

ARTICLES

Nutrition Intervention Trials in Linxian, China: Supplementation With Specific Vitamin/Mineral Combinations, Cancer Incidence, and Disease-Specific Mortality in the General Population

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Background: Epidemiologic evidence indicates that diets high in fruits and vegetables are associated with a reduced risk of several cancers, including cancers of the esophagus and stomach. Vitamins and minerals in these foods may contribute to the reduced cancer risk. The people of Linxian County, China, have one of the world's highest rates of esophageal/gastric cardia cancer and a persistently low intake of several micronutrients. **Purpose:** We sought to determine if dietary supplementation with specific vitamins and minerals can lower mortality from or incidence of cancer as well as mortality from other diseases in Linxian. **Methods:** Individuals of ages 40-69 were recruited in 1985 from four Linxian communes. Mortality and cancer incidence during March 1986-May 1991 were ascertained for 29584 adults who received daily vitamin and mineral supplementation throughout this period. The subjects were randomly assigned to intervention groups according to a one-half replicate of a 2⁴ factorial experimental design. This design enabled testing for the effects of four combinations of nutrients: (A) retinol and zinc; (B) riboflavin and niacin; (C) vitamin C and molybdenum; and (D) beta carotene, vitamin E, and selenium. Doses ranged from one to two times U.S. Recommended Daily Allowances. **Results:** A total of 2127 deaths occurred among trial participants during the intervention period. Cancer was the leading cause of death, with 32% of all deaths due to esophageal or stomach cancer, followed by cerebrovascular disease (25%). Significantly ($P = .03$) lower total mortality (relative risk [RR] = 0.91; 95% confidence interval [CI] = 0.84-0.99) occurred among those receiving supplementation with beta carotene, vitamin E, and

selenium. The reduction was mainly due to lower cancer rates (RR = 0.87; 95% CI = 0.75-1.00), especially stomach cancer (RR = 0.79; 95% CI = 0.64-0.99), with the reduced risk beginning to arise about 1-2 years after the start of supplementation with these vitamins and minerals. No significant effects on mortality rates from all causes were found for supplementation with retinol and zinc, riboflavin and niacin, or vitamin C and molybdenum. Patterns of cancer incidence, on the basis of 1298 cases, generally resembled those for cancer mortality. **Conclusions:** The findings indicate that vitamin and mineral supplementation of the diet of Linxian adults, particularly with the combination of beta carotene, vitamin E, and selenium, may effect a reduction in cancer risk in this population. **Implications:** The results on their own are not definitive, but the promising findings should stimulate further research to clarify the potential benefits of micronutrient supplements. [J Natl Cancer Inst 85:1483-1492, 1993]

Linxian, a rural county in Henan Province of north-central China, has one of the world's highest rates of esophageal cancer (1). Mortality rates from this cancer exceed the Chinese national average by 10-fold and the American average for Whites by 100-fold (2). The tumors arise not only as squamous cell carcinomas in the esophagus, but also beyond the esophageal-gastric junction as adenocarcinomas in the cardia region of the stomach. Historically, esophageal and gastric cardia cancers have been considered as a single

*See "Notes" section following "References."

clinical entity for incidence and mortality rate calculations in Linxian (1).

Reasons for the clustering of esophageal-gastric cardia cancer in Linxian are unknown; case-control studies (3,4) have failed to detect strong dietary or other risk factors. A number of investigations (5) conducted in other areas of the world have found that consumption of fresh vegetables and fruits is associated with a reduced risk of both esophageal and stomach cancers. The particular constituents of vegetables and fruits responsible for the protective effect have not been determined, but inverse trends have been shown between cancer risk and indices of intake of several micronutrients found in these foods, especially vitamin C and beta carotene (6). In experimental animals also, deficiencies of certain nutrients may enhance chemical carcinogenesis, while nutrient supplementation may inhibit tumor formation (7).

Food availability and variety in Linxian have historically been limited. Although completion of a massive agricultural irrigation system in 1965 resulted in increased production of several foods, diets typically have remained low in intake of fresh fruits and meat and other animal products. The major staples are corn, millet, sweet potatoes, and wheat. In surveys (8-11) of Linxian residents during the 1970s and early 1980s, blood levels of various micronutrients, including retinol, beta carotene, riboflavin, vitamin C, and vitamin E were consistently low by Western standards, although overt clinical deficiencies were not common.

