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COMMENTARY

Dietary Supplements and Cancer Prevention: Balancing Potential Benefits Against Proven Harms

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Nutritional supplementation is now a multibillion-dollar industry, and about half of all US adults take supplements. Supplement use is fueled in part by the belief that nutritional supplements can ward off chronic disease, including cancer, although several expert committees and organizations have concluded that there is little to no scientific evidence that supplements reduce cancer risk. To the contrary, there is now evidence that high doses of some supplements increase cancer risk. Despite this evidence, marketing claims by the supplement industry continue to imply anticancer benefits. Insufficient government regulation of the marketing of dietary supplement products may continue to result in unsound advice to consumers. Both the scientific community and government regulators need to provide clear guidance to the public about the use of dietary supplements to lower cancer risk.

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According to the 1994 US Dietary Supplement Health and Education Act, a nutritional supplement is defined as a product intended to supplement the diet, containing one or more dietary ingredients (including vitamins, minerals, herbs, amino acids, or other botanicals), and to be taken by mouth as a pill, capsule, tablet, or liquid (1). Clearly, dietary supplements are useful for the treatment of nutrient deficiencies; however, with the exception of select subgroups (2,3), such deficiencies are relatively uncommon in the United States and most industrialized countries today. According to the most recent National Health and Nutrition Examination Survey (2003–2006), half of the US adult population uses one or more dietary supplements; most of those are multivitamin and/or multimineral supplements (4). Observational studies (5–8) provide little evidence that multivitamins reduce cancer risk, and there have been no randomized studies of multivitamins for cancer prevention. Nonetheless, high supplement usage, fueled by industry claims ranging from wrinkle to cancer prevention, has resulted in a continued rise in nutritional supplement sales, estimated to be approximately US $30 billion annually (9).

Assessment of the role of dietary supplements in cancer prevention relies heavily on in vitro and animal experiments, which provide evidence of potential biochemical and molecular mechanisms of action for specific nutrients. Evidence from observational studies in human populations may also be invoked in support of a proposed relationship between a nutrient and a cancer outcome. This evidence can add to the rationale for experimental testing in humans, usually via a randomized controlled trial (RCT), regarded as the "gold standard." Compared with the large number of observational studies of diet and cancer, the number of RCTs of dietary supplements for cancer prevention conducted to date is relatively small; findings from these RCTs generally do not support the observational epidemiological data that suggest benefit. Because the number of supplements currently available in the market is large, we will limit this commentary to supplements that have been tested in adequately powered clinical trials or in large well-designed observational studies. Based on this evidence, we summarize the current knowledge about the benefits and harms of nutritional supplements for cancer prevention and comment on current needs for improving public policy and education about the use of these products.

Evidence for Benefit and Harm

Antioxidants

Several early observational studies (10–13) found that diets high in fruit and vegetables were associated with diminished risk of several cancers, including respiratory and gastrointestinal cancers. The importance of β-carotene and other carotenoids was suggested by both retrospective and prospective studies showing that low levels of β-carotene in the serum were associated with higher subsequent risk for lung cancer (14). At one point, research focused on retinoid supplementation, in light of the finding that β-carotene is converted to retinol (13). It was hypothesized that the lower risk associated with consumption of these foods, and with β-carotene, α-tocopherol, and vitamin C intake, might be attributable to the activity of antioxidants. In vitro and in vivo studies suggested that these compounds encourage growth of normal tissue and block growth of abnormal tissue (2). However, human experimental studies have uncovered the following: β-carotene does not prevent non-melanoma skin cancer recurrence (15); β-carotene and α-tocopherol with vitamin C do not protect against adenoma recurrence (16); β-carotene and vitamin A do not protect against

lung cancer incidence (17); α-tocopherol and β-carotene do not prevent lung cancer (18); β-carotene does not prevent lung cancer (19); vitamins C and E do not protect against total cancer incidence (20); and α-tocopherol, vitamin C, and β-carotene do not protect against total cancer or cancer mortality (21). Based on a review of trial data, a Cochrane report (22) concluded that there was no convincing evidence that β-carotene, vitamin A, vitamin C, or vitamin E supplements, given singly or in combination, prevent gastrointestinal cancers. The importance of oxidative stress for carcinogenesis does not establish that the administration of supplemental antioxidants will protect against the carcinogenesis that oxidative stress may induce. Supplementation by exogenous antioxidants may well be a two-edged sword; these compounds could, in vivo, serve as pro-oxidants or interfere with any of a number of protective processes such as apoptosis induction (2). In fact, as noted below, some clinical trials show that some of these antioxidant nutrients may increase cancer risk.

