Yamauchi A, et al. (2004). Unusual double primary neoplasia: adrenocortical and ureteral carcinomas in werner syndrome. *Urol Int* 72: 168-170.

13. Lynch HT and Lynch JF (2004). Lynch syndrome: history and current status. *Dis Markers* 20: 181-198.

14. Frebourg T, Abel A, Bonaiti-Pellie C, et al. (2001). [Li-Fraumeni syndrome: update, new data and guidelines for clinical management]. *Bull Cancer* 88: 581-587.

15. Borch-Johnsen K, Olsen JH, Sorensen TI (1994). Genes and family environment in familial clustering of cancer. *Theor Med* 15: 377-386.

16. Levene S, Scott G, Price P, et al. (2003). Does the occurrence of certain rare cancers indicate an inherited cancer susceptibility? *Fam Cancer* 2: 15-25.

17. Kolstad H, Lynge E, Olsen J, et al. (1992). Occupational causes of some rare cancers. A literature review. *Scand J Soc Med Suppl* 48: 1-148.

18. Rowland RE, Stehney AF, Lucas HF, Jr. (1978). Dose-response relationships for female radium dial workers. *Radiat Res* 76: 368-383.

19. Creech JL and Johnson MN (1974). Angiosarcoma of liver in the manufacture of polyvinyl chloride. *J Occup Med* 16: 150-151.

20. Macbeth R (1965). Malignant disease of the paranasal sinuses. *J Laryngol Otol* 79: 592-612.

21. IARC (1979). *IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans, Volume 21, Sex hormones (II)*. Lyon, France: International Agency for Research on Cancer.

22. IARC (1997). *IARC monographs on the evaluation of carcinogenic risks to humans, Volume 69, Polychlorinated dibenzo-para-dioxins and polychlorinated dibenzofurans*. Lyon, France: International Agency for Research on Cancer.

23. Welton ML, Sharkey FE, Kahlenberg MS (2004). The etiology and epidemiology of anal cancer. *Surg Oncol Clin N Am* 13: 263-275.

24. Guenel P, Cyr D, Sabroe S, et al. (2004). Alcohol drinking may increase risk of breast cancer in men: a European population-based case-control study. *Cancer Causes Control* 15: 571-580.

25. Very rare cancers–a problem neglected (2001). *Lancet Oncol* 2: 189.

26. Lalami Y, Vereecken P, Dequanter D, et al. (2006). Salivary gland carcinomas, paranasal sinus cancers and melanoma of the head and neck: an update about rare but challenging tumors. *Curr Opin Oncol* 18: 258-265.

27. Gerard JP, Romestaing P, Ardiet JM, et al. (1995). [Current treatment of cancers of the anal canal]. *Ann Chir* 49: 363-368.

28. Stewart AK, Bland KI, McGinnis LS, Jr., et al. (2000). Clinical highlights from the National Cancer Data Base, 2000. *CA Cancer J Clin* 50: 171-183.

29. Johnson LG, Madeleine MM, Newcomer LM, et al. (2004). Anal cancer incidence and survival: the surveillance, epidemiology, and end results experience, 1973-2000. *Cancer* 101: 281-288.

30. Fremgen AM, Bland KI, McGinnis LS, Jr., et al. (1999). Clinical highlights from the National Cancer Data Base, 1999. *CA Cancer J Clin* 49: 145-158.

31. Braiteh F and Kurzrock R (2007). Uncommon tumors and exceptional therapies: paradox or paradigm? *Mol Cancer Ther* 6: 1175-1179.

32. Belkacemi Y, Zouhair A, Ozsahin M, et al. (2006). Prognostic factors and management of rare cancers. *Cancer Radiother* 10: 323-329.

