

Editorial

To supplement or not to supplement, that is the question

There have been literally hundreds of studies of the 'fruit and vegetable epidemiology' kind, and the vast majority have shown that persons who consume more fruit and vegetables have lower cancer risk.^{1,2} But eating more fruit and vegetables, like reducing dietary fat, is challenging. As a society, we are far more inclined to 'prescription' than to 'proscription.' So, while the evidence (and prudence) most clearly supports modification of food patterns in order to lower cancer risk, both as scientists and humans, we remain reductionists, ever searching for the easy-to-take, prepackaged magic molecule.

The article by Patterson and colleagues³ in this month's *Cancer Causes and Control* reviews the published epidemiologic research on the associations of vitamin and mineral supplementation and cancer risk. The authors conclude that there is modest evidence for protective effects of supplemental micronutrients against several cancers, but that further investigation is warranted. In light of this conclusion, what additional scientific evidence is needed to make substantive health claims regarding the use of supplements as part of a cancer preventive strategy? Given the somewhat inconsistent nature of the findings and the relative weakness of the epidemiologic associations observed for vitamin/mineral supplements, have we exceeded the limits of the observational study design in providing an answer to the question? This topic is especially timely in light of the increasing popularity of nutritional supplement use in many populations.

The experimental design, such as that of a randomized, controlled clinical trial, can provide an important component in the empirical base of knowledge necessary to make prudent claims regarding the public's health. When budgetarily and ethically feasible, a randomized clinical trial of sufficient size and duration provides a powerful and valid test of a specific hypothesis. While one must be cautious in generalizing a trial's findings beyond the study population, this design evaluates the presence of causal effects better than observational designs. Overinterpretation of findings from observational studies can be misleading at times, as the example of β -carotene and lung cancer pointedly illustrates. As recently reviewed by van Poppel and Goldbohm,⁴ 12 of 19 published cohort studies

relating dietary β -carotene intake to lung cancer showed a protective association, and six of the seven studies related lower lung cancer risk to higher biochemical status of β -carotene based on prospectively collected serum. Taken together, these studies of dietary intake and serum concentrations of β -carotene and lung cancer provide perhaps the most convincing evidence available in the diet-cancer epidemiologic literature today, with respect to both the magnitude of the protective association and its consistency. In contrast, randomized intervention trials testing whether active supplementation with β -carotene can reduce lung cancer incidence produced findings that were strikingly *opposite* those expected. In both the Alpha-Tocopherol Beta-Carotene (ATBC) Cancer Prevention Study and the Beta-Carotene and Retinol Efficacy Trial (CARET),^{5,6} lung cancer rates actually were increased significantly in participants who received β -carotene supplements compared with those who did not. The results from these two clinical trials are almost certainly real, at least in smokers. The studies were large, well-designed, randomized, placebo-controlled investigations having excellent compliance, complete endpoint ascertainment, and careful analysis and interpretation. Their solid experimental design and surprising results make these trials arguably among the most informative studies of nutrition and cancer ever conducted. The message from this illustration is clear: observational epidemiology cannot be relied on as the sole basis for making health recommendations, especially with regard to vitamin and mineral supplementation.

Supported by corroborative basic research, both observational epidemiology and randomized intervention trials have a place in our scientific armamentarium. As Patterson and her colleagues point out, observational studies of vitamin/mineral supplements have inherent limitations, including: selection bias; limited or single point-in-time exposure assessment; low prevalence of single-agent, high-dose supplement use; and confounding from the clustering of healthful behaviors such as the use of nutritional supplements. At the same time, these studies offer the advantages of their exploratory nature, ability to test a range of exposure levels, and logistic and budgetary ease. Trials, on the other hand, are sometimes

ethically infeasible, are limited to selected (often high-risk) populations, typically test only single agents at fixed doses for limited periods of time, can be of long duration, and are expensive. The main strength of trials is their unbiased experimental test of specific hypotheses.