A great deal of optimism was occasioned by results of the Nutritional Prevention of Cancer (NPC) study, which was designed to test the skin cancer preventive effects of selenium, a trace mineral that is important for protection against oxidative stress (23). The first report from the NPC showed that selenized yeast did not affect skin cancer incidence but was negatively associated with the incidence of some malignancies that were secondary endpoints in that trial, including cancers of the lung, colon, and prostate, as well as total cancer incidence and mortality (23). In the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Trial, neither agent showed benefit for lung cancer (the primary endpoint), but men randomly assigned to take α-tocopherol were found to have fewer incident cancers of the prostate compared with those in the group assigned to placebo (18).

The promising results from the NPC and ATBC trials on secondary endpoints of prostate cancer were followed up in a subsequent RCT of α-tocopherol and selenium among 35 533 men at average risk for prostate cancer in the Selenium and Vitamin E Cancer Prevention Trial (SELECT) (24). After approximately 5.5 years of follow-up, SELECT was halted following an interim analysis showing that it was unlikely that either selenium or α-tocopherol imparted any benefit for prostate cancer (24). A much smaller Southwest Oncology Group (SWOG) trial of selenium supplementation among men with a lesion widely regarded as a premalignant precursor of prostate cancer also showed no benefit (25). The NPC had tested a nominally different form of selenium than the SELECT or SWOG trials tested (selenized yeast vs selenomethionine). However, a trial of selenized yeast to prevent recurrence of stage I non–small cell lung cancer was halted after interim analysis indicated that it was unlikely to show any benefit (26). Thus, organic selenium appears to provide no cancer prevention benefit.

An exception to the null findings of antioxidant nutrients for cancer prevention relates to one of the nutrition intervention trials conducted in Linxian, China, a population with low nutrient intakes (27). This trial of 30 000 individuals tested four different nutrient cocktails vs placebo, finding a modest 13% reduction in cancer mortality in participants receiving a combination of β-carotene, vitamin E, and selenium (selenized yeast); and a 21% reduction in gastric cancer mortality. However, in a smaller, 3000-person Linxian companion study of men and women with cytological evidence of esophageal dysplasia, intake of a supplement that contained 14 vitamins and 12 minerals, including β-carotene, vitamin E, and selenium, had no statistically significant effect on total cancer incidence. Although cancer of the esophagus was non-statistically significantly decreased by 16%, cancer of the gastric cardia was non-statistically significantly increased by 4%, and cancer of the gastric cardia/esophageal junction was non-statistically significantly decreased by 8% (28). Finally, the Supplementation en Vitamines et Mineraux Antioxydants (SU.VI.MAX) trial conducted in France (29) showed no overall benefit in cancer incidence with supplementation by a combination of vitamin C, vitamin E, β-carotene, selenium, and zinc, although a protective effect of the intervention appeared to be present for men but not women.

Several antioxidant trials (17,18,30,31) have actually reported increased risks with supplementation. The most prominent example, β-carotene and lung cancer, was tested in two RCTs (17,18) in high-risk populations of heavy smokers and asbestos-exposed individuals. Individuals randomly assigned to β-carotene in the Beta-Carotene and Retinol Efficacy Trial (CARET) trial had a 39% increase in lung cancer incidence compared with those in the placebo arm (17); the ATBC trial found a 16% increase in risk of lung cancer associated with β-carotene (18). With prolonged follow-up, NPC investigators found that selenium supplementation statistically significantly increased the risk of squamous cell skin cancer by 25% and total non-melanoma skin cancer by 17% (30). The increased risk was particularly marked among individuals in the highest tertile of circulating selenium levels just before the start of the trial. The most recent illustration of the possibility that pharmacological doses of antioxidants may not have the intended effect comes from the extended follow-up in the SELECT trial, which reported that α-tocopherol increased risk of prostate cancer by a statistically significant 17%; these results led the authors to conclude that consumers should be skeptical of health claims related to unregulated over-the-counter products (31).