Because of its extraordinarily high rates of epithelial cancers (i.e., esophageal and gastric) and subclinical deficiencies of several micronutrients among the population, Linxian was selected as the site for two randomized intervention trials to test whether supplementation with multiple vitamins and minerals might reduce the rates of cancer. One trial involved approximately 3300 participants with esophageal dysplasia and is the subject of another article in this issue of the Journal (12). In this presentation, we describe results from a larger trial involving nearly 30000 residents from the high-risk Linxian general population. We present tests of the initial effectiveness of four specific combinations of vitamins and minerals in reducing cancer incidence and mortality as well as mortality from other diseases during the course of the intervention.

Subjects and Methods

Participants in the trial were recruited in 1985 from four communes in Linxian. Residents aged 40-69 years without debilitating diseases or prior esophageal or stomach cancer who were willing to take part in a multiyear, daily pill-taking regimen were sought for enrollment. These individuals were given a brief physical examination, had a 10-mL blood sample collected and stored, and were interviewed regarding aspects of their medical, family, dietary, and tobacco and alcohol consumption histories.

The participants were randomly assigned to receive one of eight vitamin/mineral supplement combinations in the form of individual oral tablets. The treatment combinations were randomly assigned within blocks defined by commune (four communes), sex, and age (by single years). The eight intervention groups were derived from a one-half replicate of a 2⁴ factorial design (13). The factorial design allowed us to assess four factors (i.e., nutrient combinations) in a single experiment. The four factors, which we designate by the letters A, B, C, and D, are defined in Table 1. Doses of each nutrient ranged from one to two times U.S. Recommended Daily Allowances (RDAs).

Table 1. Types and daily doses of micronutrients by treatment factor

Factor	Micronutrients	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	Beta carotene	15 mg
	Selenium (as selenium yeast)	50 µg
	Alpha-tocopherol	30 mg

While a separate evaluation of each of the nine, and perhaps additional, nutrients listed in Table 1 would have been desirable, a 2⁹ or higher factorial experiment was impractical. The feasible options were to delete certain nutrients or to combine them into a smaller number of groups. We chose the latter approach, combining zinc, which enhances the delivery of retinol to tissues, and retinol (Factor A); the B vitamins riboflavin and niacin (Factor B); vitamin C and molybdenum, which are thought to inhibit the formation of carcinogenic nitrosamines and nitrosamine-induced esophageal carcinogenesis, respectively (Factor C); and the fat-soluble antioxidants beta carotene, vitamin E, and selenium (Factor D). A fractional factorial design was selected because it permitted testing of the main effects of four factors at less cost and complexity than a full 2⁴ factorial design. The eight intervention groups in this fractional design were defined by the following combinations of supplements: AB, AC, AD, BC, BD, CD, ABCD, or placebo. Thus, persons in group AB, e.g., received retinol, zinc, riboflavin, and niacin, while those in group ABCD received all nine vitamins and minerals and those in the placebo group received none. This choice of groups resulted in half the participants receiving each of the four factor nutrient combinations. For example, half received factor A (AB, AC, AD, ABCD) and half did not (BC, BD, CD, placebo), and the subjects that received versus those that did not receive factor A were balanced with respect to receipt of all other nutrients.

The eight vitamin/mineral combinations were packaged in coded bottles containing a 1-month supply and were distributed monthly by approximately 200 village doctors beginning in March 1986 and continuing through May 1991. Compliance was assessed in two ways: by counting unused pills and by assaying nutrient levels in blood collected from approximately 120 individuals randomly selected without replacement every 3 months during the course of the trials.

Mortality among trial participants was ascertained via follow-up by village doctors. Diagnoses of cancer were ascertained through local commune and county hospitals and supplemented by a study medical team that provided clinical and diagnostic services, including endoscopy, for participants with symptoms suggestive of esophageal or stomach cancer. Diagnostic materials (e.g., x rays, cytology, biopsy, and surgical specimens) for 85% of the cancer cases were reviewed by a panel of senior Chinese and American experts in gastroenterology, radiology, cytology, and pathology. Reviews were conducted in parallel by senior Chinese diagnosticians for the remaining cancer cases and for deaths due to causes other than cancer.

Statistical analyses focused on estimating the effects of supplementation with each of the four vitamin/mineral factors upon 5¼-year (March 1986-May 1991) total mortality and cancer mortality rates. Incidence and mortality rates were calculated for esophageal, gastric cardia, other stomach, and other cancers. In addition, we calculated rates of cerebrovascular disease mortality and other causes of death. Proportional hazards regression analyses (14) were employed to estimate relative risks (RRs) of mortality and cancer incidence and corresponding 95% confidence intervals (CIs) for the four main effects after adjustment for matching variables. Additional adjustment for baseline data on cigarette smoking and parental history of cancer, two risk factors for esophageal/stomach cancer in this population, resulted in essentially no change and is not presented. Regressions were also run with only the use of events and person-years occurring 12 or more months after the intervention began, a procedure that allowed for a latency period before a treatment effect might occur. Tests for pairwise interactions between factors were able to be calculated, but with the fractional design, only three of the six two-way interactions could be evaluated. Furthermore, because the interaction between any two of the four factors, say A and B, is mathematically equivalent to the interaction between the remaining two factors (i.e., C and D), interactive effects for one pair cannot be distinguished from the other. Thus, these tests were not

