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Antioxidant vitamins and minerals in prevention of cancers: lessons from the SU.VI.MAX study

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A voluminous body of epidemiological research concerning the potential role of antioxidant nutrients in the prevention of cancers has accumulated over the past few decades. However, results of large recent intervention trials do not support a preventive effect against cancer for supplementation with antioxidant nutrients. Seemingly contradictory results between observational studies and randomised trials can be explained by the fact that doses used in clinical trials were much higher than the highest levels attained by the usual dietary intake which, in observational studies, were found to be associated with the lowest risk of cancer. Recently, the Supplementation en Vitamines et Minéraux Antioxydants (SU.VI.MAX) study, a randomised, double-blind, placebo-controlled primary prevention trial, tested the efficacy of supplementation with a combination of antioxidant vitamins and minerals, at nutritional doses, in reducing the cancer incidence in a general population not selected for risk factors. After 7·5 years, low-dose antioxidant supplementation lowered the total cancer incidence in men only. This may be explained by a lower baseline status of certain antioxidants in men compared to women. Finally, the effect of antioxidant supplementation on the incidence of cancer could depend on baseline antioxidant status (which differs from gender and/or nutritional status) and the health status of subjects (healthy *v.* cancer high-risk subjects). Antioxidant supplementation may have a beneficial effect upon cancer incidence only in healthy subjects who are not exposed to cancer risk and who have a particularly low baseline status. High doses of antioxidant supplementation may be deleterious in subjects in whom the initial phase of cancer development has already started, and they could be ineffective in well-nourished subjects with adequate antioxidant status.

Antioxidants: Cancers: Prevention trial: Minerals: Vitamins

For the last few decades, it has been suggested that oxidative stress is involved in the aetiology of several chronic diseases, including cancer and CVD (Hercberg *et al.* 1998*a*). Oxidative stress is an imbalance between the production of various reactive species and the capacity of the organism's natural protective mechanisms to cope with these reactive compounds and prevent their adverse effects. Indeed, reactive oxygen and nitrogen species can attack various substrates in the body, including lipids, nucleic acids and proteins. Oxidation of any of these substrates, if uncontrolled, can contribute to chronic disease development, specifically at their early stage.

A voluminous body of observational epidemiological research on the potential role of antioxidant nutrients in the prevention of cancers has accumulated over the past several decades (Diplock, 1991; Hercberg *et al.* 1998*a*). Data from cross-sectional, case–control and prospective studies have shown a strong relationship between the intake of antioxidant vitamins and minerals, or foods rich in these nutrients, and the risk of cancer. A 1·5- to 2·0-fold increase in the risk has usually been observed when assessing the association between low *v.* high quartiles or quintiles of antioxidant intake groups (roughly assessed by dietary questionnaires) with cancer risk (lung, stomach, colorectal, etc.).

However, while epidemiological data generally suggested an inverse relationship between antioxidant micronutrient status and cancer risk, their design did not enable making a firm conclusion favouring a causal effect. Only randomised trials, with controlled intervention in antioxidant intake, can provide such a conclusion. Large intervention trials addressing the role of supplementation with antioxidant micronutrients in cancer prevention were first launched in the 1980s; however, results of five large intervention trials published between 1993 and 2000 showed conflicting results.

Primary intervention trials published in the 1990s

The first large published study was the Nutritional Intervention Trials in Linxian (Blot *et al.* 1993), carried out on a general Chinese population. In that study, in a population of 29 584 subjects, a daily dose of 15 mg β-carotene, 30 mg vitamin E and 50 μg Se over a 5-year period significantly reduced overall mortality by 9 %, mortality from cancers by 13 %, and specific gastric cancer mortality by 21 %. These results were consistent with results of observational studies on the protective effects of antioxidant nutrients, and especially β-carotene. However, the Chinese population of the Linxian area is known to have a

Abbreviations: ATBC, Alpha Tocopherol and Beta Carotene Lung Cancer Prevention Study; CARET, Carotene and Retinol Efficacy Trial; PHS, Physicians' Health Study; RR, relative risk; SU.VI.MAX, Supplementation en Vitamines et Minéraux Antioxydants; WHS, Women's Health Study.

