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Invited commentary

Is there a gender difference in the effect of antioxidants on cancer risk?

Prior to the publication of the SUpplementation en VItamines et Minéraux AntioXydants (SU.VI.MAX) study results last year (Hercberg *et al.* 2004), the findings of most randomized controlled trials did not support the hypothesis that antioxidant nutrient supplementation reduces total cancer incidence or mortality (reviewed in Higdon & Frei, 2005). The only exception was a trial conducted in a nutritionally deficient population in China (Blot *et al.* 1993). Evidence from randomized controlled trials for a cancer protective effect of antioxidant supplements in nutritionally sufficient populations has been limited to prostate cancer. Supplementation of Finnish smokers with 50 mg α-tocopherol/d for 6 years was associated with a 32 % decrease in prostate cancer incidence (Heinonen *et al.* 1998). In a US study, supplementation with 200 μg Se/d for 7 years was associated with a 51 % decrease in prostate cancer incidence, but the protective effect was limited to those with lower plasma Se levels at baseline (Duffield-Lillico *et al.* 2003). Similarly, supplementation of American physicians with β-carotene (50 mg on alternate days) for 12 years was associated with a 32 % reduction in prostate cancer incidence only in those with lower baseline plasma β-carotene concentrations (Cook *et al.* 1999).

In the SU.VI.MAX study, daily supplementation with a mixture of antioxidant nutrients (120 mg vitamin C, 30 mg vitamin E, 6 mg β-carotene, 100 μg Se and 20 mg Zn) for more than 7 years was associated with a significant 31 % reduction in total cancer incidence in men but not women (Hercberg *et al.* 2004). However, the protective effect in men did not appear to be related to a substantial decrease in prostate cancer incidence. In the present issue of the *British Journal of Nutrition*, additional analysis of data from the SU.VI.MAX study provides evidence of an inverse association between baseline serum antioxidant concentrations and total cancer incidence in men but not women, suggesting that the lack of effect of antioxidant supplementation on cancer risk in women cannot be entirely explained by higher baseline antioxidant levels or higher antioxidant nutrient consumption in women (Galan *et al.* 2005).

Differences in relationships between antioxidant status and the risk for gender-specific cancers may have contributed to the observed gender differences in total cancer risk. Prospective studies provide some evidence that low antioxidant status in men is associated with increased prostate cancer risk. Three prospective studies found that low Se status was associated with substantially increased prostate cancer risk, and another found a similar relationship in current and former smokers (reviewed in Waters *et al.* 2004). Serum vitamin E concentrations were inversely associated with prostate cancer risk in two cohorts of smokers (Eichholzer *et al.* 1996; Weinstein *et al.* 2005), and plasma γ-tocopherol but not α-tocopherol concentrations were inversely associated with prostate cancer risk in a prospective study of American men (Helzlsouer *et al.* 2000). An interaction between Se and vitamin E status was suggested by the finding that higher levels of Se and α-tocopherol were associated with a significant decrease in prostate cancer risk only when γ-tocopherol levels were also high. In contrast, prospective studies have not generally found plasma vitamin C, vitamin E or Se concentrations to be associated with breast cancer risk in women (Waters *et al.* 2004; Higdon & Frei, 2005). Plasma β-carotene concentrations were inversely associated with breast cancer risk in several prospective studies. However, each study found that serum concentrations of other carotenoids, such as lycopene or α-carotene, were also inversely related to breast cancer risk, suggesting that increasing consumption of a number of dietary carotenoids, instead of β-carotene in isolation, may offer some protection from breast cancer (Higdon & Frei, 2005; Tamimi *et al.* 2005).

Even for cancers that affect both men and women, there may be gender differences with regard to the influence of antioxidant nutrient status. A number of prospective studies suggest that low plasma Se and vitamin C concentrations are associated with increased total cancer risk in men but not women. Of six prospective studies that examined the relationship between serum Se concentrations and total cancer incidence, four found a significant inverse association in men, but none found a significant association in women (reviewed in Waters *et al.* 2004). All three prospective studies that examined the relationship between plasma vitamin C concentrations and total cancer risk in men found a significant inverse relationship (Eichholzer *et al.* 1996; Loria *et al.* 2000; Khaw *et al.* 2001), but neither of the two studies that also examined plasma vitamin C concentrations in women found these concentrations to be related to cancer risk (Loria *et al.* 2000; Khaw *et al.* 2001). Although plasma vitamin C concentrations were generally higher in women than men, even women with very low plasma vitamin C concentrations were not at increased risk for cancer (Loria *et al.* 2000; Simon *et al.* 2001).

DNA contains reactive groups in its bases that are susceptible to attack by reactive oxygen and nitrogen species. It has been proposed that oxidative damage to DNA occurs *in vivo* at a rate of 10^4 oxidative hits per cell per d (Woodall & Ames, 1997). At least fourteen clinical trials have examined the effect of some type of antioxidant supplementation on oxidized pyrimidines using the modified Comet assay, which measures strand breaks induced by treatment of DNA with endonuclease III. Interestingly, six of the seven trials that found antioxidant supplementation to be beneficial in lowering oxidized pyrimidine levels were conducted in men only, while only one of the seven trials that found antioxidant supplementation to be of no benefit was conducted exclusively in men (Moller & Loft, 2004). Although this observation may reflect a shortage of female participants, it highlights the possibility of a gender difference with regard to the effect of antioxidant supplementation on oxidative DNA damage *in vivo*.

The study of antioxidant nutrients and carcinogenesis is complicated by the fact that different types of cancer vary in their aetiology and pathology. Moreover, antioxidant nutrients, such as vitamin C, vitamin E, carotenoids and Se, vary considerably in their chemistry, metabolism and biological activities, not all of which are related to their ability to act directly as antioxidants. In order to make antioxidant nutrient recommendations based on chronic disease prevention, it is important to understand the extent to which gender influences relationships between antioxidant status and disease risk. Future prospective and supplementation studies should be designed with adequate power to detect gender differences in the effects of antioxidant nutrients on specific types of cancer and other cancer-related endpoints. Investigators should report the results of gender-specific analyses even when no significant differences are found. In addition to examining individual and synergistic effects of antioxidant nutrients on different types of cancer, mechanistic studies should also address potential interactions with gender-related factors.

Jane V. Higdon and Balz Frei

Linus Pauling Institute
Oregon State University
Corvallis
OR 97331-6512
USA

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