Clinical trials of vitamin and mineral supplements for cancer prevention[1–4]

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ABSTRACT

Approximately 20–30% of Americans consume multivitamin supplements daily, indicating high public interest in the prevention of cancer and other chronic diseases through a nutrition-based approach. Although several bioactive food components, including vitamins and minerals, have been investigated for their ability to affect cancer risk, few large, randomized, placebo-controlled clinical trials of multivitamins with cancer as the primary endpoint have been performed. The results of most large-scale trials of multivitamin supplements (combinations of ≥2 vitamins and minerals) to prevent cancer have been mixed. The Linxian General Population and Dysplasia trials found a decreased risk of cancer, particularly stomach cancer, for participants taking a multivitamin supplement, but this was in a borderline-deficient population in China. Two trials, the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study and the β-Carotene and Retinol Efficacy Trial, found an increased risk of lung cancer among male cigarette smokers or asbestos-exposed persons taking β-carotene—a surprising result, considering that most epidemiologic studies have suggested that consumption of fruit and vegetables appears to lower cancer risk. To clarify the effects of multivitamin supplements, several large randomized clinical trials are underway, including the Physicians' Health Study II, the Selenium and Vitamin E Cancer Prevention Trial, and a European study, Supplémentation en Vitamines et Minéraux Antioxydants (SU.VI.MAX). Because epidemiologic studies generally evaluate foods rather than specific bioactive food components, a systematic approach to determining how combinations of vitamins and minerals may interact to ameliorate cancer risk is necessary to further our understanding of the potential benefits and risks of supplement use. *Am J Clin Nutr* 2007;85(suppl):314S–7S.

KEY WORDS Multivitamin supplements, randomized clinical trials, cancer prevention, bioactive food components, nutrition

INTRODUCTION

For the past 3 decades, cancer prevention clinical trials have been based on rationales developed from laboratory and epidemiologic research that identified numerous natural and synthetic agents for further testing in people. The premise is that medical interventions that aim to prevent, arrest, or reverse either the initiation phase of carcinogenesis or the progression of premalignant cells are an important research aim for cancer prevention. Much of this effort focused on the identification of bioactive food components (BFCs) in the diet that appeared to decrease or increase the risk of cancer. Among the BFCs, investigations of vitamins and minerals produced the most intriguing results, especially in observational epidemiologic studies (1). Based largely on the results of these studies, clinical trials of vitamin and mineral supplements have been designed and conducted to establish their benefit or lack of benefit for cancer prevention. The public is likely to support cancer prevention clinical trials of multivitamins—defined as preparations with ≥2 vitamins or minerals, regardless of the form of consumption—because ≈20–30% of the population already consumes these supplements daily (2). However, only a few large, randomized, placebo-controlled clinical trials have been conducted of multivitamins with specific cancer sites as the primary endpoint. Selected larger trials are reviewed below; results from the first generation of these trials form the basis for the clinical trials now underway, which should report results within the next few years.

THE LINXIAN TRIALS

The Nutrition Intervention Trials (ie, the Linxian Trials) were conducted by the US National Cancer Institute (NCI) in collaboration with the Chinese Institute of the Chinese Academy of Medical Sciences. The Linxian Trials were based on epidemiologic evidence that the people of Linxian, China, had low intakes of numerous nutrients and the world's highest rate of esophageal cancer. The results of the 2 Linxian Trials, which were randomized, double-blind, placebo-controlled chemoprevention trials, were the first human experimental studies to show that multivitamin supplementation in a nutritionally marginal population reduced rates of cancer at any site. The Linxian General Population Trial began in 1986 and randomly assigned 29 594 adults aged 40–69 y to receive 1 of 4 combinations of multivitamin supplements containing retinal and zinc, riboflavin and niacin, vitamin C and molybdenum, or β-carotene, vitamin E, and selenium each day for 5.25 y. Doses were equivalent to 1 to 2 times

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[2] Presented at the conference "Multivitamin/Mineral Supplements and Chronic Disease Prevention," held at the National Institutes of Health, Bethesda, MD, May 15–17, 2006.

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Am J Clin Nutr 2007;85(suppl):314S–7S. Printed in USA.

the US Recommended Dietary Allowances (RDAs) (3). A second trial, the Linxian Dysplasia Trial, enrolled 3318 adults aged 40–69 y with esophageal dysplasia, a precursor to esophageal cancer. Trial participants were randomly assigned to receive either a placebo or a daily supplement of 14 vitamins and 12 minerals at 2 to 3 times the US RDA for 6 y (3).

