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# Current knowledge and future directions for research on antioxidant vitamins in prevention of cancer, cardiovascular and eye diseases

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*Abstract*: Basic research suggests plausible mechanisms for a role of antioxidant vitamins in the prevention of cancer, cardiovascular and age-related eye diseases. Observational epidemiologic studies have provided additional support by demonstrating that individuals with higher blood levels or intake of antioxidant vitamins have decreased risks of these diseases. Whether or not the antioxidant vitamins themselves decrease risks requires evidence from randomized trials of sufficient sample size, dose, and duration of treatment and follow-up.

## INTRODUCTION

Emerging evidence points to a possible preventive role for antioxidant vitamins, such as beta-carotene, vitamin E and vitamin C, against a number of chronic diseases, including cancer, cardiovascular and age-related eye diseases.

## BASIC RESEARCH AND OBSERVATIONAL EPIDEMIOLOGY

With respect to cancer, free radical damage (oxidation) to cellular components plays an important role in carcinogenesis (ref. 1-3). Antioxidants can defend against oxidative stress by scavenging free radicals and interrupting free radical induced chain reactions. Antioxidant vitamins have been shown to effectively prevent induced tumors in animals, including hormonally mediated tumors (ref. 4). In addition, evidence from numerous observational epidemiologic studies, both case-control and prospective cohort, is fairly consistent that individuals with high intake of fruits and vegetables rich in antioxidant vitamins have decreased risks of developing cancer (ref. 5,6).

As regards cardiovascular disease (CVD), laboratory evidence has shown that oxidation of lipids, particularly low-density-lipoprotein (LDL) cholesterol molecules, may promote atherogenesis and that antioxidant vitamins may effectively retard this process (ref. 7-9). Specifically, vitamin E inhibits oxidation of LDL in plasma, while beta-carotene and vitamin E may protect endothelium by decreasing uptake. Descriptive epidemiologic studies have contributed to the formulation of the hypothesis of an inverse relation between antioxidant vitamins and risk of CVD in humans (ref. 10-13). Further, most observational analytic studies have shown that individuals who consume higher amounts of antioxidant vitamins through diet or supplements tend to have lower risks of coronary heart disease and stroke (ref. 14-20).

For age-related eye diseases, including cataract and age-related macular degeneration, several lines of evidence in basic research support a possible preventive role for antioxidant vitamins (ref. 21). In addition, observational studies have demonstrated that persons with higher blood levels or intake of antioxidant vitamins have decreased risks of cataract (ref. 22-25) and age-related macular degeneration (ref. 26-30).

For many, if not most, hypotheses, basic research and observational epidemiology provide a sufficient totality of evidence upon which to base rational clinical decisions for individual patients and policy decisions for the health of the general public. For small to moderate effects, however, the amount of uncontrolled and uncontrollable confounding inherent in case-control and cohort studies is about as large

as the postulated benefits or risks. In such circumstances, only randomized trials can provide direct evidence on whether the agent is responsible for the observed effects. Thus the totality of evidence clearly supports the need for randomized trials to test the hypothesis that antioxidant vitamins may be effective in decreasing risks of cancer, cardiovascular and eye diseases. However, only trials of sufficient sample size, dose, and duration to detect the postulated small to moderate effects can answer definitively whether or not there is any direct role for a given agent.

## RANDOMIZED TRIALS

Results from randomized, double-blind, placebo-controlled trials of antioxidant vitamins have not been consistent. Four large-scale trials have been published to date. In the Chinese Cancer Prevention Study, conducted among 29,584 residents of the poorly-nourished population in Linxian, China, after 6 years, there were statistically significant reductions of 9% in total mortality, 13% in cancer mortality, and 21% in gastric cancer mortality among persons assigned to the combination of beta-carotene, vitamin E, and selenium (ref. 31).

The Finnish Alpha-Tocopherol, Beta Carotene (ATBC) Cancer Prevention Study, which evaluated beta-carotene (20 mg daily) and alpha-tocopherol (50 mg daily) among 29,133 male smokers, showed no overall benefit of either agent on total cancer risk. For beta-carotene, there were unexpected, statistically significant increases of 18% in lung cancer, 13% in lung cancer mortality, 11% in ischemic heart disease mortality, and, as a consequence, 8% in total mortality (ref. 32). For vitamin E, there were no significant reductions in lung cancer or ischemic heart disease, but a significant 50% increase in mortality from cerebral hemorrhage.

The Beta Carotene and Retinol Efficacy Trial (CARET), which was conducted among 18,134 men and women at high risk of lung cancer due to cigarette smoking and/or occupational exposure to asbestos, evaluated a combined treatment of 30 mg beta-carotene and 25,000 IU retinyl palmitate daily. After an average duration of treatment of 4 years, CARET was terminated early, primarily because of an inability to detect a benefit, but also because of findings of a similar direction and magnitude to those in the ATBC trial. Specifically, increased risks of 28% for lung cancer ($P=0.02$), 17% for total mortality ($P=0.02$), and 26% for cardiovascular disease mortality ($P=0.06$) were observed among those assigned to the combined supplement group (ref. 33). However, it is important to note that the prespecified stopping boundary for early termination of the trial ($P=0.007$) was not reached for any of these endpoints, and the finding for cardiovascular disease mortality did not reach conventional statistical significance. In addition, because two active agents were taken simultaneously in CARET, one cannot conclude that the effects seen were due only to beta-carotene. Both ATBC and CARET had relatively short durations of treatment and follow-up that may have been inadequate to yield a detectable reduction in cancer, which is a multistage disease process that often proceeds over several decades (ref. 34). Because it is plausible that antioxidant vitamins affect the earlier stages of carcinogenesis, endpoints must occur sufficiently long after the initiation of the intervention to account for the biologic latency period of the disease.