pursued. In addition to calculating 5¼-year rates, we plotted cumulative mortality and incidence by calendar quarter throughout the study period. All *P* values associated with comparisons of those receiving versus those not receiving a particular vitamin/mineral factor are nominal and based on two-sided tests, even though one-sided tests would have been appropriate because of the a priori hypotheses of beneficial effects of the supplements.

Results

Of the approximately 50000 potentially eligible participants, 16% refused to participate, 12% were out of the area, 3% were too sick, and 8% did not join the trial for other reasons. In addition, 1.4% were excluded due to self-reported cancer at screening or death or diagnosis of cancer prior to the start of intervention. After these exclusions, the study population consisted of 29584 randomly assigned participants. Characteristics of these individuals are given in Table 2. The various treatment groups were well balanced with regard to sex, age, smoking, alcohol consumption, and diet and familial cancer history.

Compliance assessed by monthly pill counts and biochemical measures was excellent throughout the study. The overall pill disappearance rate was 93% for all participants, with no difference by treatment group (range, 92%-93%) and little change during the trial (range, 92%-93% in year 1;

91%-92% in year 5). For 86% of all participants, pill disappearance exceeded 90% (range, 85%-87% across treatment groups), while just 5% were poor compliers (i.e., <50% pill disappearance) (range, 5%-6% across treatment groups). Biochemical assessments during the intervention showed significantly higher nutrient blood levels for individuals who received supplementation compared with those who did not; the proportional increase was greatest for beta carotene (Table 3). In contrast, there were no significant differences in baseline levels, except for lower ascorbate levels in those who received vitamin C and molybdenum.

A total of 2127 deaths (7.2% of the study participants) occurred during the period March 1986-May 1991. The percentages of deaths were higher among men (9.3%) than women (5.5%) and rose with age at start of follow-up (2.3% age <50, 7.3% age 50-59, and 17.3% age ≥60). Cancer was the leading cause of death, accounting for 37% of all deaths. Of the 792 cancer deaths, 87% (or 32% of all deaths) were attributed to cancers of the esophagus (360 deaths) or stomach (331 deaths; 253 from gastric cardia and 78 from other stomach cancers). There were 101 deaths from other cancers—32 from lung cancer, 28 from liver cancer, and fewer than 10 from any other specific malignancy. Cerebrovascular disease accounted for 523 (25%) of the deaths, while the remaining 812 (38%) were caused by a variety of conditions, none of which accounted for more than 9% of all deaths.

Table 4 presents numbers of deaths and the death rates among the eight intervention groups by cause of death, and these data serve as the basis for subsequent calculations. In Table 5, RRs for mortality from cancer, cerebrovascular disease, and other diseases associated with factors A (retinol, zinc), B (riboflavin, niacin), C (vitamin C, molybdenum),

Table 2. General population trial participant characteristics

Participant characteristics	All participants	Range for individual treatment groups
No. of participants*	29584	3677-3709
Age at start of intervention, y		
<50	42%	42%
50-59	35%	34%-35%
≥60	23%	23%-24%
Sex		
Male	45%	44%-45%
Female	55%	55%-56%
Education		
None	40%	39%-41%
Any	60%	59%-61%
Tobacco (ever smoke cigarettes regularly >6 mo)		
No	70%	70%-71%
Yes	30%	29%-30%
Alcohol (any use past 12 mo)		
No	77%	76%-77%
Yes	23%	23%-24%
Pickled vegetable (any use past 12 mo in winter or spring)		
No	91%	90%-92%
Yes	9%	8%-10%
Moldy food (any use past 12 mo)		
No	82%	81%-83%
Yes	18%	17%-19%
Family history of esophageal or stomach cancer		
No	68%	68%-69%
Yes	32%	31%-32%

*Data missing for variables other than age and sex on 104-109 participants, depending on the characteristic.

Table 3. Compliance assessed biochemically over the 5-year intervention

Factor	Biochemical assessment						
	Baseline*			During intervention			<i>P</i> †
	No.	Mean	SD	No.	Mean	SD	
Retinol (µg/dL, plasma)							
A	47	35.7	8.8	479	54.0	16.0	.0001
No A	60	35.5	13.1	419	43.0	14.9	
Riboflavin (EGR activation coefficient)‡							
B	56	1.73	0.34	747	1.19	0.25	.0001
No B	51	1.78	0.40	745	1.44	0.31	
Ascorbic acid (mg/dL, plasma)							
C	49	0.15	0.13	730	0.81	0.47	.0001
No C	49	0.25	0.29§	740	0.54	0.41	
Beta carotene (µg/dL, plasma)							
D	47	5.9	5.2	443	85.5	78.5	.0001
No D	60	6.8	5.8	455	12.0	15.0	

*Baseline nutritional assessment conducted in May 1985; values adjusted for season.

