Vitamin/Mineral Supplementation and Cancer Risk: International Chemoprevention Trials (44180)

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Abstract. **In this review, large-scale randomized intervention trials evaluating the effects of vitamin and mineral supplementation on cancer rates are summarized. The trials enrolled up to 30,000 adults who were followed for up to 12 years, and included assessments of multiple vitamin and mineral combinations in an area of China with limited micronutrient intake and one of the world's highest cancer rates; and of beta carotene, vitamin E, or selenium in several more well nourished western populations, some at very high risk of lung cancer. Results to date have been mixed. Significantly lower cancer mortality has been found among those supplemented with a combination of beta carotene, vitamin E, and selenium in the China trial and with selenium in the United States, but risks of lung cancer were increased in Finnish and American trials provided with high-dose beta carotene supplementation. In combination, the trials indicate that the relation between specific micronutrient intake and cancer risk is complex, but have provided information to target further research on the potential benefits of selenium, vitamin E, and combinations of vitamins and minerals.**
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Observational epidemiologic studies have consistently demonstrated that individuals with usual adult diets high in fruit and vegetable intake tend to have lower risks of several types of cancer (1). The associations exist for cancers of the oral cavity and pharynx, esophagus, stomach, large intestine, lung, and other organs, often with individuals in the highest quantiles of fruit and/or vegetable intake often having only about half the risk of the cancers as those in the lowest quantiles of intake. The findings have raised the possibility that specific nutrients in these foods may be responsible for the cancer reduction. Indeed, when indices of dietary β-carotene, vitamin C, and several other compounds are evaluated, risk of cancer tends to decrease as the estimated dietary intake of the vitamin and minerals increase (2). Furthermore, studies assessing stored blood samples often have shown reduced concentrations of several nutrients among patients who subsequently developed cancer (3). Supporting evidence of a protective effect arises from bioassays, in which lower incidences of tumors have occurred in experimental animals administered various micronutrients (3). Unlike the observational epidemiologic surveys, the experimental studies were able to isolate effects of individual compounds and provided further stimulus to the notion that specific vitamins and minerals might help inhibit the occurrence of cancer in human populations. To test whether the preventative potential suggested from the laboratory and epidemiologic field studies could be confirmed, a number of large-scale vitamin and mineral intervention trials have been conducted in human populations around the world. Herein, we summarize their findings.

Randomized Intervention Trials

Results from several trials involving supplementation for at least 4 years with specific vitamins and/or minerals have been published within the past few years. The intervention trials have been conducted both in the United States and abroad, in both well-nourished and marginally nourished adult populations. The trials involved somewhat different treatment regimens, but all implemented randomization procedures whereby individuals were randomly assigned to receive a vitamin/mineral supplement or not, and thus provided experimental tests of whether nutrient supplementation could reduce the incidence of cancer. All the trials have involved middle-aged and older adults and were

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designed to evaluate whether the interventions might interrupt the later stages of the presumed multiyear process of carcinogenesis, with the hope that the vitamin/mineral supplementation would lower the rate of occurrence of clinical cancer within about 4–8 years of intervention. Eight individual trials with cancer occurrence, as opposed to precancerous lesions or conditions, as the primary outcome are described (Table I), followed by a discussion of how their results help evaluate the role of vitamin and mineral intervention in cancer prevention.

The Linxian Trials. Two randomized vitamin/mineral intervention trials have been launched in Linxian, a rural county in north central China with one of the world's highest rates of cancer (4, 5). Lifetime probabilities of contracting esophageal/gastric cardia cancer exceed 25% in this area, an extraordinarily high incidence of these usually fatal cancers. The population historically has had a diet of limited variety, with relatively low intake of a number of vitamins and minerals, although instances of frank clinical nutritional deficiencies have been rare. The population in many ways was ideal for an intervention trial, for if vitamin/mineral supplementation were to have an effect it would seem to be most amenable to detection in a population like Linxian's, with low nutrient status and high risk of a cancer that observational epidemiologic studies have shown to be influenced by poor diet (3).