The first clinical prevention trials having cancer as their endpoint were initiated in the early 1980s. Since 1990, results from seven such trials testing vitamin and mineral supplements have been reported.⁵⁻¹¹ What have we learned from the first generation of cancer prevention trials? Most importantly, these trials have yielded a striking number of promising leads: vitamin E in prostate and colon cancer; β -carotene/vitamin E/selenium in stomach cancer; and selenium in lung, prostate, and colorectal cancer. Each deserves timely corroboration. In addition, if we assume that the main findings in these trials are real, we can speculate on a number of aspects of trial design that have enormous potential impact on planning the next generation of prevention trials. These include: (i) lag-to-effect; (ii) effective duration; (iii) efficacious doses; (iv) factorial designs; (v) intermediate endpoints; and (vi) toxicity.

First-generation trials typically either ignored or included only a minimal lag-to-effect assumption, usually six to 12 months. Experience has shown, however, that the lag-to-effect appears to be substantially longer than these initial considerations permitted. The early studies provide us with empirical data upon which to base future projections, and a lag-to-effect of 18 to 24 months now appears more reasonable.^{5,8}

Duration is influenced by both lag-to-effect and event rates. The fact that the cumulative incidence curves continued to separate until the end of the interventions in some of these trials^{5,6,8,11} suggests that the observed results may underestimate the true maximum achievable effects. To obtain the fullest benefit, it appears that these studies will need to be conducted for more than just five to six years, and perhaps as long as 10 to 15 years.

Many investigators advocate using doses of vitamins at the limits of safety and tolerance in order to maximize the likelihood of benefit. There is evidence that, in some cases, doses close to the recommended daily allowance (RDA) may incur benefit. The benefits observed in the trials in Linxian, China (for β -carotene/vitamin E/selenium and stomach cancer) and Finland (for vitamin E and prostate cancer) were derived from doses that were, with the possible exception of β -carotene, modest.^{5,8} Therefore, while more *may* be better in some cases, it appears that significant benefit can be achieved with even modest doses.

These studies also show that primary cancer-prevention trials with complicated factorial designs can be effectively implemented.^{5,8} With the *caveat* that they introduce a nontrivial multiple comparisons problem, both from the standpoint of multiple exposures as well as

multiple endpoints, we are able to test several hypotheses 'for the price of one' and gain an exploratory glimpse at potential interactions in the process. The use of factorial designs in prevention trials, particularly for interventions with vitamins and minerals, is likely to increase in the future.

Intermediate markers such as histologic dysplasia appear to be highly predictive of future cancer for at least some sites.¹² Further, the findings for the intervention effect on intermediate endpoints of esophageal and gastric dysplasia in Linxian¹³ and gastric dysplasia in Finland (unpublished data) generally appear to be concordant with the findings for the intervention effect on incident and mortal cancers. Although smaller trials using only intermediate endpoints as the final outcome cannot be fully endorsed yet, these observations suggest that such trials well may provide efficient and valid tests of intervention agents in preventing cancer itself.

The unexpected, untoward effects resulting from β -carotene in the Finnish trial⁵ and from β -carotene and retinyl palmitate in CARET establish a new paradigm for event-monitoring in prevention research. One-sided hypothesis-testing that assumes only the potential for benefit, no matter how benign the intervention may appear *a priori*, is no longer acceptable. Further, because cancer is rarely the primary cause of morbidity and mortality in a study population, monitoring non-cancer endpoints (e.g., cardiovascular disease and total mortality) is essential to the full testing of intervention effects.

In sum, we have learned an enormous amount from the first generation of cancer prevention trials. Our knowledge concerning effective trial design and implementation has grown, and a number of exciting scientific leads have been identified that will require confirmation in the next generation of trials. And we need that next generation of trials, along with informative cohort studies, because a promising result from one study – even when that study is a large, randomized clinical trial – is itself an insufficient basis for making definitive health claims.

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