Folic Acid

Folate, a water soluble B-vitamin, is required for a variety of methylation-related processes. Although the terms "folate" and "folic acid" are sometimes used synonymously, the latter refers to the synthetic oxidized form that is commonly used in fortification and supplements, whereas naturally occurring folates are reduced molecules that exist in nature in several different forms with various degrees of polyglutamation. The association of folate and folic acid with cancer risk has been most intensely studied with regard to colorectal neoplasia. Although it has been proposed that synthetic sources of folate might confer greater protection than natural forms (32), results of one meta-analysis of observational studies (33) of colorectal cancer showed that total folate (dietary plus synthetic sources) did not provide greater protection than dietary folate. In contrast to observational data (34) showing a protective association of folate status with risk, a recent meta-analysis of RCTs (35) found no effect of folic acid supplementation on risk of colorectal adenomas over the 3-year treatment period. In view of these findings, folic acid does not seem to be a promising avenue for colon cancer prevention as previously hoped.

Contrary to the hypothesized benefit, the results of one trial (36) showed that long-term folic acid supplementation increases risk of

advanced colorectal adenomas (relative risk = 1.67; 95% confidence interval = 1.00 to 2.80) and of developing three or more adenomas (relative risk = 2.32; 95% confidence interval = 1.23 to 4.35). In this RCT, increased risk of prostate cancer was also found (37). Because preclinical studies (38,39) show the potential for a pro-neoplastic effect of folate—at least in animals with preexisting neoplasms—the possibility of enhanced carcinogenesis is a concern. Consistent with this idea, observational studies (40,41) have linked higher dietary intake as well as higher circulating concentrations of folate with increased prostate cancer risk; higher risk of breast cancer has also been shown among individuals with higher folic acid intake (42). Whether folic acid supplementation can have adverse effects is a topic that needs further investigation. This is particularly important in countries such as the United States, where government-mandated folic acid fortification of the food supply, which began in 1996 (43), has resulted in higher overall intake of this nutrient and use of supplements containing folic acid is widespread (4).

Vitamin D and Calcium

Vitamin D has recently generated great interest for cancer prevention, particularly in relation to breast, colorectal, and prostate cancers. The Institute of Medicine published updated recommendations for vitamin D and calcium intake in 2011 (44), along with a finding that there was not enough evidence to state that there is a causal association between low vitamin D intake and increased cancer risk. There have been many epidemiological investigations of blood 25 hydroxy (OH) vitamin D [25(OH)D] concentrations and cancer-related endpoints (45–49), and meta-analyses of these have shown statistically significant inverse associations between serum 25(OH)D and colorectal adenoma (46,49) and colorectal cancer (45), whereas the results for prostate cancer have largely been null (45,48). For breast cancer, the relationship with serum 25(OH)D levels varies by study design; case-control studies generally demonstrate inverse associations, and prospective studies have been null (45,47,50); because blood levels are collected after the onset of cancer in case-control studies, the potential for bias in these studies must be considered (47,50). Clearly, clinical trials are needed to elucidate any preventive effect of vitamin D (51,52). To date, three short-term RCTs of vitamin D and cancer endpoints (52–55) have been completed; one showed no direct effect of vitamin D supplementation on cancer mortality (53), the second showed no reduction in breast or colorectal cancer incidence by a vitamin D/calcium combination (54,55), and the third showed a reduction in total cancer incidence by a calcium/vitamin D combination vs placebo (56). As concluded in a recent meta-analysis, because of the potential confounding inherent in observational studies and the limited data from clinical trials, evidence is currently insufficient to draw conclusions about the efficacy of vitamin D supplementation for cancer prevention (57). Targeted clinical trials of specific cancer endpoints associated with vitamin D supplements are currently ongoing.