The two trials employed different designs in different segments of the population. One randomly assigned 3,400 adults previously diagnosed with esophageal dysplasia, a precursor lesion conferring exceptionally high risk of cancer, to receive either a placebo or a multivitamin/mineral supplement consisting of 26 vitamins and minerals, typically at about one to four times U.S. recommended daily allowance (RDA) dose levels, daily for a 6-year period (4). The second enrolled nearly 30,000 adults age 40–69 from the general Linxian population into a 5-year trial (5). The larger size enabled more specific interventions, and four combinations of nutrients were evaluated in a factorial design: (i) retinol and zinc (Factor A), (ii) riboflavin and niacin (Factor B), (iii) vitamin C and molybdenum (Factor C), and (iv) β-carotene, vitamin E, and selenium (Factor D). The daily doses administered are shown in Table II. Compliance, judged both observationally and biochemically, was exceptionally high, with apparent consumption of 94% of the daily supplements over the study period.

In the smaller dysplasia trial (4), no significant differences in cancer mortality (predominantly esophageal and stomach cancer) were found over the 6-year intervention period, although those receiving the multivitamins and minerals had a significantly lower prevalence of esophageal dysplasia at the the trial's end (11). In the larger general population trial (5), with over 2,000 deaths during the follow-up, no significant effects were associated with the first three supplement regimens (A, B, and C), but total mortality and cancer mortality were significantly (9% and 13%, respectively) lower among those who received the combination of β-carotene, vitamin E, and selenium (Table III). The reduction was greater for stomach than esophageal cancers (but not significantly so) and began to be apparent about 2 years into the supplementation. Rates of lung cancer, the third most common cancer, were only about half as high among those receiving versus those not receiving β-carotene, vitamin E, and selenium, but the tumors were not common, with only 31 deaths from lung cancer (12).

Finnish Male Smokers Trial. In Finland, approximately 29,000 men age 50–69, mostly from southern urban areas, were enrolled in a 5- to 8-year randomized trial. A factorial design was used to simultaneously evaluate the effects of daily alpha tocopherol (50 mg) and β-carotene (20 mg) supplementation (6). All the participants were cigarette smokers (average 20 cigarettes/day for 36 years), although about 20% quite smoking during the trial. Compliance was not quite as high as in Linxian, with nearly a 20% drop out, but nevertheless the large majority of participants were believed to have consumed the large majority of supplements issued. The outcome of primary interest was lung cancer, with incidence cancers identified through the national Finnish Cancer Register.

Table IV shows the key findings. No significant differences in lung cancer or overall cancer incidence were seen among those receiving vitamin E, although prostate cancer incidence rates were significantly lower (by 34%) among

Table I. Large Randomized Trials Assessing Effects of Vitamin/Mineral Supplementation on Cancer Risk

Trial	No. of participants	Intervention	Mean duration of intervention (years)	No. of cancer deaths observed
Linxian—dysplasia (4)	3,318	multi vitamin/mineral	6	176
Linxian—general population (5)	29,584	4 vitamin/mineral combinations	5	792
Finnish smokers (6)	29,133	β-carotene or vitamin E	6	1116
CARET smokers (7)	18,314	β-carotene/retinol	4	254[a]
U.S. physicians (8)	22,071	β-carotene	12	765
Northern U.S. skin cancer (9)	1,720	β-carotene	4	82
Southern U.S. skin cancer (10)	1,312	seleium	4	86

[a] Lung cancer deaths only.

Table II. Vitamin/Mineral Interventions Used in the Linxian General Population Trial

Factor	Micronutrient	Dose per day
A	Retinol (as palmitate)	5000 IU
	Zinc (as zinc oxide)	22.5 mg
B	Riboflavin	3.2 mg
	Niacin	40 mg
C	Ascorbic acid	120 mg
	Molybdenum (as molybdenum yeast complex)	30 μg
D	β-Carotene	15 mg
	Selenium (as selenium yeast)	50 μg
	α-Tocopherol	30 mg

Table III. Relative Risk (RR) of Cancer Mortality according to Intervention Agent: Linxian General Population Trial

Intervention	RR	95% CI
Retinol, zinc	0.97	0.85–1.12
Riboflavin, niacin	0.98	0.85–1.13
Vitamin C, molybdenum	1.06	0.92–1.21
β-Carotene, vitamin E, selenium	0.87	0.75–1.00

men receiving the α-tocopherol supplements, and there was a 16% reduction in colorectal cancer. In contrast, total cancer death rates were significantly higher (by 9%) among those receiving β-carotene, due primarily to excesses of lung cancer (18% excess) and prostate cancer (23% excess). The increased risks of lung cancer associated with β-carotene were seen regardless of whether vitamin E was administered. Subsequent subgroup analysis (13) indicated that the β-carotene–associated lung cancer excess appeared limited to men who drank above average amounts (≥1 drink/day) of alcoholic beverages or smoked ≥20 cigarettes/day (Table V).