†*P* values are for *t* tests of factor versus no factor during intervention.

‡EGR = erythrocyte glutathione reductase. Lower EGR activation coefficient indicates higher riboflavin status.

§*P* value for C versus no C at baseline = .03.

Table 4. Numbers and rates of death by major disease category according to intervention group

Intervention group	Person-years of observation	Cause of death							
		Cancer		Cerebrovascular		Other		Total	
		No. of deaths	Deaths per 1000 person-years	No. of deaths	Deaths per 1000 person-years	No. of deaths	Deaths per 1000 person-years	No. of deaths	Deaths per 1000 person-years
Placebo	18626	107	5.7	77	4.1	96	5.2	280	15.0
AB	18736	94	5.0	66	3.5	105	5.6	265	14.1
AC	18701	121	6.5	71	3.8	104	5.6	296	15.8
AD	18745	81	4.3	55	2.9	114	6.1	250	13.3
BC	18686	101	5.4	60	3.2	107	5.7	268	14.3
BD	18729	103	5.5	58	3.1	102	5.4	263	14.0
CD	18758	90	4.8	67	3.6	92	4.9	249	13.2
ABCD	18792	95	5.1	69	3.7	92	4.9	256	13.6
Total	149773	792	5.3	523	3.5	812	5.4	2127	14.2

Table 5. RRs and 95% CIs of death by cause according to vitamin/mineral factor

Cause of death	n	Factor*							
		A		B		C		D	
		RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
Total	2127	1.00	0.92-1.09	0.97	0.89-1.06	1.01	0.93-1.10	0.91	0.84-0.99
Cancer	792	0.97	0.85-1.12	0.98	0.85-1.13	1.06	0.92-1.21	0.87	0.75-1.00
Esophageal	360	0.93	0.76-1.15	0.90	0.73-1.11	1.05	0.85-1.29	0.96	0.78-1.18
Stomach	331	1.03	0.83-1.28	1.00	0.81-1.24	1.09	0.88-1.36	0.79	0.64-0.99
Cardia	253	1.22	0.95-1.56	1.03	0.80-1.30	1.07	0.84-1.37	0.82	0.64-1.04
Noncardia	78	0.59	0.37-0.93	0.94	0.60-1.47	1.17	0.75-1.82	0.72	0.46-1.14
Esophageal/gastric cardia	613	1.04	0.89-1.22	0.95	0.81-1.11	1.06	0.90-1.24	0.90	0.77-1.05
Other	101	0.94	0.64-1.39	1.24	0.84-1.84	0.98	0.66-1.45	0.80	0.54-1.18
Cerebrovascular	523	0.99	0.84-1.18	0.93	0.79-1.11	1.04	0.88-1.24	0.90	0.76-1.07
Other	812	1.04	0.91-1.20	1.00	0.87-1.14	0.94	0.82-1.08	0.96	0.84-1.11

* A = retinol, zinc; B = riboflavin, niacin; C = vitamin C, molybdenum; and D = beta carotene, vitamin E, selenium.

and D (beta carotene, vitamin E, selenium) are shown. Significantly ($P = .03$) lower total mortality rates were observed among persons receiving pills with beta carotene, vitamin E, and selenium (factor D), but not among those receiving the three other vitamin/mineral combinations. There was a 9% reduction in overall mortality (RR = 0.91; 95% CI = 0.84-0.99) among those receiving factor D. Cancer mortality among this group was reduced 13% (RR = 0.87; 95% CI = 0.75-1.00), with esophageal/gastric cardia rates reduced 10% (RR = 0.90; 95% CI = 0.77-1.05). The decrease in cancer mortality among those receiving beta carotene, vitamin E, and selenium was more pronounced for stomach (RR = 0.79) and other (RR = 0.80) cancers than for esophageal cancers (RR = 0.96), but differences between these RRs were not significant ($P > .10$). The lower risk for those receiving factor D was seen for both cardia (RR = 0.82) and noncardia (RR = 0.72) stomach cancers. When a 1-year lag (to allow time for an intervention effect to become apparent) was incorporated into the proportional hazards regression analysis, the differences between those receiving versus those not receiving beta carotene, vitamin E, and selenium became slightly more pronounced: The RR for total cancer mortality was 0.85 (95% CI = 0.73-0.98); for stomach cancer, it was 0.77 (95% CI = 0.61-0.98). This lag