Contributors

Rosita Accardi
International Agency for Research on Cancer
150 cours Albert Thomas
69372 Lyon Cedex 08
France

Clement Adebamowo
Department of Surgery
College of Medicine, University of Ibadan
University College Hospital
Ibadan, Oyo State
Nigeria

Ben Anderson
Department of Surgery
University of Washington
Seattle, Washington 98195
USA

Philippe Autier
International Agency for Research on Cancer
150 cours Albert Thomas
69372 Lyon Cedex 08
France

Robert Baan
International Agency for Research on Cancer
150 cours Albert Thomas
69372 Lyon Cedex 08
France

Mariano Barbacid
Spanish National Cancer Research Centre (CNIO)
c/ Melchor Fernandez Almagro 3
28029 Madrid
Spain

Paolo Boffetta
International Agency for Research on Cancer
150 cours Albert Thomas
69372 Lyon Cedex 08
France

Mathieu Boniol
International Agency for Research on Cancer
150 cours Albert Thomas
69372 Lyon Cedex 08
France

Peter Boyle
International Agency for Research on Cancer
150 cours Albert Thomas
69372 Lyon Cedex 08
France

Jo Brady
Department of Medical Oncology
Churchill Hospital
Headington
Oxford, OX3
UK

Anne Brédart
Psycho-Oncology Unit
Curie Institute
26 rue d'Ulm
75246 Paris, Cedex 05
France

Paul Brennan
International Agency for Research on Cancer
150 cours Albert Thomas
69372 Lyon Cedex 08
France

Jean-Benoît Burrion
Institut Jules Bordet
1 rue Héger-Bordetstraat
1000 Brussels
Belgium

Elodie Caboux
International Agency for Research on Cancer
150 cours Albert Thomas
69372 Lyon Cedex 08
France

Franco Cavalli
Oncology Institute of Southern Switzerland
Ospedale San Giovanni
6500 Bellinzona
Switzerland

Young-eun Cho
Public Relations Team
National Cancer Center
809 Madu1-dong
Ilsandong-gu, Goyang-si
Gyeonggi-do
Republic of Korea

Gary Clifford
International Agency for Research on Cancer
150 cours Albert Thomas
69372 Lyon Cedex 08
France

Vincent Cogliano
International Agency for Research on Cancer
150 cours Albert Thomas
69372 Lyon Cedex 08
France

Maria-Paula Curado
International Agency for Research on Cancer
150 cours Albert Thomas
69372 Lyon Cedex 08
France

David Currow
Flinders University
Sturt Road
Bedford Park South Australia
Australia

Jean-Marie Dangou
Division of Prevention & Control of Noncommunicable Diseases
WHO Regional Office for Africa
Cité Djoué, PO Box: 06
Brazzaville
Congo Republic

Ketayun Dinshaw
Tata Memorial Centre
E. Borges Marg., Parel
Mumbai 400 012
India

Sylvie Dolbeault
Psycho-Oncology Unit
Curie Institute
26 rue d'Ulm
75246 Paris, Cedex 05
France

Jean-François Doré
INSERM U 590
Centre Léon Bérard
28, rue Laennec
69373 Lyon Cedex 08

Mary Doroshenk
National Colorectal Cancer Roundtable
American Cancer Society
www.nccrt.org

Eric Duell
International Agency for Research on Cancer
150 cours Albert Thomas
69372 Lyon Cedex 08
France

Mary Farfán
National Institute of Neoplastic Disease (INEN)
Av. Angamos 2520, Surquillo
Lima 34
Peru

Jill Farrington
Noncommunicable Diseases
WHO Regional Office for Europe (EURO)
Scherfigsvej 8
2100 Kobenhavn Ø
Denmark

Rodrigo Feijó
Divisão de Comunicação Social
National Cancer Institute (INCA)
Praca Cruz Vermelha 23, Centro
20230-130 Rio de Janeiro
Brazil

Jacques Ferlay
International Agency for Research on Cancer
150 cours Albert Thomas
69372 Lyon Cedex 08
France

Pietro Ferrari
Data Collection and Exposure Unit
European Food Safety Authority
Largo N. Palli 5/A
43100 Parma
Italy

Silvia Franceschi
International Agency for Research on Cancer
150 cours Albert Thomas
69372 Lyon Cedex 08
France

Pierre Hainaut
International Agency for Research on Cancer
150 cours Albert Thomas
69372 Lyon Cedex 08
France

Uzma Hasan
International Agency for Research on Cancer
150 cours Albert Thomas
69372 Lyon Cedex 08
France

Mia Hashibe
International Agency for Research on Cancer
150 cours Albert Thomas
69372 Lyon Cedex 08
France

