

## Selenium, Vitamin E, and Prostate Cancer— Ready for Prime Time?

Philip R. Taylor, Demetrius Albanes\*

In this issue of the Journal, Yoshizawa et al. (1) present findings relevant to a potential protective role for selenium in advanced prostate cancer. This report is particularly timely in light of the dramatic rise in the incidence of prostate cancer and because we have such limited understanding of risk factors for this disease beyond increasing age and being African-American. The study by Yoshizawa et al. suggests a one-half to two-thirds reduction in the risk of advanced prostate cancer for men with the highest (as compared with the lowest) selenium status. This study is distinguished by a number of strengths, including its prospective design, nearly complete follow-up, objective and time-integrated assessment of status through selenium measurement in toenails, careful appraisal and control of other potential influencing factors, and the largest number of cases studied to date. Yoshizawa et al. conclude that further prospective studies and randomized trials of selenium and prostate cancer should be conducted.

So where does this study leave us with regard to selenium and prostate cancer? The accumulated evidence is limited and inconsistent, but it is extremely provocative. Two earlier prospective studies (2,3) conducted in the United States among persons with selenium values in the normal range hinted at a benefit for higher selenium levels, but these studies were based on numbers far too small (i.e., 11 and 13 cases) to be considered informative. A third prospective study (4), conducted in Finland, where serum selenium concentrations in individuals were very low and a benefit for higher levels might be more likely, found no association between selenium levels and cancer risk based on 51 cases. The real enthusiasm for selenium in the prevention of prostate cancer, however, comes from the results of the clinical trial conducted by Clark et al. (5) in the United States among persons with low-to-normal selenium status. In that trial, 1312 persons with a history of nonmelanoma skin cancer were randomly assigned to receive selenium (200 µg/day) or placebo and were followed for an average of 4½ years for the development of basal cell or squamous cell carcinoma of the skin. Secondary analysis of the data (5) revealed that prostate cancer incidence was reduced by two thirds among those in the selenium-supplemented group compared with the placebo group (13 versus 35 cases, respectively).

The usual order of scientific investigation in humans involves exploring hypotheses through observational studies, with only the more promising treatment or prevention leads meriting testing in clinical trials. As serendipity would have it, however, the most credible leads for the primary prevention of prostate cancer have emerged as secondary findings from randomized, controlled trials, with corroborative evidence subsequently being sought from observational studies such as the one by Yoshizawa et al. (1). The other exciting recent lead in prostate cancer prevention was reported by the Alpha-Tocopherol, Beta Carotene (ATBC) Cancer Prevention Study, a randomized trial conducted in more than 29 000 male smokers in Finland. Among the 246 new cases of prostate cancer identified during the 5- to 8-year intervention period, only 99 cases occurred among participants who received 50 mg of vitamin E daily compared with 147 cases among those who did not receive vitamin E, a striking one-third reduction (6,7).

How might selenium and vitamin E supplementation inhibit the development of prostate cancer? In the ATBC Study, the effect of vitamin E was limited to the prevention of clinically evident cancers of stages II through IV, suggesting inhibition of the transformation of latent tumors to more invasive disease (7). Both selenium and vitamin E can function as antioxidants (8), but whether the prevention of DNA oxidative damage is as relevant to tumor progression as is the inhibition of cell proliferation (9) or the promotion of apoptosis (10), for example, is not known. Research aimed at identifying the cellular and molecular mechanisms operational in prostate cancer and determining how these pathways may be modified by selenium or vitamin E is needed.

Beyond gaining a clearer understanding of underlying mechanisms, we should strike while the iron is hot to resolve expeditiously and definitively whether selenium or vitamin E (or both)

\*Affiliation of authors: Cancer Prevention Studies Branch, Division of Clinical Sciences, National Cancer Institute, Bethesda, MD.

Correspondence to: Philip R. Taylor, M.D., Sc.D., National Institutes of Health, 6006 Executive Blvd., Rm. 321, Bethesda, MD 20892-7058.

have a role in prostate cancer prevention. This determination will require exploiting all of the scientific tools available to us. Prospective epidemiologic studies should further evaluate the relation of selenium and vitamin E to prostate cancer in various racial/ethnic groups (and particularly in African-American men), in early as well as late disease, and should include sufficient numbers of cases in order to delineate better the presence and shape of dose-response relations and interactions between these nutrients and with other factors. But the most important scientific evidence required now regarding the potential use of selenium and vitamin E for the prevention of prostate cancer must be in the form of empirical evidence from additional controlled studies. Only another randomized intervention trial (or trials), as the most powerful and valid approach available for testing a specific preventive strategy, can provide the level of confirmatory evidence needed to guide us with regard to the possible use of these agents to promote the public's health.

The next trial(s) of this hypothesis should build on the aforementioned scientific leads as well as on the methodologic lessons learned from the first generation of cancer prevention trials. Such a trial(s) must be large enough (with tens of thousands of participants) and long enough (potentially up to 10 years or more) to be truly informative. And it must evaluate the effects of selenium and/or vitamin E supplementation on additional important end points, such as other cancers, coronary heart disease, stroke, and total mortality, as well as on potential toxicity. Ideally, mechanistic studies (e.g., examination of effects on cell proliferation and apoptosis) should be incorporated. For the results to be as widely generalizable as possible, the study population should be as broad as possible and should include all races, smokers and nonsmokers, and persons with a wide range of intake of both selenium and vitamin E. Because selenium and vitamin E have been reported to compensate for the deficiency of each other and to act synergistically to inhibit carcinogenesis (11,12), a particularly efficient and attractive option is the 2 × 2 factorial design in which both agents can be tested simultaneously.

In summary, coupled with the recent findings from two randomized trials (5-7), the report of Yoshizawa et al. (1) in this issue of the Journal adds important, independent information in our search for effective prostate cancer prevention strategies.

Although the overall evidence does not warrant firm conclusions at this time, we have arrived at a new plateau of promise with heightened momentum and a strong desire to get on to the "final chapter in the story" regarding selenium, vitamin E, and prostate cancer. That chapter may be as close as one randomized trial away.

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