effect is displayed in Figs. 1 and 2, which plot mortality from total cancer and stomach cancer by calendar quarter for those receiving versus those not receiving beta carotene, vitamin E, and selenium. Cancer rates overlapped until approximately 1 year (total cancer; Fig. 1) or 2 years (stomach cancer; Fig. 2) after the start of the intervention and then tended to diverge. None of the other factors showed a progressive benefit of the kind seen in Figs. 1 or 2. Mortality from noncardia stomach cancer was significantly ($P = .02$) lower among those receiving retinol and zinc, but cardia cancer rates were elevated and there was no overall reduction in stomach cancer death rates in this group.

Patterns for cancer incidence resembled those for cancer mortality (Table 6). In total, 1298 persons were diagnosed with cancer during the study period. Among these diagnoses, 49% were esophageal cancer, 42% were stomach cancer (34% cardia and 8% for noncardia cancers), and 9% were other cancers. As with the mortality findings, lowered incidences of total cancer (RR = 0.93; 95% CI = 0.83-1.03), esophageal/gastric cardia cancer (RR = 0.94; 95% CI = 0.84-1.06), and stomach cancer (RR = 0.84; 95% CI = 0.71-1.00) were observed among those receiving beta carotene, vitamin E, and selenium (Table 6). The reductions for stomach cancer were equivalent for cardia and noncardia

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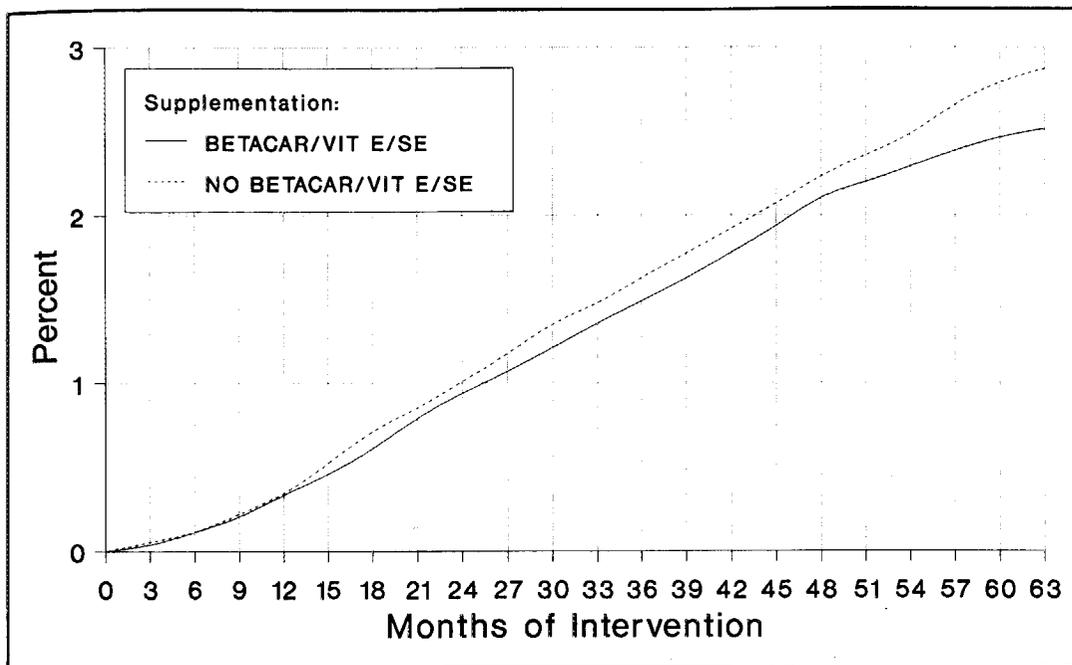


Fig. 1. Cumulative total cancer deaths as percent of study population, March 1986-May 1991.

