

Nutritional Prevention of Cancer: New Directions for an Increasingly Complex Challenge

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The prospects for cancer prevention through micronutrient supplementation have never looked worse. Several large, randomized cancer prevention trials have recently reported no reduced risk from micronutrient supplementation (1–4), and the short report by Figueiredo et al. in this issue of the Journal adds to a growing body of evidence that micronutrient supplementation may be harmful. Figueiredo et al. have conducted a secondary analysis from a trial that reported previously that folate (1 mg/d) increased the risk of recurrence of an advanced colorectal adenoma by 67% (5). They have found that folate increased the risk of prostate cancer by 163%. Among studies addressing micronutrient supplementation for the prevention of cancer, only a single randomized trial, testing 1200 mg of calcium for prevent-

ing the recurrence of colorectal polyps, has reported a statistically significant and positive result for its primary cancer outcome (6), whereas large trials testing supplementation with multivitamins,

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folate, selenium, β -carotene, and vitamins E, C, D, B₆, and B₁₂ have found no benefits. Even clinical trials designed to test agents that were found to reduce cancer risk in secondary analyses of previous trials, such as vitamin E and selenium for prevention of prostate cancer, have failed to find benefit from supplementation (3). The harmful effects of β -carotene supplementation in heavy smokers are well established (7), and it now appears that folate supplementation may increase cancer risk as well. Because the likelihood that micronutrient supplementation will be included in any public health policy for cancer control has become vanishingly small, it is a good time to step back and consider what we have learned and how we might better focus cancer chemoprevention research in the future.

The primary lesson from our experience in the nutritional prevention of cancer is that it is not simple. It was not unreasonable to test micronutrients for cancer prevention, given the findings in cohort studies that high concentrations of some serum micronutrients and high consumption of some micronutrient-rich foods were associated with reduced cancer risk. However, in hindsight, this approach appears excessively reductionist. If food patterns do indeed affect cancer risk, this benefit is more likely related to energy intakes, relative macronutrient density, and exposure to complex mixtures of bioactive compounds that may include not only micronutrients but also non-nutrients such as glucosinolates and catechins. In the trial reported by Figueiredo et al., for example, high serum folate at baseline was associated with reduced prostate cancer risk; this association likely was with foods high in folate or with a dietary pattern containing high-folate foods and not with folate itself since folate supplementation increased the risks of prostate cancer. Furthermore, the notion that some is good and therefore more is better has been proven wrong; it is more likely that for any given micronutrient, there is an optimal range of intake. We generally can define and understand the effects of micronutrient deficiency, and in deficient populations, there is limited evidence that supplementation at levels found in foods can reduce cancer risk (8,9). However, the long-term effects of micronutrient supplementation at levels below those that induce acute toxicity are not as well understood. Again, using the folate supplementation trial as an example, it is not unreasonable to assume that optimal levels of folate are associated with more fidelity in DNA replication and thus a lower risk of spontaneous mutations, but high folate may also support more rapid cell growth and promote carcinogenesis in previously initiated cells. It is safe to conclude that cancer prevention is not going to be as simple as recommending high-dose micronutrient supplements for middle-aged and older adults.

The best directions for new research in the nutritional prevention of cancer are not simple to prescribe, but we suggest two areas for consideration. First, we should turn our attention back to cohort studies. Although clinical trials are certainly the most rigorous approach to test effects of dietary patterns on cancer risk, our experience shows clearly that current dietary interventions do not achieve the sustained, substantial behavior change over the many years needed to complete a clinical trial with a cancer incidence endpoint (10). But a new and substantial investment in cohort studies will be necessary because almost all past cohort studies have relied upon a very poor tool for measuring diet, the food frequency questionnaire, which has proven to be so inaccurate that drawing

conclusions about diet and cancer from studies using it is unwise (11). New cohorts using improved dietary assessment methods, or the modification of existing cohorts to add better methods, is certainly one important direction for further research. Second, we need a concerted effort to develop human models for cancer prevention that do not require many thousands of study participants and many years of follow-up. This effort essentially entails the transition of mechanistic studies from in vitro and animal models to humans, which is difficult to organize and even more difficult to get funded because it requires cross-disciplinary and innovative collaboration between nutritional scientists, molecular biologists, oncologists, and statisticians. This model development can be illustrated by an example from our research, which addresses the association found in observational studies between broccoli consumption and reduced prostate cancer risk (12–14). From in vitro, animal, and limited human studies, we know that sulforaphane, a compound derived from broccoli, upregulates expression of genes with an antioxidant response element, including *AKR1C1* and *AKR1C2*, the enzymes that catabolize dihydrotestosterone. In a trial requiring only 100 men, we will test whether *AKR1C1* and *AKR1C2* expressions are induced and intraprostatic dihydrotestosterone is reduced following sulforaphane supplementation and whether the kinetics of prostate cancer cell proliferation are altered favorably as a result. When a trial of this type is successful, it would be followed by additional small trials designed and powered to test alternative doses and formulations of dietary compounds, as well as identify any individual genetic characteristics that strongly modify treatment response. Ultimately, this body of knowledge could be used to motivate and more rationally design large-scale trials with cancer endpoints. These suggestions may seem controversial to some. Nevertheless, they can serve as a starting point for discussions among cancer prevention scientists about new directions we can pursue for research in human nutrition and cancer risk.

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