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Obesity and colorectal cancer

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1. ABSTRACT

This review outlines the association of obesity with risk of colorectal cancer and the potential underlying mechanisms from an epidemiological perspective. Current research indicates that there is a moderate but consistently reported association between general obesity (as determined by BMI) and colorectal cancer incidence and mortality. The relative risk associated with obesity is higher for cancer of the colon than for cancer of the rectum and it is higher in men than in women. By contrast, abdominal adiposity (as determined by waist circumference or waist-to-hip ratio) is similarly strongly associated with colon cancer in men and women, suggesting that abdominal adiposity is a more important risk factor for colon cancer than general adiposity, at least in women. Putative mechanisms that may account for the link between adiposity and colorectal cancer risk include hyperinsulinemia, insulin resistance, inflammation, altered immune response, oxidative stress, as well as disturbances in insulin-like growth factors, adipokines, and sex steroids. Understanding the link between obesity and colorectal cancer may pave the way for targeted prevention of colorectal cancer morbidity and mortality.

2. INTRODUCTION

Colorectal cancer is the third most common type of cancer in men and the second most common type in women worldwide(1). For the year 2008 it was estimated that 663,000 men and 570,000 women were newly diagnosed with colorectal cancer, accounting for 10.0% and 9.4% of cancer incidence in men and women, respectively (1). There is a pronounced gradient in incidence rates between developing and developed countries, with almost 60% of the cases occurring in developed regions. Incidence rates vary 10-fold worldwide, with highest rates in Australia/New Zealand and Western Europe and lowest rates in Africa and South-Central Asia. About 608,000 deaths from colorectal cancer per year were estimated worldwide, accounting for 8% of all cancer deaths in 2008, making it the fourth most common cause of death from cancer. There is less variability in mortality rates worldwide (6-fold in men and 5-fold in women), with the highest rates estimated in Central and Eastern Europe (20.3 per 100,000 in men, 12.1 per 100,000 in women), and the lowest in Middle Africa (3.5 and 2.7, respectively) (1). The parallel of colorectal cancer disease frequency with the 'Westernization' of the countries points to the role of

Table 1. Definitions of general and abdominal obesity (based on Expert Panel, 1998) (170)[1]

		Disease risk[2] relative to normal weight and waist circumference	
Classification	BMI (kg/m^2)	Men ≤102 cm Women ≤88 cm	Men >102 cm Women >88 cm
Underweight	<18.5	-	-
Normal	18.5-24.9	-	-
Overweight	25.0-29.9	Increased	High
Obese – Class I	30.0-34.9	High	Very high
Obese – Class II	35.0-39.9	Very high	Very high
Obese – Class III	≥40	Extremely high	Extremely high

Abbreviations: BMI: Body mass index. [1] Established for non-Asian populations. The recently proposed classification for Asian populations is: BMI < 18.5, underweight; 18.5-22.9, normal weight; 23.0-24.9, overweight; 25.0-29.9, obese class I; > 30.0, obese class II 12. [2] Disease risk for type 2 diabetes, hypertension, and cardiovascular disease.

environmental factors in the etiology of the disease. In support of this hypothesis, migrants tend to acquire the risk typical of the host population within one generation (2).

Excess body weight is one of the major factors that substantially contribute to the overall burden of chronic diseases and mortality worldwide (3). Accumulating evidence suggests that excess body weight also increases the risk of several types of cancer, including colorectal cancer (4). The prevalence of overweight (defined as a body mass index (BMI) between 25.0 and 29.9 kg/m^2) and obesity (BMI≥30 kg/m^2) has increased dramatically during the last decades (5). In the EU, approximately 40–50% of men and 25–35% of women are overweight and an additional 15–25% of men and 15–25% of women are obese (6, 7). In the US, in the years 2007-2008, approximately 34.2% of adults aged 20 years and over were overweight and 33.8% were obese (8). Globally, 9.8% of the world population - 0.4 billion affected individuals – were obese in the year 2005 (20.3% in economically developed countries) (9).

This review outlines the relationship of obesity with risk of colorectal cancer incidence and mortality and the underlying pathophysiology from an epidemiological perspective. In particular, this review summarizes current knowledge on the association between general and abdominal obesity, childhood obesity, weight gain, and biomarkers related to obesity, with relevance for colorectal cancer risk.

3. OBESITY DEFINITIONS

According to the World Health Organization, obesity is "a condition of abnormal or excessive fat accumulation in adipose tissue, to the extent that health may be impaired" (10). Since the 1980s, the globally accepted criteria for the definition of overweight and obesity in adults are based on BMI, calculated as weight (in kilograms) divided by height (in meters) squared (Table 1). The classification by BMI is largely based on epidemiological studies showing that BMI is correlated with fat mass and associated with morbidity and mortality. In children and adolescents, the established BMI cut-offs to define overweight and obesity are not applicable, which is largely due to the natural rapid change in stature and body composition at young ages. Therefore, age-related reference curves of BMI are used to define overweight and obesity in childhood and adolescence (10).