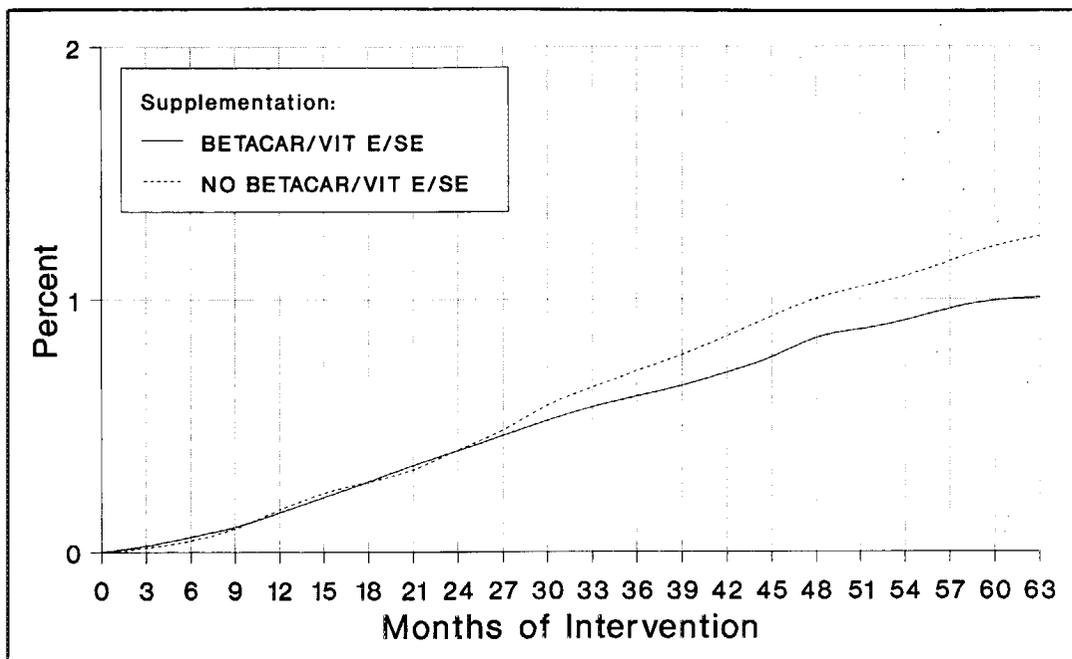


Fig. 2. Cumulative stomach cancer deaths as percent of study population, March 1986-May 1991.

tumors. Esophageal cancer incidence was lower among those receiving riboflavin and niacin (RR = 0.86, 95% CI = 0.74-1.01, $P = .06$), but rates of gastric cardia cancer were nonsignificantly elevated (RR = 1.07; 95% CI = 0.88-1.29). Total cancer incidence was 5% lower (RR = 0.95; 95% CI = 0.85-1.06) among those receiving versus those not receiving supplementation with riboflavin and niacin.

Discussion

The findings from this large randomized trial provide support for the hypothesis that intake of specific micro-

nutrients may inhibit cancer development. Reductions in total mortality and in cancer mortality and incidence, especially for stomach cancer, were observed over a 5¼-year period for the nearly 15000 individuals who received daily supplements containing beta carotene, vitamin E, and selenium. A reduction in esophageal cancer incidence was also suggested among those receiving riboflavin and niacin. No other nutrient combination demonstrated any clear beneficial effects on cancer rates.

Linxian County in north-central China offered unique advantages for this intervention trial, having a large and stable population with subclinical deficiencies of several

Table 6. RRs and 95% CIs of cancer incidence according to vitamin/mineral factor

Type of cancer	n	Factor*							
		A		B		C		D	
		RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
Total	1298	1.00	0.89-1.11	0.95	0.85-1.06	1.06	0.95-1.18	0.93	0.83-1.03
Esophagus	640	1.07	0.92-1.25	0.86	0.74-1.01	1.06	0.91-1.24	1.02	0.87-1.19
Stomach	539	0.96	0.81-1.14	1.04	0.88-1.23	1.10	0.92-1.30	0.84	0.71-1.00
Cardia	435	1.02	0.85-1.24	1.07	0.88-1.29	1.07	0.90-1.29	0.85	0.70-1.02
Noncardia	104	0.73	0.49-1.08	0.92	0.63-1.35	1.21	0.82-1.78	0.82	0.56-1.20
Esophageal/cardia	1075	1.05	0.93-1.19	0.94	0.83-1.06	1.06	0.94-1.20	0.94	0.84-1.06
Other	119	0.80	0.56-1.15	1.09	0.76-1.56	0.92	0.64-1.32	0.88	0.62-1.27

*A = retinol, zinc; B = riboflavin, niacin; C = vitamin C, molybdenum; and D = beta carotene, vitamin E, and selenium.

nutrients and an extraordinarily high incidence of epithelial cancers thought to be influenced by diet and nutritional status. The random allocation within strata of individuals to the intervention groups guaranteed equity between the groups by age and sex, facilitated balance with respect to unmeasured factors, and helped to avoid confounding. The participant compliance was exceptional: Pill disappearance (implying apparent ingestion) exceeded 90%, and blood collections from randomly selected individuals every quarter provided biochemical confirmation of excellent compliance. The large numbers of events—over 2100 deaths and nearly 1300 cancers—yielded excellent power and precise estimation of effects.