Observational studies of calcium and cancer prevention have yielded diverse results. A recent meta-analysis of observational studies supports an association between higher calcium consumption and reduced breast cancer risk (58). In contrast, results for prostate cancer have been more varied, with several observational studies reporting an increased risk for prostate cancer at higher calcium intakes (59). Although earlier observational studies of calcium and colorectal cancer were found to be equivocal (60,61), a recent meta-analysis found that higher calcium intake was associated with reduced colorectal cancer risk (62).

Results of two RCTs revealed that calcium supplementation reduces the risk for colorectal adenoma recurrence (63,64). However, in the Women's Health Initiative, the combination of 1 g of calcium and 400 IU of vitamin D had no effect on colorectal cancer risk (55). Clinical trial data for vitamin D and calcium regarding breast and prostate cancer risk are sparse. The Women's Health Initiative demonstrated no effect of its calcium and vitamin D intervention on breast cancer incidence (54); secondary analyses of another clinical trial showed no protective effect of calcium supplementation after 10.3 years of follow-up, but there was a suggestion of protection from early-stage cancers with calcium supplementation during the first 6 years on study (65).

Given that RCTs of vitamin D are relatively sparse, current assessments of potential harm from this nutrient must presently rely on observational data. Based on a report from a large observational study, there was concern regarding an association between high vitamin D concentrations and pancreatic cancer (66); however, a recent meta-analysis showed that higher concentrations were associated with a reduction in risk (67). Therefore, the picture for pancreatic cancer remains unclear. With regard to prostate cancer, a recently published study (67) revealed a statistically significant increased risk for prostate cancer among men with the highest concentrations of 25(OH)D (68), and the authors of the report advised caution in recommending vitamin D for cancer prevention.

Lessons From Experimental Studies

Observational research regarding nutritional supplements is challenging. The use of supplements is likely highly confounded by other personal characteristics associated with cancer risk, including dietary intake of the other nutrients in the supplements. Moreover, variation in the formulations and doses of supplements available in the marketplace is substantial, a particular problem for multivitamins (69). These factors highlight the need for RCTs of nutrient supplements. However, interpretation of results from experimental studies must take into account the characteristics of the study population and setting. Interventions that involve nutrients are tested in the setting of specific dietary backgrounds, which can have important effects and must be considered in the analysis and interpretation. This situation is different from RCTs of many drugs, in which placebo groups are not generally exposed to the agent being tested, and is a key issue, given that participants in chemoprevention trials tend to be health conscious and typically do not have low or deficient nutrient intakes. Testing the efficacy of nutritional supplements among individuals with high background nutrient status means that efficacy is tested among those who cannot benefit from reversal of deficiency (70,71), and risk is accentuated if there can be harm at higher doses. Even though the NPC trial was conducted in a region of the United States in which marginal selenium deficiency was common, the apparent benefits of selenium were confined to individuals with the lowest baseline blood selenium levels (30); a similar pattern was also observed in the trial of selenium supplementation

conducted among men at high risk of prostate cancer (25). Had these and other trials been conducted exclusively among individuals who started out with low or marginally low nutrient status, the overall balance of benefit and harm might have been different. Individuals with marginal or deficient nutrient intakes may benefit from supplementation, but those whose intake has already exceeded the threshold of adequacy may experience harm.

Another lesson from experimental studies is that different tissues may vary markedly because of different carcinogenesis pathways, as well as tissue-specific genetic mutations (72). Because of these differences, it may not be reasonable to assume that consumption of a single nutrient would exert chemopreventive effects equally in all tissues. In fact, a nutrient may be associated with protection in one tissue and harm in another (73).

An important limitation of RCTs is their treatment duration: Efficacy and harm are tested typically over a period of several years (17,18,23,24,27). Given that the natural history of carcinogenesis can take decades, this relatively short period might not be sufficient to reveal the benefits or deleterious effects of an intervention. Thus, a limited duration could be an important shortcoming of many trials involving nutritional supplements; adequate follow-up may be needed to uncover benefits and adverse effects. The already noted adverse effects of folic acid supplementation were not evident in the initial treatment period of the adenoma trial that tested them (36); it was revealed only in the extended follow-up period. In addition, extended follow-up of the SELECT trial was needed to reveal that α-tocopherol supplementation increased prostate cancer risk (74).