Results from the General Population Trial showed that those who received the β-carotene–vitamin E–selenium combination had a 13% reduction in cancer mortality, including a 21% decrease in stomach cancer mortality, a 41% decrease in gastric noncardia cancer mortality, and a 4% decrease in deaths from esophageal cancer (4). Results from the Dysplasia Trial showed that supplementation reduced the likelihood of having esophageal dysplasia after both 30 and 72 mo of intervention (4). Adding to these important findings, postintervention follow-up indicated that the beneficial effects of the β-carotene–vitamin E–selenium combination in the General Population Trial remained evident up to 10 y after the intervention. These benefits were consistently greater in participants who were younger (<55 y) at the beginning of the intervention.

THE β-CAROTENE AND RETINOL EFFICACY TRIAL AND THE ALPHA-TOCOPHEROL, BETA-CAROTENE CANCER PREVENTION STUDY

Other clinical trials of multivitamin supplement use and cancer prevention have produced null or possibly harmful results for the primary endpoints regarding supplement use. The Finnish–NCI collaborative trial, the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC) of 29 133 male smokers aged 50–69 y did not observe a reduction in lung cancer with intervention as hypothesized before the trial (5). Participants were randomly assigned to 1 of 4 supplementation regimens, including α-tocopherol (50 mg) and β-carotene (20 mg) together, individually, or placebo. Contrary to expectation, men who took β-carotene had a 16% increase in lung cancer incidence; results for α-tocopherol indicated a statistically insignificant 2% decrease in lung cancer incidence (5). Interestingly, prostate cancer, a secondary endpoint, was reduced by one-third during the intervention, although the benefit diminished after supplementation concluded (6). The β-Carotene and Retinol Efficacy Trial (CARET) reported a 39% increase in lung cancer incidence among male smokers who received a combination of β-carotene and retinyl palmitate (7). These results were surprising because observational and epidemiologic studies had suggested that individuals who consumed high dietary amounts of β-carotene, generally from high vegetable and fruit intake, had a lower risk of cancer (8). Since the results of ATBC and CARET were reported, the causes for these negative results have been much discussed (9).

THE SELENIUM AND VITAMIN E CANCER PREVENTION TRIAL

Selenium inhibits the growth of prostate carcinoma cells in vitro through proposed mechanisms such as antioxidant effects, enhancement of immune function, induction of apoptosis, and inhibition of cell proliferation. Vitamin E inhibits lipid peroxidation, which contributes to carcinogen-induced DNA damage (10). The Selenium and Vitamin E Cancer Prevention Trial (SELECT), sponsored by the NCI, is a randomized, double-blind, placebo-controlled, population-based trial. Previous studies such as the Nutritional Prevention of Cancer Trial (NPCT) and the ATBC suggested that selenium and vitamin E could be effective in preventing certain cancers, including prostate cancer (5, 11). In the ATBC, there was a reduction in prostate cancer incidence in men receiving vitamin E (6); in the NPCT, men receiving selenium also had a reduced prostate cancer incidence as a secondary endpoint. The NPCT found that prevention apparently was more effective in men with the lowest baseline plasma selenium status (11).

SELECT began in 2001 and is investigating the efficacy of selenium (200 μg L-selenomethionine) and vitamin E (400 IU *dl*-α-tocopherol acetate), alone and in combination, for the prevention of prostate cancer in 35 534 healthy men (10). Study participants include white (78%), African American (14%), Hispanic (6%), and other (2%) men aged ≥55 y (because of their increased prostate cancer rates, African American men aged ≥50 y were enrolled). The trial is being conducted at 435 SELECT sites in the United States, Puerto Rico, and Canada and will last 12 y, including 7 y of intervention plus follow-up, with a primary endpoint being the clinical incidence of prostate cancer. Secondary goals of SELECT are to assess the effect of selenium and vitamin E on the incidence of other cancers, including lung, colorectal, and all cancers combined, and on overall mortality rates. In addition, SELECT will assess the effect of selenium and vitamin E on health-related quality-of-life, will evaluate associations of biological and molecular markers as well as diet with cancer risk, and will explore the potential modification of supplements on cancer risk by genetic factors and dietary intake. Three special ancillary studies also have been added to SELECT: the Prevention of Alzheimer's Disease with Vitamin E and Selenium (PREADVISE) will define the effect of selenium and vitamin E on the incidence of Alzheimer disease, the Prevention of Cataract and Age-Related Macular Degeneration with Vitamin E and Selenium—SELECT Eye Endpoints (SEE)—will test whether these supplements reduce age-related macular degeneration or cataracts, and the Prevention of Lung Function Decline with Vitamin E and Selenium—Respiratory Ancillary Study (RAS) will investigate whether these supplements prevent pulmonary function decrease. A fourth ancillary study evaluating the effect of the supplements on colon polyps is anticipated. An important feature of SELECT is the collection and preservation of blood samples that will permit the evaluation of a wide variety of biochemical and molecular hypotheses, particularly those that are prominent in prostate carcinogenesis (ie, polymorphisms in hormone-related genes such as *AR*, *CYP17*, *SRD5A2*, and *HSD3β2*) (12). This study will provide a better understanding of response to vitamin E and selenium and potentially will identify markers useful in future studies of prostate and other cancers.