Although BMI is associated with a number of chronic diseases in a wide range of populations, there are a number of limitations. First, within each category of BMI there is substantial individual variation in body composition. Thus, an important drawback of BMI is the inability to distinguish between fat mass and lean mass. For example, muscular people (such as manual workers and power athletes) have a relatively high BMI, despite having relatively little body fat. Vice versa, many individuals not labeled as obese based on BMI might indeed have excess adiposity (11). Second, BMI may vary across different ethnic populations and may not be sensitive to capture associated health risks in certain populations. Ethnic-specific BMI cutoffs have been proposed and start being adopted in some regions, such as Asian countries (12). Third, BMI does not take body fat distribution into account. Viscerally deposited fat is metabolically more active and secretes greater amounts of cytokines and hormones compared with subcutaneous adipose tissue (13). Further, a higher influx of portal fatty acids, cytokines and hormones into the liver from omental adipose tissue may specifically distort hepatic metabolism, including abnormal lipoprotein synthesis, hepatic insulin resistance and increased gluconeogenesis (14). Fat distribution is gender-specific, with women having a greater amount of peripherally located subcutaneous fat and men having a greater amount of centrally located visceral fat. Body fat distribution can most easily be assessed by measurement of the waist and hip circumferences. Current guidelines suggest a waist circumference of 102 cm in men and 88 cm in women, or a waist-hip ratio of 0.95 in men and 0.80 in women, as being the cut-off points for abdominal obesity that are purportedly associated with an increased risk of morbidity (Table 1) (15, 16). Large studies have indicated that measurement of waist circumference or waist-hip ratio in addition to BMI may improve the prediction of health outcomes (17), and intensive research is still ongoing as to which variable(s) are the most accurate and precise predictors of disease risk.

Measurement of changes in BMI or waist circumference during adulthood was suggested to be more sensitive for the assessment of adiposity than static measures. Thus, attained BMI in adulthood depends on both, lean mass and fat mass; whereas, increases in body weight during adulthood mostly depend on accumulation of fat rather than lean tissue and may thus better reflect adiposity4. However, assessment of changes in BMI and waist circumference in large scale studies is usually not readily available or often depends on recalled weight.

Although studies show that there is a moderate to strong correlation between self-reported and measured past weight in the range of 0.64 to 0.95, the assessment of recalled weight may introduce measurement error or bias, and has thus been the subject of criticism (18, 19).

Several alternative diagnostic tools are available to assess body fat composition, such as measurement of (subcutaneous) skinfold by means of a caliper or ultrasound, bioelectrical impedance analysis, densitometry or imaging procedures (computerized tomography, NMR). However, most of these innovative procedures to assess body fat composition are not readily available in clinical practice and the practicality of their application in large-scale epidemiological studies is to be evaluated. In addition, it is questionable to what extent these measures add information for the prediction of health outcomes beyond BMI and waist circumference.

In summary, BMI and waist and hip circumference are currently the standard parameters to assess the degree of adiposity in adulthood. While BMI can be considered as a marker for assessment of general adiposity, waist and hip circumference – particularly when considered in addition to BMI – can be considered as markers for assessment of abdominal fat distribution.

4. OBESITY AND RISK OF COLORECTAL CANCER

4.1. General adiposity and risk of colorectal cancer

The association between general adiposity, as assessed by BMI, and risk of colorectal cancer has been examined in a number of epidemiological studies, and several systematic reviews and meta-analyses have summarized the existing evidence (Table 2). Bergström and colleagues in 2001 were the first to review the epidemiological literature and to quantitatively summarize the relationship between excess weight and the risk of several cancer types, including colorectal cancer (20). The authors identified 19 studies that reported predominantly positive associations with an average RR of colorectal cancer of 1.03 (95% CI 1.02–1.04) per 1 unit higher BMI. This association was somewhat less consistent among women compared to men. The association was confirmed by an authoritative review by the World Cancer Research Fund (WCRF) expert panel based on 60 cohort and 86 case-control studies4. In that review, most of the cohort studies showed a higher risk of colorectal cancer in obese compared to normal weight subjects, which was statistically significant in approximately half of these studies. In meta-analysis, a linear relationship between BMI and colorectal cancer risk was observed with a summary relative risk estimate of 1.03 (95% CI 1.02–1.04) per 1 unit higher BMI (kg/m^2). When the studies were examined according to cancer site, stronger associations and more consistent results were seen for colon cancer than for rectal cancer. The most recent systematic review came from Ning et al., including 7 213 335 individuals from 56 populations with 93 812 colorectal cancer cases. Similar to the previous reviews, in that report the association of BMI with colorectal cancer was stronger for men than women, and for colon than rectal cancer (21).

Little is known as to what extent the association of obesity and colorectal cancer differs across countries or ethnicities. Such information would be helpful to tailor regional public health prevention programs that aim to reduce the incidence of colorectal cancer. Most studies and systematic reviews conducted so far have included Caucasian populations or did not specifically address differences in the association between obesity and colorectal cancer risk between countries or ethnicities. Interestingly, Matsuo and colleagues recently addressed the association of obesity and colorectal cancer in an Asian population (22). By pooling data of 8 population-based cohort studies with ~300 000 Japanese, the authors found relative risks of colorectal cancer associated with obesity that were in a range that was similar to what was found in other studies including other populations. Also, the association was again stronger in males than in females and it was stronger for colon cancer than for rectal cancer. Thus, the sex and cancer-site specific findings that were observed for Western countries showed to be replicable also for Asian populations.