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high incidence of gastric and oesophageal cancers and a high frequency of nutritional deficiency.

The trials which followed did not confirm those encouraging results. The Alpha Tocopherol and Beta Carotene Lung Cancer Prevention Study (ATBC) in Finland (ATBC Cancer Prevention Group, 1994) was performed in 29 133 male heavy smokers 50–59 years of age. The intervention consisted of daily supplementation with 20 mg β-carotene and 50 mg α-tocopherol in a 2×2 factorial design. No benefit was observed in the β-carotene group; indeed, the incidence of lung cancers increased by 16 % (95 % CI 2, 33 %).

Similar results were reported in The Carotene and Retinol Efficacy Trial (CARET; Omenn *et al.* 1996). This US multicentre trial, which included 18 314 heavy smokers or professionally exposed subjects, was interrupted 21 months earlier than planned. Indeed, after 4 years, a 28 % increase in lung cancer incidence was observed in the group supplemented with daily 30 mg β-carotene and 25 000 IU (13 664 retinol equivalents) of retinyl palmitate.

In contrast with findings from the ATBC and CARET studies, the Physicians' Health Study PHS; Hennekens *et al.* 1996), which began in 1982 and which included 22 071 US male physicians aged 40–84 years, showed no difference in the lung cancer incidence after 12 years of supplementation (50 mg β-carotene on alternate days *v.* placebo). No adverse or beneficial effects were observed in the β-carotene group, even among the small number of smoking participants (11 %). As in the previous study, the Women's Health Study (WHS; Lee *et al.* 1999) did not demonstrate any effect of vitamin E (600 IU) or β-carotene (50 mg on alternate days) on 39 876 apparently healthy female health professionals aged 45 years and older, after a treatment duration of 2·1 years and a median total follow-up of 4·1 years.

Finally, results of trials published in the 1990s concerning high-risk populations did not confirm the preventive effect of antioxidant nutrient supplementation in cancer prevention which had been shown in observational studies.

The seemingly contradictory results between observational studies and randomised trials can be explained by the fact that the doses used in those clinical trials were much higher than the highest levels attainable by the usual dietary intake, which have been found to be associated with the lowest risk of cancer in observational studies. Indeed, the only trial which did observe a beneficial effect on cancer incidence used nutritional doses of a combination of several antioxidant vitamins and minerals, and was performed in a Chinese population with very low baseline micronutrient status due to poor living conditions in this region (Blot *et al.* 1993).

The SU.VI.MAX study

We recently published results of the Supplementation en Vitamines et Minéraux Antioxydants (SU.VI.MAX) study (Hercberg *et al.* 2004), a randomised, double-blind, placebo-controlled primary prevention trial performed in 12 741 middle-aged subjects who received a combination of 120 mg vitamin C, 30 mg vitamin E, 6 mg β-carotene, 100 μg Se and 20 mg Zn, *v.* placebo (Hercberg *et al.* 1998*b*).

Background of the SU.VI.MAX study

Different types of arguments justified the specificities of the study (Hercberg *et al.* 1998*c*). First, we used a combination of antioxidants at nutritional doses: most observational studies that showed a protective effect of dietary antioxidant intake on cancers concerned subjects who consumed the highest intakes of antioxidants. These subjects had a high level of consumption of these nutrients, but their intake was always at a nutritional level and not at a pharmacological level. Moreover, the high concentrations of antioxidant vitamins or trace elements in blood associated with a lower risk of cancer concerned values obtained with high dietary intakes, not with high levels of supplementation. In intervention studies (ATBC, CARET) showing an apparent negative effect of β-carotene supplementation on the lung cancer incidence rate in high-risk subjects, the relatively high levels of supplementation were associated with a substantial increase in plasma concentrations of β-carotene (initial levels multiplied, respectively, by 18 in ATBC and by 12 in CARET). These levels were much higher than those associated with lower risk of disease in observational studies.