American Male Smokers and Asbestos-Exposed Workers Trial. In the United States, approximately 18,000 men age 45–69 from the Seattle area and several other regions of the country were enrolled in a randomized trial evaluating daily supplementation with the combination of β-carotene (30 mg) and retinol (25,000 IU) versus placebo (7). Almost all (99%) of the participants had been smokers, about 60% of whom were current smokers at the start of the trial, and somewhat over 20% were believed to have been occupationally exposed to asbestos. The trial, designated the CARET study, was intended to run for a 6-year average intervention period, with lung cancer as the primary end point, but was halted early at the end of 1995, after a mean of 4 years of supplementation and follow-up. The premature ending was due to the confluence of the reporting of the Finnish trial results with the observation of a significantly increased risk of lung cancer among those receiving the β-carotene/retinol supplements.

There was a 28% excess of lung cancer incidence (7),

Table IV. Relative Risk (RR) of Cancer Incidence according to Intervention Agent: Finnish Smokers Trial

Cancer type	Intervention	RR	95% CI[a]
Total	α-tocopherol	0.98	0.92–1.03
	β-Carotene	1.09	1.03–1.15
Lung	α-tocopherol	0.98	0.86–1.12
	β-Carotene	1.18	1.03–1.36
Prostate	α-tocopherol	0.66	0.53–0.80
	β-Carotene	1.23	1.04–1.46
Stomach	α-tocopherol	1.26	0.97–1.57
	β-Carotene	1.26	0.97–1.57
Colorectal	α-tocopherol	0.84	0.65–1.06
	β-Carotene	1.04	0.82–1.30

[a] Estimated values; except for that of lung cancer, 95% CI not present in original article (6).

Table V. Relative Risk of Lung Cancer Incidence Associated with β-Carotene (Finnish Trial) or β-Carotene/Retinol (CARET Trial) according to Smoking and Drinking Status

Cohort subgroup	Finnish (no. lung cancer = 876)	CARET[a] (no. lung cancer = 388)
Heavy or current smokers[b]	1.25	1.40
Light or exsmokers	0.97	1.04
Drinkers[c]	1.35	1.42
Light or nondrinkers	1.03	1.07

[a] Relative risks from unweighted analysis (14).
[b] Smoked ≥20 cigarettes/day in Finnish trial and current smokers at baseline in CARET trial.
[c] Consumed ≥1 drink/day in Finnish trial and any amount in CARET trial.

which rose to a 36% excess when an alternate statistical technique discounting the importance of the first 2 years of intervention was used (14), and a 17% excess of total mortality, in the supplemented group. Subgroup analysis indicated that the β-carotene/retinol–associated lung cancer excess was primarily limited to men who were current smokers at the start of the trial, with little incresae among supplement users in the subset of former smokers versus a 40% excess among the subset of current smokers (Table V). Similar to the Finnish trial, there was also some suggestion of an interaction with alcohol-drinking status: the relative risks associated with the supplement were higher for drinkers than nondrinkers, although the trend in risk with amount drunk was not smooth.

The American Male Physicians Trial. The vitamin intervention trial of longest duration has been conducted among physicians throughout the United States. Approximately 22,000 male doctors age 40–84 enrolled in the early 1980s were randomly assigned to receive either β-carotene (30 mg every other day) or placebo for a period of 12 years (8). Loss to follow-up was minimal, and compliance with the regimen considered excellent, with 80% of survivors stating they had taken the supplement over the full

course of the trial. The physicians studied had a number of healthful behaviors, most notably that only 11% were smokers when the trial started, a figure that had declined to 4% at the trial's end.