4.2. Abdominal obesity and risk of colorectal cancer

The reasons for the apparent discrepancy in the association between obesity and colon cancer risk between men and women have long been unclear, and it has been suggested that one potential reason is that men and women have different body compositions. This has further inspired research efforts to look at parameters alternative to BMI to assess colorectal cancer risk. Thus, women generally have a higher percentage of body fat (healthy range of 20-25%) than men (10-15%). It is important to note that approximately 30% of fat in normal weight men can be stored in visceral area, while normal weight women have low quantities of visceral fat. Visceral fat accumulation in women starts only after considerable weight gain. The reasons for the difference in body fat distribution between men and women are largely unknown, although differences in hormones, hormone receptors, and enzyme concentrations may be involved (23). Research conducted over the past decades established visceral adipose tissue as an active endocrine organ, secreting a variety of molecules (selectively named adipokines) that were shown to be involved in inflammation, coagulation, and other metabolic actions (13, 24). Abdominal obesity is closely associated with adverse metabolic profiles such as insulin resistance, dyslipidemia, and systematic inflammation (24-26), which play essential roles in the pathogenesis of CVD, diabetes mellitus, and probably also for certain types of cancer. Assuming that it is primarily visceral adipose tissue and not non-visceral adipose tissue that is involved in tumorigenic processes, body weight and BMI may not accurately reflect the colon cancer risk that is associated with abdominal fat accumulation, at least in women. This hypothesis has been supported by findings from the European Prospective Investigation into Cancer and Nutrition (EPIC) that have indicated that abdominal obesity (as defined by waist circumference or waist-to-hip ratio) is an equally-strong risk factor for colon cancer in men and women, whereas body weight and BMI are associated with colon cancer risk in men but not in women (27). Thus, men and women in

Table 2. Meta-analyses on association of general obesity as measured by body mass index (BMI) with risk of colon and rectal cancer

		Year	Study design	Exposure categories	Cancer endpoint	
					Colon	Rectal
					RR (95% CI)[a]	RR (95% CI) [1]
1	Bergström et al.(20)	2001	2 case-control, 4 cohort	per unit increase of BMI	All colon: 1.03 (1.02, 1.04)	
2	Dai et al.(28)	2007	15 cohort studies	highest vs. lowest quantiles of BMI	Men: 1.59 (1.35, 1.86) Women: 1.22 (1.08, 1.39)	Men: 1.16 (0.93, 1.46) Women: 1.23 (0.98, 1.54)
3	Moghaddam et al(171).	2007	23 cohort, 8 case-control	BMI ≥30 vs. BMI <25	Men: 1.53 (1.33, 1.75) Women: 1.09 (0.93, 1.28)	Men: 1.27(1.17, 1.37) Women: 1.02 (0.85, 1.22)
4	Larsson and Wolk(148)	2007	30 cohort, 1 case-control	per 5 units increase in BMI	Men: 1.30 (1.25, 1.35) Women: 1·12 (1·07, 1.18)	Men: 1.12 (1.09, 1.16) Women: 1.03(0.99, 1·08)
5	WCRF report(4)	2007	28 cohort	per unit increase of BMI	All colorectal: 1.03 (1.02-1.04)	
6	Renehan et al.(172)	2008	29 (unspecified)	per 5 units increase in BMI	Men: 1.24 (1.20, 1.28) Women: 1.09 (1.05, 1.13)	Men: 1.09 (1.06, 1.12) Women: 1.02 (1.00, 1.05)
7	Guh et al.(173)	2009	12 cohort	BMI ≥25 vs. BMI <25 BMI ≥30 vs. BMI<30	Men: 1.51 (1.37, 1.67) Women: 1.45 (1.30, 1.62) Men: 1.95 (1.59, 2.39) Women: 1.66 (1.52, 1.81)	NA
8	Harris et al.(34)	2009	29 datasets	per 5 units increase in BMI	Men: 1.24 (1.20, 1.28) Women: 1.09 (1.05, 1.13)	Men: 1.09 (1.05, 1.14) Women: 1.02 (0.99, 1.43)
9	Ning et al. (21)	2010	44 cohort, 14 case-control	BMI ≥30 vs. BMI <25	Men: 1.60 (1.53, 1.69) Women: 1.25 (1.12, 1.39)	Men: 1.30 (1.17, 1.43) Women: 1.14 (1.02, 1.27)
10	Matsuo et al. (22)	2011	8 cohort (Asian populations)	BMI ≥30 vs. BMI <30	Men: 1.67 (1.15, 2.44) Women: 1.47 (1.05, 2.06)	Men: 1.87 (1.21, 2.88) Women: 0.98 (0.95, 1.01)

Abbreviations: BMI: body mass index, WCRF: World Cancer Reaserch Fund, RR: relative risk, CI: confidence interval [1]Pooled relative risk estimates from meta-regression Note: The literature search included studies published up to August, 2011.

the highest compared with the lowest gender-specific quintile of waist-to-hip ratio had a 50% higher risk of developing colon cancer over a mean follow-up period of 6 years. Several systematic reviews reported similar findings (Table 3). For example, a meta-analysis by Dai and colleagues (28) reported a pooled estimate of 1.68 (95% CI 1.36, 2.08) for the highest vs. lowest quintile of waist circumference in men and 1.48 (95% CI 1.19, 1.84) in women. The respective estimates for rectal cancer were 1.26 (95% CI 0.90, 1.77) for men and 1.23 (95% CI 0.81, 1.86) for women (Table 3). These data support the hypothesis that abdominal obesity is a risk factor for colon cancer in both sexes and suggest that fat distribution is more important than body weight or BMI for disease risk in women.

In summary, current research indicates that there is a moderate but consistently reported association between general obesity (as determined by BMI) and colorectal cancer incidence. The relative risk is greater for cancers of the colon than of the rectum and in men than in women. The sex risk differences are likely to mirror the differences in the distribution of the adipose tissue between men and women. Thus, when abdominal obesity (as determined by waist circumference or waist-to-hip ratio) was studied, the apparent sex differences were greatly reduced.