THE PHYSICIANS' HEALTH STUDY

The first Physicians' Health Study (PHS) was a 12-y (1982–1995) randomized, double-blind, placebo-controlled trial with a 2 × 2 factorial design that tested aspirin and β-carotene (50 mg on alternate days) for the prevention of cardiovascular disease (CVD) and cancer in ≈22 000 male US physicians (13, 14). β-Carotene recipients showed no benefit or harm for either CVD or cancer in this predominantly nonsmoking population; the aspirin component was stopped in 1987 after the data indicated a

44% reduction in the risk of a first heart attack with aspirin use. PHS II, a follow-on, randomized, double-blind, placebo-controlled trial to the PHS, is in progress and is expected to be completed in 2008 (13). PHS II includes ≈15 000 male US physicians, about one-half of whom also participated in PHS I. PHS II is investigating vitamin E, vitamin C, and multivitamin supplementation, alone or in combination, on cancer, CVD, and eye disease. This is the only randomized trial to test a multivitamin pill [Centrum Silver (Wyeth Consumer Healthcare, Madison, NJ) as formulated at the start of the trial] rather than selected vitamins or minerals in the primary prevention of cancer.

THE WOMEN'S HEALTH INITIATIVE

Observational studies suggest that increased intake of calcium and vitamin D is associated with decreased risk of colorectal cancer and polyps. Vitamin D also has been observed to modify the effect of calcium supplementation on adenoma risk in a clinical trial in which the supplements lowered risk only among subjects with vitamin D intake above the median (15). The calcium plus vitamin D component of the Women's Health Initiative was designed to test the ability of calcium and vitamin D supplementation to lower the risk of hip fracture; the effect of these supplements on colorectal cancer risk was included as a secondary endpoint. Women (36 282 participants) were assigned to receive either placebo or a tablet consisting of 500 mg elemental calcium as calcium carbonate and 200 IU vitamin D_3 twice daily for 7 y (16). In contrast with previous studies, results from this trial found that daily calcium and vitamin D supplementation had no effect on colorectal cancer incidence among postmenopausal women (17). The differences between these results and observational studies remain to be explained, although the women's relatively high intakes at baseline (mean calcium intake of 1151 mg, mean vitamin D intake of 367 IU) may have hindered the ability to see a protective effect (17).

SUPPLEMENTATION EN VITAMINES ET MINERAUX ANTIOXYDANTS

The Supplémentation en Vitamines et Minéraux Antioxydants (SU.VI.MAX) study was a large, population-based, double-blind, placebo-controlled, randomized trial that assessed the effect of daily supplementation with antioxidant vitamins and minerals on risk of cancer and heart disease in men and women (18). The SU.VI.MAX trial enrolled 5141 men and 7876 women and provided either placebo or a single capsule containing a combination of 120 mg vitamin C, 30 mg α-tocopherol, 6 mg β-carotene, 100 μg Se, and 20 mg Zn daily for 8 y (18). These dosages are substantially lower than those used in the ATBC, CARET, and PHS trials examining the effects of one or more supplements on cancer risk. Supplementation in men was associated with a moderate, nonsignificant reduction in prostate cancer rate (18). There was, however, a statistically significant reduction in prostate cancer incidence in the 94% of men in the trial with a baseline prostate-specific antigen (PSA) concentration <3 μg/L (48% decrease in prostate cancer incidence; hazard ratio = 0.52, 95% CI: 0.29, 0.92) who received the supplements. In the 6% of the men in the trial with a higher PSA concentration at baseline (≥ 3 μg/L), supplementation was associated with a nonsignificant increased risk of prostate cancer (hazard ratio = 1.54, 95% CI: 0.87, 2.72). This result suggests that supplementation may be beneficial in preventing early stages of prostate carcinogenesis but raises concerns that antioxidant supplementation could have adverse effects for subjects at high risk of prostate cancer or for those with undiagnosed cancers, similar to what was postulated for β-carotene in the ATBC and CARET. Supplementation did not affect the concentrations of PSA or insulin-like growth factor.