Although dietary supplements have been in widespread use in the United States for many years and are generally assumed to be safe, understanding of their toxicity is actually incomplete. Clinical trials are crucial for uncovering adverse effects, because the adverse effects may be modest and supplement use in observational studies can be highly confounded with other characteristics of the users. In fact, clinical trials have disclosed several adverse effects of high-dose vitamin and mineral supplementation. In two of the three large β-carotene trials (18,75), the intervention also increased the risk of all-cause mortality. A higher risk of type 2 diabetes was shown to be associated with selenium intervention, and this risk increased with increasing baseline selenium concentrations (76). In a Cochrane report published in 2008, Bjelakovic et al. (22) concluded that with the exception of selenium, antioxidant supplements appear to increase gastrointestinal cancer mortality (22). Furthermore, although the data for calcium and prostate cancer risk are inconsistent (59,65), results of a recent meta-analysis of RCTs showed a statistically significant increase in myocardial infarction associated with calcium supplementation (77).

Dietary Supplement Regulation

Given that RCT data show that dietary supplements have either no effect on cancer risk or that they can sometimes have adverse effects, why do messages still abound in the popular press about the cancer-fighting properties of these supplements? The "apple-a-day" and "we are what we eat" axioms resonate strongly within us, and they may well be true. However, these fundamentally positive beliefs about the connections between nutrition and health can be exploited by nutritional supplement manufacturers to suggest cancer-fighting effects of supplements that exceed the objective evidence (78). The basic sales pitch is that if a little of a nutrient is good, then a lot must be better. This is not simply a matter of economic exploitation in the marketplace; the safety of dietary supplements is a valid public health issue.

How can there be such a discrepancy between the scientific evidence and public perceptions about dietary supplements? A review of the regulatory history of supplements provides some perspective (Figure 1). The US Food and Drug Administration (FDA) was created in 1906 to regulate the production and marketing of foods and drugs, but it was not until the 1960s that FDA began to attempt to regulate dietary supplements. With many different pieces of legislation, the US Congress has limited the authority of FDA to regulate manufacturing and marketing of supplements, leaving them in a gray zone somewhere between foods and drugs (79). Even health claims for foods were not regulated by the FDA until 1990 when, in response to a growing number of unsubstantiated health claims by food manufacturers (including anticancer advertisements for specific foods), the Congress passed the Nutrition Labeling Education Act (NLEA) (80). Under the NLEA, the FDA began investigations and rule-making to apply standards of scientific evidence to health claims for nutritional supplements, but this effort was short-lived. Sensing that supplement marketing might be adversely affected by this scrutiny, the nutritional supplement manufacturers organized mass media campaigns and a write-in campaign to put pressure on the Congress to limit FDA authority over nutritional supplements. As a result, in 1994, Congress passed the Dietary Supplement Health and Education Act, which classified dietary supplements as food and substantially limited the role of the FDA in regulating the manufacture or marketing of dietary supplements (81).

As a result of the Dietary Supplement Health and Education Act, the US nutritional supplement industry has been relatively

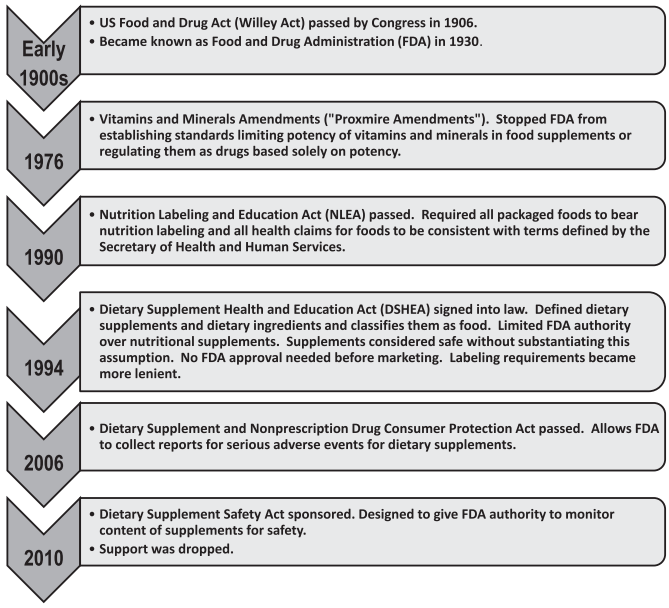

Figure 1. Regulatory history of dietary supplements in the United States.