5. OBESITY DURING CHILDHOOD AND ADOLESCENCE AND COLORECTAL CANCER RISK

Obesity during childhood and adolescence poses a major public health problem worldwide through immediate and long-term adverse health outcomes such as insulin resistance, early-onset type 2 diabetes mellitus, hypertension, and dyslipidemia (29, 30). However, the impact of early life obesity on cancer risk later in life is less well studied (31, 32). Since initial steps of colorectal carcinogenesis may occur early in life, body fatness during childhood and adolescence may be etiologically related to risk of colorectal cancer later in life. Early life obesity is associated with alterations in basal insulin levels (33), which might influence early steps in carcinogenesis (34).

The association between body fatness in early life and colorectal cancer later in life has been addressed in a few epidemiological studies with heterogeneous study designs (35-43). A recent publication of the Nurses' Health Study II reported positive associations between childhood obesity and risk of colorectal adenoma (a precursor of colorectal cancer) (41). Comparing women who were overweight at age 5 years with women with the leanest body shape at the same age, a 44% increased risk of colorectal adenoma later in life was observed, which was independent of adult body mass index (BMI). A historical cohort study found a non-significantly elevated risk of colorectal cancer later in life for children (mean age 8 years) with body fatness (RR highest versus lowest BMI quartile 1.36, 95% CI 0.57-3.24) (37). Several studies investigated the association between body fatness in young adults, mostly college or university students, and risk of colorectal cancer incidence or mortality (35, 38-40, 42, 43). The largest study of this type observed significant positive associations between BMI between the age of 14 and 19 years and colon cancer mortality in men and women (RR 85th versus 25th-75th BMI percentile 2.1, 95% CI 1.1-4.1 in men and 2.0, 95% CI 1.2-3.5 in women) (35), and three smaller studies found positive associations between BMI during young adulthood and colorectal cancer incidence (38, 39) or death (40) in men. Two further studies observed no association between BMI at college entry and colorectal cancer incidence (43) or death from colorectal cancer (42). Many of the studies conducted to elucidate the association between early life obesity and risk of colorectal cancer later in life have substantial limitations such as low statistical power (40, 44) and lack of ability to adjust for potential

Table 3. Meta-analyses on the association of waist circumference (WC) and waist-to-hip ratio (WHR) with colon and rectal cancer

		Year	Study design	Exposure categories	Cancer endpoint	
					Colon	**Rectal**
					RR (95% CI)[a]	**RR (95% CI) [1]**
1	Dai et al.(28)	2007	15 cohort	highest vs the lowest quantile of WC highest vs the lowest quantile of WHR	Men: 1.68 (1.36, 2.08) Women: 1.48 (1.19, 1.84) Men: 1.91 (1.46, 2.49) Women: 1.49 (1.23, 1.81)	Men: 1.26 (0.90, 1.77) Women: 1.23 (0.81, 1.86) Men: 1.93 (1.19, 3.13) Women: 1.20 (0.81, 1.78)
2	Moghaddam et al.(171)	2007	8 cohort	WC<102 cm versus <94 cm; or <88 cm versus <80 cm	All colorectal: 1.50 (1.35, 1.67)	
3	Larsson and Wolk(148)	2007	5 cohort 3 cohort	per 10-cmWC increase per 0.1-unit WHR increase	Men: 1.33 (1.19, 1.49) Women: 1.16 (1.09, 1.23) Men: 1.43 (1.19, 1.71) Women: 1.20 (1.08, 1.33)	Men: 1.12 (1.03, 1.22) Women: 1.09 (0.99, 1.20) Men: 1.22 (0.81, 1.83) Women: 1.15 (0.95, 1.39)
4	Guh et al.(173)	2009	12 cohort	WC <94 cm in men or <80 cm in women vs WC ≥94 cm in men or ≥80 cm in women WC <102 cm in men or <88 cm in women vs. WC ≥102 cm in men or ≥88 cm in women	Men: 1.88 (1.47, 2.41) Women: 1.25 (0.98, 1.59) Men: 2.93 (2.31, 3.73) Women: 1.55 (1.27,1.88)	
5	WCRF report(4)	2007	4 cohort 5 cohort	per 2.5-cm WC increase per 0.1-unit WHR increase	All colorectal: 1.05 (1.03, 1.07) All colorectal: 1.30 (1.17, 1.44)	

Abbreviations: WC: waist circumference, WHR: waist to hip ratio, RR: relative risk, CI: confidence interval, WCRF: World Cancer Research Fund; [1] Pooled relative risk estimates from meta-regression Note: The literature search included studies published up to August, 2011.

confounders (38, 39, 43). Furthermore, some studies date back to time periods before the second World war (38-40), when children in poorer families might have suffered from undernutrition, and may thus reflect different relationships than would be observed during more wealthy time periods. In summary, there is a plausible hypothesis for early life obesity to influence colorectal cancer risk, and some studies showed significant positive associations; however, more research is warranted to investigate whether obesity is a risk factor for colorectal cancer that is relevant already in early life.

