EDITORIAL

Learning From History in Micronutrient Research

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George Santayana, the Spanish philosopher, is credited with the often paraphrased quote that “those who cannot remember the past are condemned to repeat it.” In our most cynical moments, these words ring true as a commentary on micronutrient supplements for cancer prevention. Four years ago, Tim Byers (1) eloquently summarized in an editorial titled “Anticancer Vitamins du Jour: The ABCED’s So Far” that chemoprevention trials of vitamin supplements have been largely fruitless (pardon the pun). This year, John Potter (2) wrote a review, “The Failure of Cancer Chemoprevention,” which was sharply critical of chemoprevention research. Each of these essays noted that, based on results of trials thus far, a single-agent, supraphysiologic dose of a nutrient does not typically have its intended effect. Missing from the design of these supplementation trials is a nuanced understanding of human nutrition. There is reasonable agreement on the intakes of micronutrients that are required to prevent clinical manifestations of deficiency and on intakes high enough to cause acute toxicity; but optimal micronutrient intakes are likely within more narrow ranges than between these two extremes, and studies have demonstrated repeatedly that micronutrient intakes well below those associated with acute toxicity can increase the risks of several cancers.

Evidence is now accumulating that selenium is a micronutrient that can cause harm at intakes well below the US Tolerable Upper Limit of 400 μg/d. Overall, clinical trials of selenium supplementation have yielded inconsistent results. In the latter half of the 1990s, Clark et al. (3) published results from the Nutritional Prevention of Cancer (NPC) trial, which was a small (n = 980 men and n = 332 women), randomized trial testing whether 200 μg/d (from high-selenium yeast) would reduce the recurrence of nonmelanoma skin cancers. Endpoints considered after the trial was completed include total cancer incidence (excluding nonmelanoma skin cancers) and cancer incidence at several common sites. Although selenium had no effect on squamous or basal cell carcinoma of the skin when the trial had stopped in 1993, it did substantially reduce the risk of prostate cancer. Specifically, there was a 86% (95% confidence interval [CI] = 39% to 97%) reduction in risk among men in the lowest tertile of baseline plasma selenium, a 67% (95% CI = 18% to 87%) reduction among men in the second tertile, and a statistically nonsignificant 14% (95% CI = -49% to 159%) increase among men in the highest tertile (4). But further follow-up of NPC participants found that selenium supplementation actually increased the risk of squamous cell skin cancer by 25% (95% CI = 3% to 51%, P = .03) (5). A later small trial (6), testing 200 μg/d and 400 μg/d of selenium for prevention of prostate cancer among 699 men with elevated PSA but negative diagnostic biopsies, found no effect of selenium supplementation either overall or stratified by baseline plasma selenium levels. More recently, the Selenium and Vitamin E Cancer Prevention Trial (SELECT) of 35533 men found no effect of 200 μg/d on prostate cancer incidence (7). However, in a prespecified secondary analysis, we reported no effect of selenium supplementation among men in the lower 60th percentile of baseline toenail selenium, but an increased risk for high-grade (Gleason 7–10) prostate cancer among men in the upper 40th percentile (hazard ratio [HR] = 1.91, 95% CI = 1.20 to 3.05, Pinteraction = .02) (8). This suggests that the levels of selenium achieved by supplementation of men with already high baseline levels were harmful, although it required an enormous trial to detect this subacute toxicity.

In this issue of the Journal, Kenfeld et al. (9), examine use of selenium supplements and the risk of prostate cancer death and biochemical recurrence among a cohort of 4459 men diagnosed with prostate cancer in the Health Professionals Follow-up Study (HPFS). Prior reports from the HPFS found that higher baseline toenail (10) and plasma selenium (11) were associated with reduced risk of advanced prostate cancer. But this new report finds that use of 140 μg/d or more of selenium postdiagnosis was associated with over two and a half–fold excess risk of prostate cancer death (HR = 2.60, P trend = .001). Presumably, the discrepancy between the biomarker studies of risk in HPFS and the current analysis of mortality is explained by very high selenium exposure that could only be achieved through supplementation. Parenthetically, we note that there was no association with risk of biochemical recurrence (HR = 1.14, P trend = .47); this discrepancy between the findings for cancer death and PSA recurrence is important, because it illustrates the dangers of using surrogate markers that are not rigorously validated (12).

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The current list of trials finding increased cancer risk from micronutrient supplementation is now quite large. Increases in prostate cancer risk specifically have been reported for selenium (8), vitamin E (13), and folate (14). And although observational studies are by no means consistent, there are several that suggest U-shaped or increased risks of several nutrient biomarkers with prostate cancer risk (15–19).

Dietary supplement use is nearly ubiquitous in the United States. They are used by nearly one-third of children and over one-half of adults, among whom less than a quarter report doing so on the advice of a physician (20,21). Given the high prevalence of use, it is disappointing that the sale of supplements is “regulated” under the ironically titled Dietary Supplements Health Education Act (DSHEA) of 1994. Under DSHEA, supplement manufacturers do not need to demonstrate safety or efficacy; rather, the act purposefully minimizes oversight by the Food and Drug Administration (FDA) and focuses on the value of the industry for the US economy (For further reading, see [22]).

Given the current state of scientific knowledge on the risks of high-dose selenium supplementation to US men and further and that these supplements are marketed specifically for support of “prostate health,” the FDA should take action. Kenfield et al. (9), conclude that prostate cancer patients should be cautioned against the use of selenium supplements. Although data from other studies are needed, we agree. Further, we believe that urologists should query their patients about their use of selenium supplements and recommend avoiding any supplement containing more than the US recommended dietary allowance of 55 µg/d.

Note

The authors declare no competing financial interests.

References