There are several caveats, however, that should be considered in interpreting the trial findings. Some concern the study design. An advantage of the factorial design is the ability to test several hypotheses simultaneously. However, with four independent tests of main effects, the chance that one will be significant at the $P \leq .03$ level is .11 (i.e., $1 - .97^4$) as a result of the multiple comparisons. Secondly, the fractional factorial design confounds main effects with three-way interaction effects, so what we attribute to factor D might actually be an ABC interaction. Such interactions are typically rare and seem much less likely than an effect due to a single factor, however, and can likely be dismissed. Finally, the special features of the Linxian setting, a relatively remote, rural area of China with a population marginally deficient in a number of nutrients, suggest caution in extrapolating the findings to other populations.

This trial revealed a significant reduction in total mortality, due mostly to a lowered risk of cancer, among those receiving the combination of beta carotene, vitamin E, and selenium. There was a differential effect between mortality from stomach cancer (21% reduction) and other cancers (20% reduction) versus esophageal cancer (4% reduction), suggesting that the benefit may vary by site and/or cell type. However, the CIs for these RRs all overlapped; thus, we are reluctant to emphasize the site-specific differences. Nevertheless, it may be noteworthy that the stomach cancers were adenocarcinomas, while the esophageal cancers were nearly all squamous cell carcinomas.

Studies in experimental animals (6,7) have demonstrated the cancer inhibitory properties of beta carotene, vitamin E,

and selenium. For example, beta carotene has inhibited formation of UV-induced skin cancers, oral carcinomas caused by dimethylbenzanthracene exposure, and colon tumors that develop following dimethylhydrazine exposure. Vitamin E and selenium have also lowered the incidence of tumors in a number of experiments involving exposure to different carcinogens, although some studies (6,7) suggested either no effect or enhancement of carcinogenesis. Vitamin E has been shown to inhibit nitrosamine-induced esophageal cancer in mice (15).

The epidemiologic evidence is also consistent with a beneficial role of beta carotene, vitamin E, and selenium on cancer risk (5,6). It has repeatedly been shown that intake of fresh fruits and vegetables is associated with reduced risks of esophageal, stomach, and total cancer (5). Risks among persons having the highest intakes often are as low as one half of those having the lowest intakes for several foods, especially citrus and other fruits and fresh green, orange, and yellow vegetables. Although it has been difficult to identify specific components of these foods that may be responsible for the decreased risk, a role for beta carotene and possibly other carotenoids has been suggested by case-control studies of esophageal and stomach cancers, including studies in China (5,6,16-18). Difficulty in estimating dietary intakes of vitamin E and selenium has limited evaluation of their effects. However, in Italy, the largest case-control study (19) of stomach cancer conducted to date found that risks of cancers of the stomach, including gastric cardia, were more closely correlated with an index of dietary vitamin E than of beta carotene, although the opposite pattern was reported in Canada (20).

Further supporting evidence for a protective effect of beta carotene, vitamin E, and selenium comes from observations of inverse associations of blood levels of these nutrients with risk of several cancers, including those of the esophagus and stomach. Ecologic surveys (21-23) across rural Chinese counties found that plasma levels of selenium were inversely correlated with mortality rates for both esophageal and stomach cancers, while plasma beta carotene was significantly lower in counties with high stomach cancer rates. In Linxian, blood levels of beta carotene and alpha-tocopherol are consistently lower than Western norms, while levels of selenium are near normal or only marginally lower (8-11). In evaluation of nutrients in stored sera for persons who

subsequently developed stomach cancer, prediagnostic levels of serum beta carotene were depressed in studies in the United States, Great Britain, and Switzerland (24). Differences with respect to serum vitamin E and selenium in these studies were less pronounced. A study in Finland (25), however, found that serum levels of selenium were significantly lower in men who subsequently developed stomach cancer.

Only a few observational studies have evaluated risk of cancer in relation to use of vitamin or mineral supplements. In a U.S. hospital-based study (26) of 133 male esophageal cancer patients, risk was 50% lower among users of vitamin E supplements. A 50% reduction in risk of oral cancer also was reported among users of vitamin E supplements in a national study (27) that enrolled over 1000 American patients.

Several clinical trials have shown beneficial effects of beta carotene or vitamin E on precancerous lesions. In a 20-month randomized trial in Uzbekistan (28), daily doses of 40 mg of beta carotene together with weekly supplements of 100000 IU of retinol and 80 mg of vitamin E were associated with endoscopically determined regression of chronic esophagitis (although the effect was not statistically significant) and with a significant reduction in oral leukoplakia. Several other trials (29-31) have also reported reversals in oral leukoplakia, thought to be a precursor to oral cancer, following supplementation with beta carotene or vitamin E. Furthermore, beta carotene combined with retinol lowered the frequency of buccal micronuclei among betel chewers in the Philippines (32), while beta carotene alone reduced the prevalence of micronuclei in the sputum of smokers in the Netherlands (33).