6. WEIGHT CHANGE AND COLORECTAL CANCER

Most studies on obesity and colorectal cancer relied on a single measurement of BMI, which is a static indicator of obesity status. However, BMI tends to fluctuate over time and it is important to understand whether a dynamic obesity indicator such as weight change over time is also related to cancer risk. Despite extensive evidence on the link between overweight and obesity and colorectal cancer, previous studies of weight change and risk of colon adenoma and cancer showed inconsistent results (38, 45-58). In 2000, the International Agency for Research on Cancer (IARC) reported that there is limited evidence for an association between weight change and risk of colorectal cancer (59). More recently, positive associations between adult weight gain and colon cancer risk have been reported by several cohort (53, 57, 60) and case-control studies (49, 61-63). In a recent analysis in the Health Professionals Follow-up study, the use of multiple repeated BMI measurements over time yielded considerably stronger RRs for colon cancer than the use of a single baseline assessment (57). A case-control study in Canada reported that men who gained 21 kg after the age of 20 had a 60% higher risk for colorectal cancer than men who had gained 1–5 kg (61). The association was stronger after exclusion of rectal cancers. Although most of these studies reported only weak or null associations for women, in two other studies excessive adult weight gain among women but not men was associated with a higher risk of colon cancer (64, 65). In a recent report from the Melbourne Collaborative Cohort among 16,188 men and 23,438 women followed-up of for 14 years, adult weight change was positively associated with colon cancer risk for men (HR, 1.11 per 5-kg increment; 95% CI, 1.03-1.20), but not women (HR, 1.00; 95% CI, 0.94-1.07)60. Men who gained ≥20 kg from age 18 had a higher risk of colon cancer compared with men whose weight was stable. Further large population-based prospective studies are needed to shed more light on the potential effects of weight change throughout adult life on risk of colon and rectal cancer in men and in women.

7. METABOLIC SYNDROME AND COLORECTAL CANCER

Abdominal adiposity is associated with other metabolic abnormalities, such as elevated blood pressure (BP), abnormal glucose metabolism, and dyslipidaemia, which tend to cluster and increase the risk to develop cardiovascular disease and type 2 diabetes mellitus. This clustering of metabolic abnormalities is described as "Metabolic Syndrome" (MetS). Several international expert groups have provided unified criteria of MetS (Table 4). Recent evidence suggests that components of MetS may

Table 4. Definitions of Metabolic Syndrome

Definition	**NCEP/ATPIII (2005 revision) (16)**	**IDF (2005)(15)**	**Harmonized definition (2009) *(76)***
Components:	**Three or more of the following:**		**Any three of the following:**
Abdominal adiposity	≥102 cm in men, ≥88 cm in women	≥94 cm in men, ≥80 cm in women (for European population) **plus any 2 of the following:**	≥94 cm in men,≥ 80 cm in women (for European population)
Elevated TG	≥150 mg/dL (1.7 mmol/L)	≥150 mg/dL (1.7 mmol/L) or specific treatment for lipid metabolism	150 mg/dL (1.7 mmol/L) or specific treatment for lipid metabolism
Reduced HDL-C	<40 mg/dL (1.03 mmol/L) in men <50 mg/dL (1·29 mmol/L) in women	<40 mg/dL (1.03 mmol/L) in men <50 mg/dL (1.29 mmol/L) in women	<40 mg/dL (1.03 mmol/L) in men <50 mg/dL (1.29 mmol/L) in women or specific treatment for lipid metabolism
Elevated BP	systolic≥130, diastolic≥85 mmHg or treatment of previously diagnosed hypertension	systolic≥130, diastolic≥85 mmHg or treatment of previously diagnosed hypertension	systolic≥130, diastolic≥85 mmHg or treatment of previously diagnosed hypertension
Abnormal Glucose Metabolism	fasting glucose levels ≥100 mg/dl (≥5.6 mmol/l) or previously diagnosed type 2 diabetes	fasting glucose levels ≥100 mg/dl (≥5.6 mmol/l) or previously diagnosed type 2 diabetes	fasting glucose levels ≥100 mg/dl (≥5.6 mmol/l) or drug treatment for elevated glucose

Abbreviations: WC: waist circumference, TG: tryglyceride, BP: blood pressure, NCEP/ATPII: National Cholesterol Education Program/Adult Treatment Panel III, IDF: International Diabetes Federation

also be associated with risk of colorectal cancer (66), particularly abdominal adiposity, abnormal glucose metabolism (67), and dyslipidaemia (68). These findings supported the hypothesis that MetS may also be used to identify individuals at risk of colorectal cancer. As a result, a number of studies investigated the association between MetS and colorectal cancer, and most of them reported positive associations (69-74). However, a comparison of results of these studies is difficult because different MetS criteria were used (70, 73). It is important to note that the definitions of MetS components are based on dichotomised arbitrary cut-off points; proposed for use in clinical practice. Further, MetS is a heterogeneous condition that may reflect various combinations of metabolic abnormalities, and it is not clear whether the potential association of MetS with colorectal cancer may be accounted for by its components. The answer to this question is crucial for understanding whether complex assessment of MetS may be more useful for identifying subjects at risk of colorectal cancer compared to assessing certain MetS components. These questions were recently addressed in the EPIC cohort (75). In that study, MetS was defined according to the criteria of the National Cholesterol Education Program/Adult Treatment Panel III (NCEP/ATPIII)16, the International Diabetes Federation (15) and the 2009 harmonized definition (76). Among the five components of MetS, only abdominal obesity and abnormal glucose metabolism were associated with risk of colorectal cancer independent of the other components. Thus, although MetS was associated with colon cancer risk, this association was largely accounted for by abdominal obesity and abnormal glucose metabolism. These findings highlight the role of abdominal fatness and abnormal glucose metabolism (related to insulin resistance and hyperinsulinemia) for risk of colorectal cancer.

