Vitamin and mineral supplements for cancer prevention: issues and evidence1–4

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ABSTRACT

Trials of nutritional supplements for cancer prevention must overcome a variety of challenges not shared in the usual paradigm of pharmaceutical agents for prevention of cardiovascular disease. Unlike for cardiovascular disease, for cancer we typically do not have well-established causal risk factors as targets for intervention. Also, for most likely cancer interventions, the expected time to achieve an effect is much longer, more variable, and far less well understood than for cardiovascular disease, and the progression of pathophysiology is much harder—or impossible—to follow, in contrast with imaging for progression of atherosclerosis in cardiovascular disease. Also, cancers at various sites have a wide range of etiologies. The optimal age for intervention, best dose, and duration needed to test nutritional agents for cancer prevention are largely unknown, making null findings hard to interpret. Unlike with drugs, baseline nutritional status can be critical. Moreover, because the nutritional agents are often readily available, adherence in control groups in trials can be impaired. Several gene-nutrient and nutrient-nutrient interactions have been identified that could affect trial results. Some studies suggest that particular nutrients may be effective only in subgroups defined by genotypes or by nutritional status of another nutrient. All these challenges must be considered in planning informative trials. Long-term prospective cohort studies, especially with repeated measures and high follow-up, can provide useful data for planning trials as well as the basis for rational recommendations while awaiting trial results or in settings where trials may be infeasible. 

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INTRODUCTION

Large population-based intervention trials for chronic diseases have been most successful in cardiovascular disease prevention and treatment. The sharp contrasts in prevention trials between cancer and cardiovascular disease are instructive and highlight some of the major challenges that make the study of cancer prevention much more difficult. One clear difference is that a variety of well-defined causal risk factors have been identified in cardiovascular disease. Several of these, such as elevated LDL cholesterol or hypertension, can be targeted for intervention. In contrast, far fewer risk factors have been identified with confidence for cancer, and typically, these are difficult to intervene on (eg, smoking, obesity). Cardiovascular disease risk factors not only provide targets for intervention, they also allow for better testing of agents for clinical outcomes, because one can evaluate their effect on risk factors before testing in a trial of clinical endpoints.

Another major advantage in studying cardiovascular disease is that the disease process can be monitored and followed much more closely. For most cancers there is no direct analogy, for example, to the progression of atherosclerosis that can be identified in patients at high risk of a clinical endpoint. In addition, neoplasms arising in various tissues have myriad differences in possible etiology.

A third major difference in studying cardiovascular disease is that many of the processes involved in cardiovascular disease can be rapidly altered. For example, statins (inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A reductase) rapidly lower LDL cholesterol. In trials of statin therapy, the clinical event rates in the treated group begin to diverge relatively quickly, within 1–2 y, from the placebo group. For trials using intermediary endpoints, the divergence is even quicker. In contrast, for most cancers we do not have a clear idea of when an intervention might be effective. For example, for breast cancer, use of combined hormone therapy (estrogen plus progestin) noticeably increases the risk of breast cancer within a few years (1). In contrast, we do know that exposure to radiation increases subsequent risk of breast cancer among young women, whose tissue has not undergone ductal differentiation, whereas exposure in older women does little to alter risk (2).

Thus, in designing a trial of a nutritional supplement to prevent breast cancer, the issues of timing—when to initiate treatment and how long it should be given—loom large. If the intervention works through altering hormonal pathways, such as might be expected for weight loss (as adipose tissue is the main source of estrogen in postmenopausal women), one might expect a fairly rapid benefit for breast cancer reduction to emerge. In contrast, if the putative agent is thought to work by countering whatever possible etiology.

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mechanism is involved for the radiation exposures among young women (presumably, DNA damage), then an otherwise effective agent initiated among mature women would yield null results even if the trial were carried out for a long duration.

TIMING AND DURATION OF TRIALS OF CANCER PREVENTION

For some cancers, sufficient knowledge is available to provide clues regarding the likely necessary duration of treatment required to observe a benefit if one is present. For example, with colon cancer, most tumors arise from large adenomatous polyps. However, only a fraction of such polyps become cancerous. Different agents may act at various points in this sequence leading from a normal epithelial cell to a small, well-differentiated polyp, to a large polyp, to carcinoma in situ, and finally to invasive cancer. Because these events occur over decades, they are quite difficult to study in observational designs and may be impossible to study in randomized trials. The evolving research on folate and colon cancer provides an illuminating example. In the Nurses’ Health Study, Giovannucci et al (3) noted a link between higher folate intakes and decreased risk of colon cancer. The relation was apparently dose dependent. Multivitamin use represented a significant contributor to total folate intake, and a striking pattern emerged relating duration of multivitamin intake to risk. Recent intake of multivitamins was unrelated to subsequent colon cancer risk, and a statistically significant reduction in risk was observed only among women who had used multivitamins for ≥15 y. This corresponds well with what we understand about the biology and timeline for colorectal cancer development.