free from message regulations (82). In response to several high-profile deaths from ephedra, the Congress passed the Dietary Supplement and Non-prescription Drug Consumer Protection Act in 2006 (83). Although that act defined new roles for FDA in collecting reports of acute adverse events from supplements, it gave the agency no new powers to regulate dietary supplement health claims or marketing. In 2010, in response to the continued need for better regulation of nutritional supplements, as evidenced by the problem of steroids being included without labeling in some sports supplements, US Senators John McCain and Byron Dorgan sponsored the Dietary Supplement Safety Act (DSSA), designed to give FDA the legal authority to monitor supplement safety and to withdraw from the market any deemed to be potentially hazardous to health (84). Again, fearing FDA encroachment into marketing, the powerful supplement industry protested; after an entreaty from Senator Orrin Hatch, a known supporter of the dietary supplement industry (85), Senator McCain, withdrew his support for the DSSA. More recent attempts to set guidelines for assessing supplement safety have also come under attack by the industry, even though some experts argue that those guidelines do not go far enough (9).

Some of the marketing by the dietary supplement industry, especially by online retailers, can be deceptive. In 2009, even after publication of the null findings from SELECT, Bayer stopped advertising that its *One-A-Day Men's Health Formula* supplement could prevent prostate cancer because it contained selenium and vitamin E (86) only after it was threatened by a lawsuit. Perhaps, the most current direct evidence of this practice relates to vitamin D, which is being marketed in the popular media for its benefits in reducing cancers of the colon, breast, pancreas, and prostate. Even without such direct statements, anticancer effects can be implied. For example, even though the manufacturers of Pill X cannot openly advertise that it prevents prostate cancer, they can create an advertisement that states that prostate cancer is a major health problem, that Pill X has a role to "support prostate health," and that a particular study found that the compounds in Pill X reduced the growth of prostate cells in culture. Their website can then be accompanied by advertisements for Pill X and can contain links to testimonials that are free to expound the benefits of Pill X as experienced by real people. The absence of credible scientific evidence that taking Pill X confers anti-prostate cancer properties in men can be easily obscured by this constellation of claims that collectively suggest anticancer effects. As a result of limited regulatory authority, manufacturers who cannot overtly claim anticancer benefits of supplements without scientific proof are

Table 1. Select consensus recommendations on multivitamin/mineral supplements for cancer prevention or chronic disease prevention*