8. POTENTIAL MECHANISMS FOR THE ASSOCIATION BETWEEN OBESITY AND COLORECTAL CANCER

8.1. Insulin resistance, hyperinsulinemia, and elevated insulin-like growth factors

Obesity, particularly abdominal obesity is associated with insulin resistance, a state when insulin is less effective than normal in lowering blood glucose levels (77). As a consequence, more insulin is released to the blood, resulting in chronically increased insulin levels, which has been hypothesized to be an explanatory link between obesity and colorectal cancer risk. Insulin may increase colorectal cancer risk by either direct mitogenic effects or by increasing the bioavailability of the potent mitogen insulin-like growth factor 1 (IGF-1) (78). Circulating insulin may increase the bioactivity of IGF-1 by up-regulating hepatic IGF-1 synthesis, or by reducing hepatic secretion of two IGF binding proteins (IGFBP-1 and IGFBP-2), resulting in higher free or bioactive IGF-1 levels (77, 79). The responses of insulin and IGFs are mediated by insulin receptors (IR) and IGF-1 receptors (IGF1R), both of which are widely expressed on normal tissues as well as on cancerous colorectal epithelia cells (79). There is evidence from in vitro and in vivo studies that both insulin and IGF-1 may directly influence growth of various neoplasms through stimulatory effects on cell proliferation and inhibition of apoptosis (80, 81). Furthermore, animal studies have demonstrated that restriction of energy intake is associated with reduced carcinogenesis, which may be due to reduced levels of insulin and IGF-1 as a consequence of energy restriction (80).

The hypothesis that hyperinsulinemia may explain the positive association between obesity and colorectal cancer is supported by numerous epidemiologic studies that observed that individuals with adult type 2 diabetes mellitus (which is associated with insulin resistance and increased insulin secretion), are at increased risk of colon cancer (82). Positive associations between pre-diagnostic insulin levels and risk of colorectal cancer have been observed in a small prospective cohort study (83), whereas only non-significant positive associations were observed in a second larger study (84). Several prospective studies have observed positive associations between pre-diagnostic plasma C-peptide (which is a valid indicator of insulin secretion that has a longer half-life than insulin) and colorectal cancer risk (85-87). In the EPIC cohort, elevated serum C-peptide levels were associated with an increased risk of colorectal cancer, and, although no statistically significant interaction was observed, higher

C-peptide was more strongly associated with colorectal cancer risk in participants with high waist circumference, strengthening the hypothesis that hyperinsulinemia plays an etiologic role in the development of colorectal cancer (88). Further, in EPIC, a high percentage of glycosylated hemoglobin (HbA1c), a marker for hyperglycemia, was statistically significantly associated with a higher colorectal cancer risk (67). The positive association of circulating levels of insulin, C-peptide and glycosylated hemoglobin with risk of colorectal cancer was confirmed by a meta-analysis (89).

The majority of prospective studies investigating circulating IGF-1 levels in relation to colorectal cancer risk showed positive albeit mostly non-significant associations (85, 87, 90-99). For example, in EPIC, which poses so far the largest study investigating IGF-1 levels in relation to colorectal cancer risk, there was no significant association (98). A meta-analysis of 11 prospective studies including the null-finding from EPIC showed a moderately significantly increased risk of colorectal cancer, with a RR of 1.07 (95% CI 1.01-1.14) associated with one standard deviation higher IGF-1 levels (98). Very few studies examined the joint association of insulin exposure and IGF-1 concentrations. The Nurses' Health Study revealed that either high IGF-1 or high insulin exposure (represented by high plasma C-peptide) was sufficient to substantially elevate colon cancer risk, while being high in both did not additionally increase risk (99), suggesting the IGF-1 exposure may be more relevant in individuals with a lower degree of hyperinsulinemia. Taken together, serologic evidence supports the hypothesis that the positive association between obesity and colorectal cancer is at least partly explainable by hormonal changes related to hyperinsulinemia.

8.2. Chronic inflammation

Inflammation has been hypothesized to play an important role in carcinogenesis, particularly for colorectal cancer (100). This is supported by studies which have shown that individuals with chronic inflammatory bowel disease have a higher risk of colorectal cancer compared to the normal population (101-103), and that use of aspirin or other anti-inflammatory drugs is associated with a lower risk (104). Adiposity is associated with a state of chronic low-grade inflammation, characterized by increased secretion of pro-inflammatory cytokines, such as tumor necrosis factor alpha (TNF-alpha) and interleukin (IL)-6, that induce hepatic secretion of acute phase proteins, including C-reactive protein (CRP) (105). Many of the 'classic' cytokines and growth factors that are synthesized and released by adipose tissue are believed to have direct pro-tumorigenic properties in the gastrointestinal tract.

Epidemiologic research suggests a modest association between biomarkers of chronic inflammation (particularly CRP) and colorectal cancer risk. A recent meta-analysis suggested that CRP concentrations are weakly positively associated with risk of colon cancer (RR = 1.1, 95% CI: 1.0–1.3) and that this relationship is stronger in men than in women, whereas no association was found for rectal cancer (106). In a large nested-case control study within the EPIC cohort elevated concentrations of CRP were associated with a higher risk of colon cancer, but not rectal cancer, predominantly among men. Interestingly, adjustment for BMI and waist circumference, C-peptide, glycated hemoglobin, and high density lipoprotein cholesterol did not attenuate the results, suggesting that elevated CRP concentrations are related to a higher risk of colon cancer independently of obesity, insulin resistance, and dyslipidemia.

Weight loss in obese individuals has been shown to reduce the level of inflammation systemically as shown by reduced CRP levels, (107), as well as locally in the colorectal mucosal, as shown by decreased levels of inflammatory cytokines, less inflammatory cells, down-regulated inflammatory and cancer gene pathways, and reduced expression of transcription factor gene sets that are relevant for inflammation and cancer (108). These data imply that obesity is accompanied by inflammation systemically as well as in the colorectal mucosa and that diet-induced weight loss reduces this inflammatory state and may thereby lower colorectal cancer risk.