Mary Heanue
International Agency for Research on Cancer
150 cours Albert Thomas
69372 Lyon Cedex 08
France

Julia Heck
International Agency for Research on Cancer
150 cours Albert Thomas
69372 Lyon Cedex 08
France

Zdenko Herceg
International Agency for Research on Cancer
150 cours Albert Thomas
69372 Lyon Cedex 08
France

Lisa-Maree Herron
Cancer Australia
Level 1 - Northbourne Avenue
Lyneham, PO Box 1201
Dickson ACT 2602
Australia

Rayjean J. Hung
Samuel Lunenfeld Research Institute
60 Murray St.
Toronto M5T 3L9
Canada

Mazda Jenab
International Agency for Research on Cancer
150 cours Albert Thomas
69372 Lyon Cedex 08
France

Miklos Kasler
National Institute of Oncology
Rath Gyorgy u. 7-9
1122 Budapest
Hungary

David Kerr
Department of Clinical Pharmacology
University of Oxford
Old Road Campus Research Building
Off Roosevelt Drive
Headington, Oxford OX3 7DQ
UK

Namory Keita
Service de Gynécologie/Obstétrique
Université de Conakry
CHU Donka, route de Dixinn
B.P. 921 Conakry
Guinea

Heinrich Kovar
Children's Cancer Research Institute
St. Anna Kinderkrebsforschung
Kinderspitalgasse 6
1090 Vienna
Austria

Carlo La Vecchia
Laboratory of General Epidemiology
Mario Negri Institute of Pharmacological Research
Via La Masa, 19
20156 Milan
Italy

Maria Leon-Roux
International Agency for Research on Cancer
150 cours Albert Thomas
69372 Lyon Cedex 08
France

Bernard Levin
2628 Broadway
New York
NY 10025
USA

Ni Li
International Agency for Research on Cancer
150 Cours Albert Thomas
69372 Lyon Cedex 08
France

Haifa Madi
WHO Regional Office for Eastern Mediterranean and North African Region (EMRO)
P.O. Box 7608
Nasr City
Cairo 11371
Egypt

Patrick Maisonneuve
Epidemiology Unit
European Institute of Oncology
Via Ripamonti 435
20141 Milan
Italy

Kirsten McArdle
Department of Surgery
City Hospital
Dudley Rd
Birmingham B18 7QH
UK

James McKay
International Agency for Research on Cancer
150 cours Albert Thomas
69372 Lyon Cedex 08
France

Gordon McVie
Scientific Directorate
European Institute of Oncology
Via Ripamonti 435
20141 Milan
Italy

Richard Muwonge
International Agency for Research on Cancer
150 cours Albert Thomas
69372 Lyon Cedex 08
France

Maria-Claudia Nascimento
London School of Hygiene & Tropical Medicine
Keppel Street
London WC1E 7HT
United Kingdom

Twalib Ngoma
Ocean Road Cancer Institute
PO Box 3592
Dar es Salaam
United Republic of Tanzania

Hiroko Ohgaki
International Agency for Research on Cancer
150 cours Albert Thomas
69372 Lyon Cedex 08
France

Shigeru Omi
WHO Regional Office for the Western Pacific (WPRO)
United Nations Avenue
PO Box 2932
Manila 1000
Philippines

Claudio Pelucchi
Laboratory of General Epidemiology
Mario Negri Institute of Pharmacological Research
Via La Masa, 19
20156 Milan
Italy

Luis Pinillos Ashton
National Institute of Neoplastic Disease (INEN)
Av. Angamos 2520, Surquillo
Lima 34
Peru

Samlee Plianbangchang
WHO Regional Office for South-East Asia (SEARO)
World Health House - Indraprastha Estate
Mahatma Gandhi Marg
New Delhi 110 002
India

Martyn Plummer
International Agency for Research on Cancer
150 cours Albert Thomas
69372 Lyon Cedex 08
France

Amelie Plymoth
International Agency for Research on Cancer
150 cours Albert Thomas
69372 Lyon Cedex 08
France

Qing Qing
Division of Environmental Health Sciences
Yale School of Public Health
60 College Street, PO Box 208034
New Haven, CT 06520-8034
USA