Source	Recommendations
Kushi LH, Doyle C, McCullough M, et al. American Cancer Society Guidelines on Nutrition and Physical Activity for Cancer Prevention: Reducing the Risk of Cancer With Healthy Food Choices and Physical Activity, 2012 (87).	Present knowledge indicates that dietary supplements do not lower cancer risk.
Bjelakovic G, Nikolova D, Simonetti RG, Gluud C. Cochrane Review on Antioxidant Supplements for Preventing Gastrointestinal Cancers, 2008 (22).	No convincing evidence that antioxidant supplements prevent gastrointestinal cancers. On the contrary, antioxidant supplements seem to increase overall mortality. Antioxidant supplements cannot be recommended for gastrointestinal cancer prevention.
American Institute for Cancer Research/World Cancer Research Fund. Food, Nutrition, and Physical Activity and the Prevention of Cancer: A Global Perspective, 2007 (88).	Dietary supplements are not recommended for cancer prevention. Aim to meet nutritional needs through diet alone.
NIH State-of-the Science Conference Statement: Multivitamin/Mineral Supplements and Chronic Disease Prevention, 2006 (89).	No strong evidence for beneficial health-related effects of supplements taken singly, in pairs, or in combinations. Insufficient evidence to recommend either for or against the use of multivitamin/mineral supplements by the American public to prevent chronic disease.
Huang HY, Caballero B, Chang S, et al. Agency for Healthcare Research and Quality. Multivitamin/Mineral Supplements and Prevention of Chronic Disease, 2006 (90).	Multivitamin/mineral supplement use may prevent cancer in individuals with poor or suboptimal nutritional status. The heterogeneity in the study populations limits generalization to populations in the United States. Regular supplementation with a single nutrient or a mixture of nutrients for years has no substantial benefits in the primary prevention of cancer, cardiovascular disease, cataract, age-related macular degeneration, or cognitive decline. The overall quality and quantity of the literature on the safety of multivitamin/mineral supplements is limited.
Coutler I, Hardy M, Shekelle PG, et al. Agency for Healthcare Research and Quality. Effect of the Supplemental Use of Antioxidants Vitamin C, Vitamin E, and Coenzyme Q10 for the Prevention and Treatment of Cancer, 2003 (91).	No support for the hypothesis that supplements of vitamins C or E or coenzyme Q10 help prevent or treat cancer.
US Preventive Services Task Force. Routine Vitamin Supplementation to Prevent Cancer and Cardiovascular Disease: Recommendations and Rationale, 2003 (92).	The evidence is insufficient to recommend for or against the use of supplements of vitamins A, C, or E; multivitamins with folic acid; or antioxidant combinations for the prevention of cancer or cardiovascular disease. Recommends against the use of β-carotene supplements, either alone or in combination, for the prevention of cancer or cardiovascular disease.

* These recommendations were selected from the major systematic reviews and consensus panels over the past 10 years, which have assessed the published evidence of effects of nutritional supplements on cancer risk.

nonetheless free to imply those benefits in ways that make it difficult for the consumer to discern innuendo from scientific fact (82). As evidence of this practice, a recent investigation by the US Government Accountability Office (GAO) found that certain herbal dietary supplements were deceptively or questionably marketed to consumers, and when GAO investigators posed as consumers, they were given potentially harmful medical advice (78).

Concluding Remarks

We have argued that dietary supplements should not be directly or indirectly marketed for cancer prevention, absent findings from clinical trials documenting efficacy and safety. Given the current state of the science, do we need to conduct more RCTs of dietary supplements to assess their efficacy for cancer prevention? We do, but these trials must be designed strategically and in light of lessons learned from previous studies. In the absence of convincing evidence that more will be better, we probably do not need more trials in nutrient-replete populations. The value of conducting trials in populations with poor nutrient status has been shown in results of primary and secondary analyses reviewed above. In any case, we will require studies that evaluate the impact of many years, rather than a few years, of nutritional supplementation.

RCTs are currently ongoing in the United States, including a calcium alone or in combination with vitamin D factorial design study in colorectal adenoma prevention, selenium as selenized yeast in colorectal adenoma prevention, and vitamin D for overall cancer prevention. Whether these trials will find benefits from supplementation for cancer prevention is unknown. In considering the current evidence, many expert committees and organizations have made public health recommendations, generally concluding that nutritional supplements have little to no benefit in preventing cancer (Table 1).

Given this general consensus, why do so many people in the United States continue to use dietary supplements? A large part of the answer lies in messages from supplement manufacturers, who suggest that there are health benefits, including cancer prevention, from supplements. Undoubtedly, use is driven by a common belief that supplements can improve health and protect against disease, and that at worst, they are harmless. However, the assumption that any dietary supplement is safe under all circumstances and in all quantities is no longer empirically reasonable. Believers in supplements are sometimes quick to discredit caution over supplement use, as they suggest that the tendency of mainstream science to ignore nonconventional evidence is tainted or that mainstream science is somehow corrupted by its link to a medical–industrial complex that seeks to protect profits rather than prevent disease. Results of a recent survey showed that most US supplement users report that they would continue to use supplements even if scientific evidence found them to be ineffective or if the FDA specifically deemed them ineffective (93). Perhaps, it is generally assumed by supplement users that these products are as well regulated as over-the-counter medications (93). These beliefs underscore the need for efforts by scientists and government officials to encourage the public to make prudent decisions based on sound evidence with respect to use of dietary supplements for cancer prevention.

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