8.3. Hyperleptinemia

Leptin, a product of the obese (ob) gene, is a 16 kDa peptide hormone, expressed primarily in the adipose tissue (109). Originally discovered in 1994 as a long-term regulator of food intake and energy balance acting in the hypothalamus (110), it is today recognized that leptin has effects on energy homeostasis, neuroendocrine function, metabolism, immune function, bone metabolism, and, potentially, also on cancer (111). Leptin exerts a number of effects purportedly relevant for carcinogenesis, such as inducing tumor angiogenesis, promoting cell proliferation and migration, interacting with metabolic and growth factors, and increasing estrogen biosynthesis (112, 113). Experimental studies have shown that leptin stimulates the proliferation and invasiveness of human colon cancer cells and may be directly related to risk of colorectal cancer (114-116). Only a few epidemiological studies have investigated the relationship between leptin concentrations and colorectal cancer risk in humans (117-121) and the results provided have been inconsistent. Two prospective studies observed an association between leptin concentrations and colon cancer but not rectal cancer, which was apparent in men but not in women. Stattin and colleagues first reported that elevated concentrations of circulating leptin were associated with a higher risk for colon cancer in men, but not in women over a follow-up even after adjustment for BMI; whereas no association was seen for rectal cancer (120). Another study confirmed these results for men, reporting approximately a 3-fold higher risk of colon cancer for the highest versus the lowest levels of serum leptin concentrations over a follow-up period of 17 years (119). Conversely, another nested case-control study conducted in women only, reported that elevated leptin concentrations were associated with colorectal cancer (121). A more recent prospective study suggested that only very high levels of leptin concentrations confer a higher risk of colorectal cancer (72). These conflicting results of previous studies may partly be explained by the small study sample sizes, different measurement techniques of leptin

concentrations and potentially differential control for confounding factors. Energy balance, inflammation and insulin-signaling have been identified as contributors to the development of colon cancer and are also partly regulated by leptin. Because of these complex interrelationships it is difficult to specify whether leptin has a causative role in colorectal cancer development, or whether it is merely a marker for other risk factors (122). In addition, the effects of leptin are mediated by membrane protein receptors, which also circulate in soluble form in plasma (123-125). Leptin acts by binding to the long form of the leptin receptor (mainly in the hypothalamus) and is cleared by the short form of leptin receptor, which is mainly expressed in the kidneys. The major leptin binding protein, soluble leptin receptor (sOB-R), (126, 127) acts as a negative regulator of leptin's physiological functions (128-134) and is inversely associated with obesity (135). It has thus been proposed that the ratio of leptin to the soluble leptin receptor may be important to assess the activity of the leptin system (130, 131, 136); however, the potential role of the soluble leptin receptor for colorectal cancer risk is unknown.

8.4. Hypoadiponectinemia

Adiponectin is an adipose tissue derived hormone that – in contrast to most other adipokines – is inversely associated with body weight, insulin resistance, diabetes mellitus, and cardiovascular disease (137, 138). Adiponectin is involved in the regulation of energy homeostasis, vascular reactivity, inflammation, cell proliferation and tissue remodeling (139, 140). Studies suggest that adiponectin may also be inversely associated with cancer, in particular with colorectal cancer, through direct mechanisms such as inhibiting cancer cell growth (141) and inducing apoptosis (142), as well as indirectly through pathways related to glucose metabolism and insulin resistance (143, 144).

Evidence on a potential link between adiponectin and colorectal cancer risk from prospective epidemiological studies is conflicting (111). In a large prospective Health Professionals Follow-up study, Wei and colleagues (145) found that plasma adiponectin levels were inversely associated with risk of colorectal cancer. Individuals in the highest adiponectin quintile had an approximately 60% reduced risk of colorectal cancer compared to the lowest quintile, independent of body mass index, waist circumference, waist-to-hip ratio and physical activity (145). In contrast, the Norwegian Janus Project reported no statistically significant association between serum adiponectin and risk of colorectal in men (146).

Adiponectin consists of three domains including a signal peptide, a collagen-like motif and a globular domain. In addition, adiponectin exists in the circulation in at least two forms, low molecular weight (LMW) oligomers (i.e, hexamers, two trimers) and high molecular weight (HMW) oligomers (126, 127) consisting of four to six trimers. Although the majority of intracellular adiponectin consists of HMW oligomers, LMW oligomers are the predominant form of adiponectin in the circulation. It has recently been suggested that HMW adiponectin is the major source of the active form of this protein (147). Therefore, the effects of adiponectin may depend on its complex quaternary structure in plasma, and HMW-adiponectin was reported to be more closely related to insulin sensitivity and risk of type 2 diabetes than the complexes with lower molecular weight (i.e., non-HMW adiponectin), suggesting that it may be the metabolically more active form (27). However, the association of HMW adiponectin with risk of colorectal cancer has not been investigated so far.

8.5. Other mechanisms

In addition to the metabolic pathways discussed above, other potential mechanisms for the association between body fatness and colorectal cancer risk have been proposed. Thus, changes in sex hormone levels associated with obesity (i.e. estrogen, testosterone) were suggested to be linked to colorectal cancer risk. For instance, differences in the association between body fatness and colorectal cancer risk between men and women may be related to sex differences in the way adiposity affects testosterone concentration (148). Furthermore, high body fatness is associated with higher endogenous estrogen levels, and a prospective study among postmenopausal women observed a significant association between high endogenous estradiol levels and higher risk of colorectal cancer (91). The positive association was unaffected by adjustment for waist circumference, insulin and free IGF-1, which led the authors to the conclusion that a pathway involving endogenous estradiol may exist that is independent of the pathway broadly associated with obesity, hyperinsulinemia and IGF-1. A second prospective study in postmenopausal women observed positive associations between endogenous estrone but not estradiol and colorectal cancer risk (149).