Kunnambath Ramadas
Regional Cancer Center
P.O. Box 2417
Trivandrum 695011
Kerala State
India

Giorgia Randi
Laboratory of General Epidemiology
Mario Negri Institute of Pharmacological Research
Via La Masa, 19
20156 Milan
Italy

Darius Razavi
Jules Bordet Institute
121 boulevard de Waterloo
Brussels 1000
Belgium

Sabina Rinaldi
International Agency for Research on Cancer
150 cours Albert Thomas
69372 Lyon Cedex 08
France

Ulrik Ringborg
Cancer Center Karolinska
Radiumhemmet
Karolinska University Hospital Solna
171 76 Stockholm
Sweden

Stefania Rizzo
European Institute of Oncology
Via Ripamonti 435
20141 Milan
Italy

Alan Rodger
Beatson West of Scotland Cancer Centre
Gartnavel General Hospital
Great Western Road
Glasgow
Scotland, UK

Mirta Roses
Regional Office for the Americas/Pan American Sanitary Bureau (AMRO)
525, 23rd Street NW
Washington, DC 20037
USA

Massoud Samiei
Programme of Action for Cancer Therapy (PACT)
Department of Nuclear Sciences and Applications
International Atomic Energy Agency (IAEA)
Wagramerstrasse 5
PO Box 100
1400 Vienna
Austria

Rengaswamy Sankaranarayanan
International Agency for Research on Cancer
150 cours Albert Thomas
69372 Lyon Cedex 08
France

Catherine Sauvaget
International Agency for Research on Cancer
150 cours Albert Thomas
69372 Lyon Cedex 08
France

Ghislaine Scelo
School of Public Health
UC Berkeley
2150 Shattuck Ave., Suite 500
Berkeley, CA94704-7380
USA

Mary Jane Schier
M. D. Anderson Cancer Center
The University of Texas
1515 Holcombe Blvd
Houston, TX 77030
USA

Vladimir Semiglazov
N.N. Petrov Research Institute of Oncology
68 Leningradskaya Str., Pesochny 2
Saint Petersburg 197758
Russian Federation

Hai-Rim Shin
International Agency for Research on Cancer
150 cours Albert Thomas
69372 Lyon Cedex 08
France

Sudhir Srivastava
Cancer Biomarkers Research Group
Division of Cancer Prevention
National Cancer Institute
6130 Executive Boulevard, Suite 3142
Rockville, MD 20852
USA

Eva Steliarova-Foucher
International Agency for Research on Cancer
150 cours Albert Thomas
69372 Lyon Cedex 08
France

Kurt Straif
International Agency for Research on Cancer
150 cours Albert Thomas
69372 Lyon Cedex 08
France

Bakary Sylla
International Agency for Research on Cancer
150 cours Albert Thomas
69372 Lyon Cedex 08
France

Sean Tavtigian
International Agency for Research on Cancer
150 cours Albert Thomas
69372 Lyon Cedex 08
France

Massimo Tommasino
International Agency for Research on Cancer
150 cours Albert Thomas
69372 Lyon Cedex 08
France

Murat Tuncer
Cancer Control Department
Ministry of Health
Ilkiz Sokak No. 4/2
Sihhiye
06434 Ankara
Turkey

Lawrence von Karsa
International Agency for Research on Cancer
150 cours Albert Thomas
69372 Lyon Cedex 08
France

Joachim Weis
Department of Psychooncology
Tumor Biology Center at the University of Freiburg
Breisacher Str. 117
79106 Freiburg
Germany

Yi-Xin Zeng
Sun Yat-Sen University Cancer Center
651 Dongfeng Road East
Guangzhou 510060
China

Yawei Zhang
Division of Environmental Health Sciences
Yale School of Public Health
60 College Street, PO Box 208034
New Haven, CT 06520-8034
USA

Ping Zhao
Cancer Hospital and Institute
CAMS and Peking Union Medical College
17 South Pan Ji Yuan Lane
PO Box 2258
Beijing 100021
China

Tongzhang Zheng
Division of Environmental Health Sciences
Yale School of Public Health
60 College Street, PO Box 208034
New Haven, CT 06520-8034
USA

Subject index