After 12 years of β-carotene supplementation, no significant effects upon cancer mortality were found, with nearly equal rates of cancer among those receiving β-carotene versus placebo. There were no significant differences for lung cancer, with a 6% reduction (the 95% confidence interval [CI] on the relative risk was 0.75–1.17) among those in the β-carotene group.

American Second Primary Skin Cancer Prevention Trials. Two long-term randomized trials have been conducted enrolling patients with basal- or squamous-cell skin cancers and following them primarily for the occurrence of second primary skin cancers, but also for other types of cancer. In one, approximately 1700 patients at several dermatology centers, mostly in northern states, were randomly assigned to receive 50 mg of β-carotene daily over a 4-year (on average) period (9). No significant reduction in skin cancer incidence was seen. After median 8 years of follow-up, effects of the supplementation on total and cancer mortality were presented (15). Rates of total mortality were about the same in the β-carotene and placebo groups, but a nonsignificant 17% reduction (relative risk 95% CI = 0.54–1.29) in cancer deaths was found, based on 38 cancers in the supplemented group versus 44 in the placebo groups.

For the second trial, 1312 patients aged 18–80 were enrolled during 1983–1991 from dermatology clinics in the eastern United States, mostly in southern cities, where forage crop selenium levels tended to be low (10). The individuals were randomly assigned to one of two groups, one receiving daily supplementation with 200 μg of selenium (*via* a high-selenium brewer's yeast tablet) and the other a look-alike placebo. The treatment continued through 1993, an average of 4 years (range: 0–10 years), by which time about half the living participants were still taking the tablets. Follow-up lasted until 1996, averaging 6 years, with no loss to follow-up. The patients were scheduled for biennial clinic visits for the ascertainment of second primary skin cancers, the primary study outcome.

Approximately 140 second skin cancers were diagnosed, with the tumors appearing nonsignificantly more often (by about 10%) in the supplemented than in the placebo group. The trial revealed, however, a significant, nearly 40% reduction in nonskin cancers in the group receiving selenium. There were 196 incident cases of these other cancers, and 86 deaths. The reductions in risk among the selenium group were apparent for a number of different types of cancer, including lung, prostate, and colorectal cancers, but the numbers of cases involved were small (Table VI). The greatest reduction among the supplemented group was for esophageal cancer (67% reduction, 95% CI on the relative risk = 0.03–1.84), but only eight cases were observed. The reduced risk in total cancer incidence began to be apparent after about 2 years of supplementation.

Table VI. Relative Risk (RR) of Cancer Incidence Associated with Selenium Supplementation in Southern U.S. Skin Cancer Trial

Cancer	No. of cases	RR	95% CI
Total	196	0.63	0.47–0.85
Lung	48	0.54	0.30–0.98
Prostate	48	0.37	0.18–0.71
Colorectal	27	0.42	0.18–0.95
Other	73	1.15	0.90–1.44

Discussion

The randomized trials described above present a mixed message regarding the effects of supplementation with the vitamins and/or minerals tested upon cancer risk. Only two trials (the Linxian general population and the southern U.S. skin cancer trial) showed significant reductions in total cancer rates among the supplemented, while the Finnish and CARET trials suggested that β-carotene supplementation may adversely affect segments of the population at exceptionally high risk of lung cancer.

Special attention is warranted regarding the possibility of untoward effects. The increased risks of lung cancer first reported in the Finnish β-carotene trial raised some concern, but the report of a similar excess in a second trial had a substantial impact on the consensus evidence regarding the effectiveness of vitamin supplementation in general and β-carotene in particular as potential inhibitors of cancer. Prior to their reporting, the possibility of serious adverse effects was considered so unlikely as to be almost dismissed from serious consideration.