Alterations in the immune response, in the nuclear factor kappa B (NF-kappa B) system, in oxidative stress, and in peroxidation are alternative mechanisms that may link obesity to colorectal cancer risk (150). For example, case-control studies have shown increased blood levels of oxidative stress markers in patients with familial adenomatous polyposis and colorectal cancer (151-153). However, a recent nested case-control study in EPIC suggested that the association between oxidative stress indicators, such as reactive oxygen metabolites (ROM), and colorectal cancer risk is a result of reactive oxygen species (ROS) production by preclinical tumours, rather than a causal factor in carcinogenesis (reverse causation) (154). In this study, ferric reducing ability of plasma (FRAP), another marker of oxidative stress, was not associated with colorectal cancer risk. Studies with longer follow up and combined measures of reactive oxygen exposure and antioxidant status are needed to further explore the association between oxidative stress and colorectal cancer risk.

In summary, a number of biomarkers have been identified that may reflect pathways that may be responsible for the association of obesity with risk of colorectal cancer, particularly insulin, IGF-1, inflammatory markers, as well as adipokines and sex hormones. Because biomarkers reflecting these pathways are highly interrelated it is difficult to specify the exact roles and mechanisms of

action with regards to each other. Also, current evidence relies mostly on observational studies, and, therefore, causality remains to be established. One approach to test for causality is to conduct 'Mendelian randomization' studies. This design can assess gene-related risk factors for causal association with clinical outcomes under the assumption that individuals inherit gene variants randomly from their parents. Few studies examined the association between single nucleotide polymorphisms (SNPs) within the CRP, ADIPOQ, LEP and LEPR genes with colorectal cancer risk and results have been inconsistent (155, 156). For example, a recent study applying the Mendelian randomisation approach demonstrated that polymorphisms in the CRP gene that are associated with increased circulating levels of CRP are not associated with higher risk of cancer (157), whereas various genotype combinations of LEPR,LEP and ADIPOQ variants were shown to be associated with colorectal cancer risk (143, 147). Further research, particularly from prospective studies, is needed to investigate the role of obesity biomarkers for risk of colorectal cancer. Recent advancements of genomics and molecular epidemiology may be used to provide insights on causality of obesity-related biomarkers and risk of colorectal cancer.

9. OBESITY AND COLORECTAL CANCER SURVIVAL

Compared with the vast amount of literature with respect to colorectal cancer incidence, there is a paucity of data about the effect of obesity on colorectal cancer recurrence and survival. After diagnosis, individuals with colorectal cancer remain at higher risk of colorectal cancer recurrence, secondary cancer, other chronic diseases, and cancer death. Their clinical outcome depends on tumor characteristics, treatment methods, but also on differences in nutritional or other lifestyle factors. A recent review summarized the evidence for the role of BMI before, at the time of, and after colorectal cancer diagnosis in colorectal cancer recurrence and survival from 21 observational studies (158). According to that review, obesity as assessed by BMI before or at time of diagnosis was shown to be associated with higher all-cause mortality, colorectal cancer–specific mortality, or recurrence, however results appeared to differ according to sex, tumor location, and molecular subtype of the tumor, and no firm conclusions can be drawn. Only two studies examined the association between waist and hip circumference and colorectal cancer survival; however both of these studies suggest that central adiposity prior to the diagnosis of colorectal cancer is associated with poorer overall and disease specific survival (158-160). Emerging evidence shows that metabolic or bariatric surgery can provide sustained weight loss and reduced obesity-related mortality (161-163). Two large cohort studies suggested that extensive weight loss after bariatric surgery reduced the risk for cancer death (164, 165). In a Canadian study, bariatric surgery resulted in a significant reduction in the mean percentage of excess weight loss (67.1%, P <.001) (166). Risk reduction was especially observed in obesity-related cancers, incl. colorectal cancer (166, 167).

10. ATTRIBUTABLE RISKS FOR COLORECTAL CANCER ASSOCIATED WITH OBESITY

It has been suggested that colorectal cancer is among the cancer sites that are most strongly affected by obesity (4). Although the relative risk of colorectal cancer associated with obesity is moderate, due to the high prevalence of overweight and obesity and the high incidence of colorectal cancer, many colorectal cancer cases may be prevented by reducing the prevalence of obesity. According to the most recent estimates from 30 European countries, 45% (15,844 cases) of new colorectal cancers are attributable to obesity (168). In the US, 35.4% colorectal cancer cases in men and 20.8% of the cases in women are estimated to be attributable to obesity (169). In Asian countries, where the prevalence of overweight and obesity is lower than in Western countries, excess colorectal cancer risk associated with a BMI over 25 kg/m^2 is 3.62% for men and 2.62% for women (22). It is important to note that these estimates are based on BMI. Given that BMI is probably not the best indicator of adiposity to assess colorectal cancer risk, one may speculate that the attributable risk of colorectal cancer that is due to "adiposity" is likely to be even higher.

11. PERSPECTIVE

Adiposity, and in particular abdominal adiposity, is now recognized as a major risk factor for colorectal cancer; however the mechanisms behind this association are not fully understood. Important questions to be answered refer to the most appropriate measures of adiposity in terms of cancer risk; the underlying mechanisms of the risk differences by gender and cancer site; the effects of weight-change in the life-course of individuals, as well as the interactions with other risk factors. Further observational studies in colorectal cancer survivors are warranted; in particular, on markers of abdominal adiposity in addition to general adiposity. Finally, there is a need of clear evidence on effective obesity management interventions in children and adults that take into account contemporary obesogenic environments. Such knowledge will essentially form the basis for the formulation of public-health initiatives to effectively prevent colorectal cancer morbidity and mortality.

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