These findings have important implications and illustrate some of the difficulties of planning and conducting trials of supplements for cancer prevention. If these data reflect a true cause-and-effect relation, they suggest that a randomized trial of folate supplementation for prevention of colorectal cancer would require ≥15 y to observe a benefit. A trial that would be considered very long term for cardiovascular disease prevention—say, 10 y—might well be too short and uninformative in this setting. In this example, the observational data can be quite informative for predicting the required duration for a randomized trial. However, in most settings this would largely be a guess. If a supplement had an effect only at the earliest stages of carcinogenesis, even a trial of decades’ duration might miss the benefit if the participants were past that window.

The Women’s Health Initiative (WHI) Trial of calcium plus vitamin D supplementation for colorectal cancer prevention provides a good example of this phenomenon (4). This trial was an add-on to the main WHI trials and was not specifically designed to test the hypothesis that these supplements would reduce risk of colorectal cancer. The main finding was of no difference in the incidence of invasive colon cancer between women assigned to calcium plus vitamin D supplementation versus those assigned to placebo. However, women with low concentrations of circulating 25-hydroxyvitamin D, the best reflection in circulation of overall vitamin D status, were at significantly higher risk of colorectal cancer during the follow-up. If vitamin D acts early in the sequence of events leading to colorectal cancer, then the trial was simply too short to be informative, even with an average 7-y duration of exposure. Nonetheless, the findings were interpreted by some as evidence against the hypothesis that calcium and vitamin D prevent colorectal cancer.

This trial also provides an example of the difficulties in choosing the best dose of an agent for a trial. Recognizing the upper limit of intake of vitamin D, set at the (unrealistically low) level of 2000 IU/d, the investigators chose a dose of 400 IU/d. This modest dose was too low to substantially alter blood concentrations and would not have provided an adequate test of the vitamin D hypothesis even if the trial had been carried out for a much longer duration. A fuller appreciation of the dosage issues became more widespread in the scientific community as further evidence emerged after the trial was designed. Because cancer prevention trials may require long durations, new knowledge that emerges during that interval may render the results less relevant than they appeared at the outset.

The dosage issue bears on a related problem in some nutrient trials, that of the baseline nutritional status of the population. Again in contrast with drugs, the control group for nutrients is not unexposed but rather exposed at a lower dose. This can be of critical importance if the effect of the nutrient under study is limited to those who have very low levels at baseline and have no further dose effect. Such a situation is highly plausible biologically. For example, if the critical nutrient acts as a cofactor for an enzyme, once sufficiency is reached, one might expect no further functional benefit. The nutrient intervention trials in Linxian, for example, were highly meritorious and informative and established an important proof of principle (5). However, they leave open important questions of generalizability because of the low baseline nutritional status of the participants. The opposite can also occur: if most trial participants are nutritionally replete, one might fail to see a benefit from a nutrient that is critical for those with low levels. In the WHI, most participants were already likely consuming sufficient calcium, leaving little possibility for observing a benefit from consuming more (4).

The WHI calcium and vitamin D trial illustrates yet another problem inherent in testing nutritional supplements for cancer prevention: that of adherence to the assigned treatment regimen. Unlike many drug trials, most of the nutritional agents likely to be tested are readily available without a prescription to all participants. To effectively test an agent, a clear contrast between the experimental and control groups is essential. To the extent that those in the control group take the experimental agent on their own and those in the experimental group cease adherence, the contrast decreases with a consequent loss in statistical power such that a test of a truly effective agent might yield null findings. In the WHI calcium and vitamin D trial, 69% of women reported taking calcium outside the trial by year 9 and one-third or more reported taking vitamin D (4).

The difficulties in interpreting the timing for nutrient interventions for cancer prevention are also well illustrated in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (6). In that randomized trial of β-carotene in Finnish smokers, the incidence of lung cancer was higher in the β-carotene group. The incidence started to increase from the beginning of the trial and reached statistical significance, compared with placebo, after about 5 y. However, after termination of the trial, the cohort was further followed. The incidence of lung cancer in the β-carotene group began to drop compared with the placebo group and was statistically significantly lower at ≈6 y after the trial was stopped. Does this mean that β-carotene stimulated the growth of
tumor cells that were already initiated, leading to earlier diagnosis? Was this simply a chance finding despite the statistical significance? The issues cannot be resolved with certainty but the data illustrate the complexity of cancer prevention trials.

GENE-NUTRIENT AND NUTRIENT-NUTRIENT INTERACTIONS

Genetic analyses can provide further insight to assessing nutrient-cancer relations. Studies of folate and colorectal cancer provide a useful illustration. A common polymorphism in the gene that codes for the enzyme methylenetetrahydrofolate reductase (MTHFR) leads to a variant enzyme with impaired ability to convert 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate. Our group and others found a strong link between this polymorphism and risk of colorectal cancer (7). Men who are homozygous for the variant had about one-half the risk of colorectal cancer as did other men. In further analyses, we found that this association was limited to those without folate deficiency in whom the homozygous variant carried about a two-thirds reduction in risk. These findings provide powerful support for a causal interpretation of the link between folate and colorectal cancer. The presence or absence of the variant gene is almost certainly unrelated to dietary intake of folate or any other personal characteristic. Thus, it is difficult to attribute any observed associations of that gene with colon cancer risk to confounding factors. A further finding of a biologically plausible interaction between this variant enzyme and folate status renders the noncausal interpretation implausible. Without evidence from this gene-nutrient interaction, one might plausibly interpret the relation of high folate status to lower risk of colorectal cancer to other healthy behaviors that are correlated with folate intake. The finding of gene-nutrient interactions substantially reduces these concerns.

