Vitamin E in the Prevention of Prostate Cancer: Where Are We Today?

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In their landmark study in 1981, Doll and Peto estimated that 35% of cancer deaths in the United States could be attributed to dietary factors (1). One of the mechanisms they proposed for this association was “deactivation, or prevention of formation, of short-lived intracellular species” by antioxidants in the diet. At that time, the National Cancer Institute had also begun its focus on cancer prevention (2) and had funded large-scale randomized clinical trials to test antioxidant vitamins and minerals in cancer prevention (3–11). Among the antioxidant vitamins of great interest, both among scientists and the general public, was vitamin E. The results of these vitamin E trials (3–5, 9–11), however, have generally been disappointing because they have indicated that intake of this vitamin provides little protection against cancer overall in well-nourished populations.

To date, few completed trials have provided data on vitamin E intake and prostate cancer risk. The Alpha-Tocopherol, Beta-Carotene Prevention (ATBC) Study reported that among male smokers, those assigned to receive 50 mg of α-tocopherol daily had a statistically significant 32% lower prostate cancer incidence (specifically observed only for clinical but not latent disease) and a statistically significant 41% lower prostate cancer mortality than those assigned to receive placebo (11). However, the Heart Outcomes Prevention Evaluation—The Ongoing Outcomes (HOPE-TOO) trial, which enrolled men with or at high risk for cardiovascular disease, observed no effect of supplemental vitamin E at 400 IU/day on prostate cancer incidence (10).

A study (12) in this issue of the Journal provides additional information on the possible role of antioxidant intake, including vitamin E intake, in the reduction of prostate cancer risk. In a prospective analysis of data from 29,361 men in the screening arm of the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial, Kirsh et al. (12) report no overall associations between intakes of dietary or supplemental vitamin E and prostate cancer risk, a finding that is consistent with data from the HOPE-TOO trial (10) and several other observational studies (13–14). However, Kirsh et al. (12) reported an intriguing subgroup finding: Among men who were current smokers or who had quit smoking within the past 10 years, those with supplemental vitamin E intakes greater than 400 IU/day had a statistically significant 71% reduction in risk of advanced prostate cancer compared with those who did not take supplemental vitamin E.

How can we assess the validity of this subgroup finding of a reduced risk of advanced prostate cancer among smokers and recent quitters who use supplemental vitamin E? The observation of a reduced risk of prostate cancer among smokers is consistent with the findings from the ATBC trial (11), as well as with those from most (14, 15, 17, 18), but not all (16), observational analyses of vitamin E intakes or plasma levels. Three of these studies (11, 14, 15) have reported a reduced risk specifically of advanced prostate cancer among smokers who used supplemental vitamin E. Although it is unclear how cigarette smoking might modify the association between vitamin E intake and prostate cancer risk, some investigators have hypothesized that carcinogens in cigarette smoke may induce mutations in oncogenes or in tumor suppressor genes involved in prostate cancer progression and aggressiveness, as well as increase plasma levels of testosterone and dihydrotestosterone, which has been associated with increased risks of advanced prostate tumors (15). Thus, vitamin E may halt the progression of localized prostate cancer to advanced-stage prostate cancer, which may explain the observed association between vitamin E intake and a reduced risk of advanced disease.

A particular strength of this observational study by Kirsh et al. (12) is that all subjects were screened for the presence of prostate...
cancer at baseline, thus avoiding the potential bias of differential screening prior to study entry. To date, none of the completed trials or observational studies of vitamin E intake and prostate cancer has included this criterion for study entry. However, as with all observational studies, alternative explanations for the findings by Kirsh et al. are possible. Individuals who choose to participate in research studies of disease prevention generally tend to be healthier than those who do not (19). For example, in the screening arm of the PLCO study, the proportion of men who reported using vitamin E supplements either as multivitamins or as a single supplement (52%) appears to be greater than that reported in a national survey, in which 22% of men reported using multivitamins containing vitamin E and 9% reported using vitamin E as a single supplement (20). Thus, it is possible that smokers in the PLCO trial might also have been more health conscious than the general population of smokers and might have tried to compensate for this risky behavior—smoking—by being more diligent about other health-related behaviors. For example, in the Health Professionals’ Follow-up Study, current smokers were most likely to undergo prostate cancer screening compared with never smokers or past smokers (21).

All participants in the screening arm of the PLCO trial were screened for prostate cancer at study entry. During the trial, all participants were further supposed to undergo uniform screening as part of the trial protocol, thereby providing an equal opportunity for to be diagnosed with prostate cancer. However, because Kirsh et al. (12) do not provide data on compliance with the PLCO trial protocol, it is not clear whether the screening rate among smokers was higher than that among nonsmokers in the trial and/or whether smokers underwent additional health screening outside of the trial more frequently than did nonsmokers. If this was the case and smokers also compensated for smoking by taking high doses of vitamin E supplements, we might expect early-stage prostate cancers to be picked up more frequently among the more health-conscious smokers who underwent screening more often and who also took vitamin E supplements, compared with less health-conscious smokers who may have been less likely to undergo screening and to take vitamin E supplements, with a resulting decrease in the incidence of more advanced cancers in the former group. The data from the Kirsh et al. study appear to support this alternate explanation: Among smokers, increasing supplemental vitamin E intake was associated with a statistically significant trend for an increase in the incidence of nonadvanced prostate cancer (P_trend = .03), commensurate with a statistically significant trend for a decrease in the incidence of advanced cancers (P_trend = .01).

How might the role of vitamin E in the prevention of prostate cancer be further clarified? With regard to the PLCO study, additional follow-up beyond the current average follow-up of 4.2 years should reveal whether the present finding of decreased risk of advanced prostate cancer with supplement vitamin E intake among smokers persists. Extended follow-up is important because carcinogenesis is a multistage process, and the transformation of a cell from normal tissue to an invasive tumor may take a decade or longer (22). Two ongoing randomized clinical trials will also provide additional information about the effects of vitamin E supplementation in the coming years. The Physicians’ Health Study II, which began in 1997 and is scheduled to be completed in 2007, is testing the effect of 400- IU vitamin E supplementation every other day (in addition to a multivitamin and vitamin C, as separate arms) on the prevention of a variety of chronic diseases, including cancer, among 14,642 apparently healthy men (23). The Selenium and Vitamin E Cancer Prevention Trial (SELECT), which began in 2001, is testing 400 IU/day of vitamin E, alone and in combination with selenium, in prostate cancer prevention among approximately 35,000 men for a planned duration of 7–12 years (24). Smokers are not expected to be a large proportion of participants in either trial because neither trial is selecting participants on the basis of smoking status. However, both trials will provide additional long-term randomized data beyond what is currently available. In addition to these human studies, basic and animal studies that can shed light on mechanistic processes for a plausible differential effect of vitamin E on prostate cancer development in smokers and nonsmokers may help to clarify the overall picture.

In the meantime, what do the present PLCO findings mean for vitamin E and prostate cancer prevention? We agree with the overall conclusions of Kirsh et al. (12) that the data “do not provide strong support for population-wide implementation of high-dose antioxidant supplementation for the prevention of prostate cancer.” However, whether vitamin E supplementation is beneficial for certain subgroups—such as smokers—or for certain forms of the disease—such as advanced prostate cancer—remains unclear. In contrast, there are clear and well-documented risks associated with cigarette smoking, not only for cancer but also for many other chronic diseases (22). Now and in the future, regardless of the eventual findings on vitamin E supplementation and prostate cancer risk, an important course of action for overall cancer prevention is to continue efforts to prevent the initiation of smoking and to promote the cessation of smoking among those who do smoke.

References