Experimental works have also demonstrated that high doses of antioxidants may become pro-oxidants and can have antagonistic effects (Hercberg *et al.* 1998*a*). Thus, in contrast to nutritional levels which seem to have a protective effect, high doses of antioxidants may have deleterious effects on cell defence mechanisms, thereby facilitating, under certain circumstances, the development of cellular processes terminating in pathologies and, in particular, cancers. Several arguments support the hypothesis of the specific efficiency of a combination of antioxidants. Metabolic interrelationships exist between antioxidant nutrients with beneficial mutual protection and regeneration; the efficiency of an antioxidant differs according to the type of oxidative stress. The advantage of using a combination of different antioxidants is also supported by the fact that there is a complementary effect of antioxidant nutrients in protecting different tissues or cellular compartments (Hercberg *et al.* 1998*c*).

Although in intervention studies the strategy of choosing subjects at high risk for the studied outcome (e.g. smokers for lung cancer) leads to an increase in statistical power, the SU.VI.MAX study did not include selected participants with specific risk factors for cancers (or CVD). The study population included 'free-living' adult subjects. Results of interventions such as those of ATBC and CARET highlight the potential adverse effects of increasing the intake of antioxidant nutrients in populations at high risk of developing some diseases. It is possible that heavy smokers in ATBC or in CARET had, upon inclusion, reached an irreversible but not yet detectable stage of cancer, for which prevention by antioxidant nutrients could no longer have any benefit and could even have a negative impact.

Main results of the SU.VI.MAX study

During the 7·5 years of follow-up, 562 new cancers were validated. When the placebo group was divided into quintiles of baseline serum β-carotene concentrations, the incidence of cancer among men was higher in the lowest quintile than in the highest quintile (relative risk (RR) highest quintile=0·55, 95 % CI 0·30, 0·99). These effects were not seen in the placebo group in women (RR highest quintile = 0·98, 95 % CI 0·54, 1·08). No other association between baseline antioxidant nutrients and cancer could be observed.

There was no significant difference in overall cancer incidence between the supplemented and placebo groups (267 cases in the intervention group *v.* 295 in the placebo group). However, a gender × group interaction was observed, indicating a significant difference between treatment effects according to gender (RR = 0.66, 95 % CI 0·47, 0·94; *P*=0.02). A significant protective effect of antioxidant supplementation was found in men: eighty-eight men developed cancers in the intervention group *v.* 124 men in the placebo group (RR = 0·69, 95 % CI 0·53, 0·91; *P*=0.008). This difference was reflected in a higher incidence of digestive, respiratory and skin cancers in the placebo group. In women, no statistically significant difference in the occurrence of cancer was observed between the groups (RR = 1·04, 95 % CI 0·85, 1·29; *P*=0·67).

In conclusion, our study showed that a combination of antioxidants at nutritional doses reduced the incidence of cancers in apparently healthy men by 31 %, without an evident increased cancer risk. These doses are attainable through a healthy diet with high consumption of fruits and vegetables, confirming the results of prospective observational studies.

Comparisons of results of the SU.VI.MAX study and other randomised trials

The main difference between our study and previous primary prevention trials which did not find a protective effect (PHS, WHS) of antioxidant supplementation on cancer incidence, or which found a deleterious effect (ATBC, CARET), lies in the doses and types of antioxidants used and the selection criteria and characteristics of the population. Firstly, most of the former trials used higher doses of antioxidant nutrients than in the SU.VI.MAX study, mainly alone or in pairs. Only the Linxian trial, showing a protective effect on cancer incidence, used a balanced combination of several antioxidant nutrients at nutritional doses, as in our trial. Secondly, the SU.VI.MAX trial was performed in an apparently healthy population, in contrast to the ATBC and CARET studies, which included subjects at high cancer risk (heavy smokers and professionally exposed subjects). The Linxian trial was performed in a general population with a very low baseline micronutrient status, due to poor living conditions in that region.

Conclusions

The effect of antioxidant supplementation on cancer may depend on baseline antioxidant status (which differs from gender and/or nutritional status) and on the health status of subjects (healthy *v.* cancer high-risk subjects). Antioxidant supplementation may have a beneficial effect on cancer incidence only in healthy subjects who are not exposed to cancer risk, and who have a particularly low baseline status (Galan *et al.* 2005). High doses of antioxidant supplementation may be deleterious in subjects without any clinical symptoms, in whom the initial phase of cancer development has already started, and they may be ineffective in well-nourished subjects with adequate antioxidant status.

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