The Physicians' Health Study (PHS) randomized 22,071 US male physicians to alternate day beta-carotene (50 mg), aspirin (325 mg), both active treatments, or both placebos. The trial has already recorded an average duration of beta-carotene treatment and follow-up of more than 12 years, twice the length of any other trial. Overall, after 12 years, there was no significant evidence of benefit or harm of beta-carotene on risk of total malignant neoplasms, cardiovascular disease, or total mortality (ref. 35). There was also no evidence in the PHS of any harm (or benefit) among smokers, although a small absolute effect could not be ruled out. From years 5 to 9, there was a 12% reduction in risk of total cancer ($P=0.03$) and 22% reduction in risk of prostate cancer ($P=0.01$). In addition, preliminary subgroup analyses of prerandomization blood specimens are compatible with the possibility of small benefits for total and prostate cancer among those with the lowest serum levels of beta-carotene at baseline, a finding which, if real, is consistent with the results of the Linxian, China trial. For cardiovascular disease, preliminary subgroup analyses of beta-carotene were performed at the time the aspirin component was terminated early, based on the 44% reduction in risk of a first myocardial infarction among participants allocated to aspirin. These analyses suggested that beta-carotene supplementation among the small subgroup of PHS participants with pre-existing coronary artery disease may decrease the risk of subsequent important vascular events by 54% (ref. 36). More recently, after

12 years of supplementation, data from the PHS are compatible with possible, and more plausible, benefits of 20-30% among these high-risk participants.

## CONCLUSIONS

For beta-carotene supplementation, the findings from completed large-scale randomized trials indicate no overall benefits in well nourished populations on the middle-to-late stages of carcinogenesis, or on the incidence of cardiovascular disease among those at usual risk. The available data are inadequate, however, to answer definitively whether beta-carotene supplementation is effective over the longer term, or in subgroups at high risk due to low blood levels of beta-carotene or prior coronary heart disease. In light of the long induction period associated with many chronic disease risk factors, such as smoking, which requires 20 years of exposure to markedly increase risk of lung cancer, it is plausible that the effects of preventive factors on cancer, such as beta-carotene supplementation, might also take that many years to become evident. Whether or not there is a true hazard of beta-carotene supplementation among current cigarette smokers, as raised by the ATBC and CARET trials, will be evaluated by a collaborative overview of the post-publication results of continued follow-up in all completed trials of beta-carotene (ref. 37). If the apparent excess risk observed in those trials is in fact real, it should persist with longer follow-up. Conversely, if, as is still possible, there is eventually some benefit from beta-carotene supplementation, then this too may emerge with longer follow-up. A common protocol for a collaborative analysis of the post-publication results of all the beta-carotene trials is therefore being devised, with the first analyses planned for sometime around the year 2000. This will provide the most reliable evidence on whether the long-term effects are favorable, unfavorable, or null.

For vitamin E, the ATBC trial showed no evidence of benefit on cancer or ischemic heart disease, but the Cambridge Heart Antioxidant Study (CHAOS) of 2,000 subjects with angiographically-proven atherosclerosis suggested benefits on subsequent myocardial infarction, but not vascular death (ref. 38). With respect to vitamin C, there are no completed trials of this agent alone.

Further randomized trial data are necessary to evaluate definitively the potential role of antioxidant vitamins in disease prevention. The Physicians' Health Study will continue randomized treatment with beta-carotene in order to provide more reliable evidence on this agent. Utilizing a factorial design, the trial will also add vitamin E, vitamin C, and a multivitamin, in order to also evaluate the effects of these agents on cancer, cardiovascular, and eye diseases. Several other trials are also ongoing, including the Heart Prevention Study, which is evaluating a cocktail of beta-carotene, vitamin E, and vitamin C among 20,000 high-risk patients in the United Kingdom; the Heart Outcomes Prevention Evaluation (HOPE) study, which is testing vitamin E among 9,000 high-risk subjects in Canada; and the GISSI Prevention Trial, which is evaluating vitamin E among 11,000 high-risk patients in Italy (ref. 39). In the United States, the Women's Health Study is evaluating vitamin E in primary prevention in 40,000 apparently healthy women (ref. 40), while the Women's Antioxidant Cardiovascular Study is testing beta-carotene, vitamin E, and vitamin C in 8,000 high-risk women (ref. 41). The availability of data from all of these trials should allow rational clinical decision-making for individual patients and policy decisions for the health of the general public. In the meanwhile, antioxidant vitamins represent a promising, but unproven, means to lower risks of cancer, cardiovascular, and eye diseases.

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