Another example illustrating a different aspect of gene-nutrient interactions is the relation between antioxidants and risk of prostate cancer. Previous observational studies showed that men with low circulating concentrations of vitamin E, lycopene, and selenium have a higher risk of future development of advanced prostate cancer (8, 9). All 3 of these nutrients are potent antioxidants. Vitamin E and selenium were shown in randomized trials to reduce the risk of prostate cancer (10, 11). However, these trial results have not been fully accepted, largely because neither trial specified prostate cancer reduction as a primary a priori outcome. Both of these agents are currently being tested in a large randomized trial, the Selenium and Vitamin E Cancer Prevention Trial (SELECT) (12). A common polymorphism with apparently functional consequences has been identified in the gene coding for manganese superoxide dismutase, the principal antioxidant enzyme in mitochondria. Because of the strong hypothesis that antioxidants might be important for prostate cancer risk, our group studied the effect of this polymorphism. Overall, we found no significant association. However, we found a highly statistically significant interaction between the variant genotype and these 3 antioxidants, such that men homozygous for the variant allele were remarkably sensitive to dietary antioxidants (13). We observed a 10-fold gradient in risk comparing those in the highest quintile of a combined antioxidant score (based on blood concentrations of vitamin E, lycopene, and selenium) with those in the lowest quintile, but only among men homozygous for the variant allele. This kind of gene-nutrient interaction, analogous to folate-MTHFR, strongly supports a causal interpretation for these antioxidants. However, of note, no main effect was observed for the variant allele. Instead, we found that the variant defined a subgroup that is quite sensitive to exogenous antioxidants. This finding suggests that SELECT may fail to observe an overall effect if most of the benefit is limited to the minority of men who are homozygous for the variant allele. Unlike in studies of drugs, which are novel exogenous agents, one might strongly expect the presence of gene-nutrient interactions because the nutrients have long been part of human evolutionary history. Because of the issues of timing and duration described earlier, gene-nutrient interactions may potentially provide sufficiently strong evidence for dietary recommendations if definitive randomized trials are infeasible.

Nutrient-nutrient interactions are also likely. For example, in the Calcium Polyp Prevention Trial, Grau et al (14) observed a significant reduction in polyp recurrence in the calcium group compared with the placebo group, but the effect was limited to those with 25-hydroxyvitamin D values above median [29.1 ng/mL; relative risk = 0.71, 95% CI: 0.57, 0.89] and not seen in those with lower 25-hydroxyvitamin D concentrations [relative risk = 1.05; 95% CI: 0.85,1.09]. Thus the nutrient status of the trial participants may affect the results of an intervention trial using a different nutrient in unpredictable ways.

CONCLUSIONS

Ethical and feasibility issues impose considerable constraints on the potential scope for randomized trials of supplements for cancer prevention. It is difficult to consider testing substances that may have potential harm. These may be more common than suspected. For example, although substantial evidence supports a role for calcium in reducing the risk of colorectal cancer, data from a variety of sources suggest that high calcium intakes may increase the risk of advanced prostate cancer (15, 16). Preformed vitamin A, tested in the β-Carotene and Retinol Efficacy Trial (17, 18), might increase the risk of fractures and could interfere with the activity of vitamin D (19). Likewise, it is well-known that selenium has a narrow range between deficiency and toxicity. These examples illustrate the point that safety of nutritional supplements cannot simply be assessed.

Data from appropriately designed and conducted randomized trials provide the soundest basis for causal inference and consequent policy decisions. However, nutrient trials for cancer prevention are fraught with numerous difficulties, and even well-designed trials may yield results that are difficult to interpret. These difficulties do not mean that such efforts should cease; to the contrary, the need for informative trials is acute. However, it is only by scrutiny of these issues during the design phase that we can increase the likelihood for deriving useful information from these expensive efforts. For many potential nutritional interventions, the challenges of randomized trials will be insurmountable in the near term, and we will need to continue to rely on long-term prospective studies. Such designs have their own well-known limitations, especially the potential for results to be distorted because of confounding factors. The value of these prospective observational studies can be markedly enhanced by use of repeated measures with validated instruments, prolonged follow-up to assess long-term effects, and the incorporation of repeated collection of biological samples to test for gene-diet interactions. A nuanced approach, based on all available evidence, provides the only sound
basis for recommendations and to guide further research for nutrient supplements and cancer prevention.

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