Whether the increased rates of lung cancer observed within 4 years of β-carotene or β-carotene–plus–retinol supplements in the Finnish and CARET trials were in fact caused by the supplements is not clear. One of the key advantages of randomization is to provide balance among treatment groups and thus remove the effects of potential confounding factors, but even large randomized trials are not immune to disturbances resulting in confounding, bias, or chance that could cause the observed differences. Nevertheless, the consistency of the nearly 20%–30% increases in lung cancer among those taking the supplements is noteworthy and has prompted *ex post facto* speculation as to potential biologic mechanisms for the increased risks (16). The Finnish and CARET trials employed high doses of β-carotene (20 and 30 mg/day, respectively), with the CARET trail also adding a high dose of retinol. Each showed markedly higher serum β-carotene levels than either the Linxian or U.S. physicians trials, which employed only moderately lower β-carotene doses, and matched the blood levels of the northern skin cancer trial, which employed 50 mg/day doses of β-carotene. It is possible that the high-dose β-carotene and/or retinol interfered with other

nutrients or compounds that may confer protection. In each trial, the increased risk of lung cancer among supplement users seemed to be limited to similar subsets of the population, namely heavy smokers and drinkers. It is possible that the high doses of β-carotene/retinol resulted in alteration of metabolic processes, especially among those with existing changed metabolism due to heavy tobacco and/or alcohol intake, that influences lung cancer risk. It may also be that in smokers' lungs β-carotene behaves more like a pro-oxidant than an antioxidant, and/or that the supplements among these high-risk groups enhanced promotion of early-stage nonclinical tumors (16).

The Finnish and CARET trials do not provide sufficient evidence to declare β-carotene a lung cancer promoter, but they caution against widespread use of high-dose β-carotene and retinol supplements in a heavy smoking population. The American physicians trial provides assurance that long-term supplementation with 15 mg/day of β-carotene in a healthy population does not result in excess total or lung cancer mortality, and the Linxian general population trail suggests that in a marginally nutrition deficient population, 15 mg of β-carotene in combination with vitamin E and selenium might lower total and lung cancer mortality. On balance, however, because of the possibility of adverse effects, supplementation with β-carotene cannot be generally recommended.

The strongest evidence of a cancer benefit of vitamin/mineral supplementation arises from the large Linxian general population trial. Among those receiving the combination of β-carotene, vitamin E, and selenium, cancer rates were modestly but significantly reduced, whereas no effects were seen for three other specific vitamin/mineral regimens. The Linxian trial differed from the other trials with respect to various characteristics. The Linxian participants had a blander diet, with little meat, fish, or dairy intake, and could be considered less well nourished than the Western populations studied. The Linxian trial included fewer smokers (and those who smoked consumed fewer cigarettes per day than those in the Finnish and CARET studies) and had hardly any heavy alcohol drinkers. Residents of Linxian were at risk of different types of cancer than elsewhere, with the population especially susceptible to esophageal and stomach cancers. In the Finnish trial, where stomach cancer was moderately common, no reduction in risk with beta carotene or vitamin E was noted. There were also differences in the interventions used in Linxian versus elsewhere. Thus, population characteristics and/or intervention differences could have contributed to the different results seen in Linxian.

The recent data from the southern U.S. selenium intervention trial raise the possibility that selenium may be a (or the) key ingredient in the reduced risk observed in Linxian among those receiving β-carotene, vitamin E, and selenium. The skin cancer trial involved only 86 cancer deaths (and 196 incident cancers), but both mortality and incidence of total cancer were lower by about 40% or more among those who received the selenium (200 μg) supplements. The sharpest decline (a 67% decrease) was for esophageal cancer, but there were only eight cases of this cancer. These findings are striking but must be tempered against the rather small numbers of events and the fact that the primary outcome measure, second primary skin cancer, was unrelated to selenium supplementation. Nevertheless, the findings buttress the possibility that selenium supplementation may have lowered cancer risk in a population with skin cancer, but otherwise healthy, and that additional attention be paid to the potential for selenium's role in cancer prevention. Similarly, although not a primary end point, the significantly lower risk of prostate cancer among those supplemented with vitamin E in the Finnish trial raises hypotheses for additional test.

In summary, the large randomized trials indicate that the relation between specific micronutrient intakes and cancer risk is complex. No "magic bullet" has emerged that could be considered a definite cancer inhibitor, and the determinants responsible for the lower risks of cancer associated with fruit and vegetable consumption remain unclear. The trials have warned against high-dose supplementation with β-carotene and/or retinol in heavy smokers, but have also provided information to target additional research on potential benefits from vitamin E, selenium, and combinations of vitamins and minerals.

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