UNRESOLVED ISSUES AND FUTURE RESEARCH NEEDS

Factors contributing to the variable results observed in trials of multivitamin supplements include issues of dose and form, effects of combinations of nutrients, and modulation by lifestyle behaviors. In several trials, doses substantially above the recommended dietary intake were used; the Linxian and SU.VI.MAX trials are exceptions to this. Too high a dose of an antioxidant vitamin possibly may interfere with the generation of reactive oxygen species needed for beneficial processes, such as normal immune response and induction of apoptosis in precancerous cells (19). Toxicity (as in the increased cancer rates observed for β-carotene in the ATBC and CARET) may also be a consequence of pharmacologic dosing. The form of vitamin or mineral used may affect the outcome of a trial. For example, vitamin E comprises 8 tocopherols and tocotrienols, each with 4 different forms. The most biologically available form of vitamin E is α-tocopherol, which is the most common form in supplements, whereas γ-tocopherol is the most prevalent form of dietary vitamin E. This difference in form by intake source could complicate analysis of studies assessing the effect of vitamin E intake on cancer prevention (20). The Women's Health Study, for example, found that dietary folate and vitamin B-6 but not supplemental forms of these nutrients reduced the risk of colorectal cancer despite the increased bioavailability of the supplemental forms (21). Besides nutrient form, other possible explanations for these apparently discrepant findings exist. Dietary intake might better reflect long-term nutrient intake, which, because cancer has a long latency period, might have more of an effect on risk than the relatively short-term use of supplements. Alternatively, dietary amounts of folate and vitamin B may act as markers for other relevant constituents of foods rich in these nutrients, such as fiber.

Combinations of nutrients may have a greater effect on cancer risk than individual nutrients, which underscores the need to investigate multiple vitamins and minerals simultaneously. To illustrate, Grau et al (15) found that vitamin D modified the effect of calcium supplementation on adenoma risk; calcium supplements lowered risk only among subjects with vitamin D concentrations above the overall median. In addition, vitamin D was associated with reduced risk only among subjects who received calcium.

Lifestyle behaviors also are likely to modify an individual's response, in terms of cancer risk, to nutrient supplementation. Results from the Linxian trials strongly suggest that supplementation is most likely to be beneficial for individuals who are low or borderline deficient for various nutrients. Conversely, supplementation may be harmful for some groups, as in the case of the increased lung cancer risk for smokers who received β-carotene

in CARET. Vitamin E showed the clearest benefits for the prevention of prostate cancer risk only among smokers (20). Similarly, folate supplementation may mitigate women's breast cancer risk associated with alcohol consumption (22), and smokers may differ from nonsmokers when using folate supplementation to decrease colon cancer risk (23). Results from some studies raise a concern that certain combinations of multivitamins could promote growth of preexisting tumors; thus, recommendations for use of supplements must take into account, where possible, based on genetics, lifestyle behaviors, or other relevant factors, the likelihood that an individual may have a preexisting tumor or a precancerous lesion (18, 24).

The complex and subtle interactions among the numerous vitamins and minerals in foods likely contribute to the disconnect between decreases in cancer risk associated with a healthy, varied diet and the null or weak associations observed when individual vitamin regimens are tested. Lifestyle differences such as alcohol consumption and exposure to smoke or other pollutants also will need to be considered. A systematic approach to discerning optimal combinations for preventing specific cancers is being conducted through work in basic experimental science that will lead to additional human trials. NCI currently is supporting studies of supplements of vitamin-mineral combinations in >20 trials, many of them small phase 1 and phase 2 trials, to determine safety and efficacy. Results from these small trials as well as the ongoing large-scale clinical trials will help to direct future research to answer the many questions that remain about the potential use of supplements for cancer prevention, but a more intensive clinical trial research program on multivitamin supplementation for chronic disease prevention is needed.

PG and PRT provided the concept and structure of this review, including guidance concerning the scope of the manuscript and the trials reviewed. All authors significantly contributed to the collection of background materials and references and the writing and editing of the manuscript. None of the authors had any financial or personal interest in any company or nonfederal organization sponsoring the research, including advisory board affiliations.

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