No other randomized clinical trials have reported on the effects on esophageal or stomach cancers of supplementation with beta carotene, vitamin E, or selenium. In the only reported cancer trial (34), daily 50-mg beta carotene supplementation was not found to be effective in inhibiting second primary basal or squamous cell skin cancers among patients with nonmelanoma skin cancer. In the smaller parallel trial that we conducted among persons with esophageal dysplasia in Linxian, described in a companion paper (12), total cancer mortality and incidence rates were similar between those receiving 6 years of supplementation with 26 vitamins and minerals (including beta carotene, vitamin E, and selenium) and those receiving placebo. Intervention trials involving beta carotene, vitamin E, and/or selenium and assessing cancer end points are ongoing in populations in the United States and Finland. Although the numbers of esophageal or stomach cancers likely to arise in these trials will be considerably smaller than in Linxian, evaluation of the effects of supplementation on these cancers should be possible.

The mechanisms by which beta carotene, vitamin E, or selenium inhibit cancer development are not clear, but might involve their antioxidant properties (6). These compounds, especially beta carotene, can quench free radicals and protect against oxidative damage to DNA. The nutrients also inhibit the endogenous formation of *N*-nitroso compounds, some of which are potent carcinogens in animal experiments and are

suspected risk factors for stomach and esophageal cancers in human populations, including Linxian's (35,36). Beta carotene, vitamin E, and selenium may also possess immunologic and other properties that influence carcinogenesis (6). We could not directly evaluate mechanistic pathways, although we are currently assessing differences in cytologically and endoscopically determined precancerous lesions as well as immune function by treatment group.

Despite its high (90%) power to detect reductions of 14% and 23% in total and cancer mortality, respectively, the trial failed to find significant protective effects on total, esophageal, or stomach cancer mortality during the 5¼-year supplementation period for retinol and zinc, riboflavin and niacin, or vitamin C and molybdenum. A significant reduction in noncardia stomach cancer mortality was observed among those receiving retinol and zinc, but it was counterbalanced by an increase in gastric cardia cancer mortality in this group. A potential benefit of retinol on cancer risk has been postulated on the basis of its role in maintaining cell integrity and on the ability of certain retinoids to inhibit chemically induced tumors in laboratory animals, although in some experimental models, vitamin A and its analogues have enhanced carcinogenesis (6). Epidemiologic support for a beneficial effect of vitamin A, although suggestive at one time, has waned since the trial began. Several recent analytic studies have found no evidence of a protective effect of dietary or serum retinol for esophageal or stomach cancers, with the consensus suggesting that benefits are associated with the vitamin A precursor beta carotene (37). In clinical trials (38), however, high doses of the synthetic retinoid isotretinoin have proven effective in reducing the incidence of second primary cancers of the head and neck in oral cancer patients. Although human data on the relationship between zinc and cancer are limited, zinc was included because it enhances delivery of retinol to body tissues and because esophageal carcinogenesis is promoted in zinc-deficient rats (39). It is noteworthy that in a randomized trial (40) in a county neighboring Linxian, 13 months of supplementation with retinol (50000 IU per week) and zinc (50 mg per week) along with high doses (200 mg per week) of riboflavin had no effect on the prevalence of precancerous esophageal lesions. The frequencies of buccal micronuclei also were similar in the treated and placebo groups, although esophageal micronuclei were reduced following supplementation with retinol, zinc, and riboflavin (41).

One of the characteristics of areas of the world (e.g., Linxian and parts of Iran and South Africa) with markedly elevated esophageal cancer rates is low dietary intake of B vitamins, particularly riboflavin and niacin (42). Indeed, riboflavin status as measured by erythrocyte glutathione reductase activity was severely depressed in Linxian when compared with the United States; over 90% of the Linxian population was termed deficient in this nutrient (8-11). Riboflavin deficiencies have induced esophageal hyperplasia in baboons and altered the metabolism of nitrosamines (43,44). Supplementation with riboflavin and niacin, along with zinc, magnesium, and molybdenum, inhibited esophageal carcinogenesis in corn-fed rats (45). In Uzbekistan,

however, supplementation with riboflavin for 20 months was not successful in reversing chronic esophagitis (28). We found that esophageal cancer incidence and mortality were 14% and 10% lower, respectively, among those receiving daily riboflavin and niacin supplements, with the 14% reduction in esophageal cancer incidence of borderline statistical significance. Total cancer incidence or mortality, however, was only slightly reduced among those receiving B vitamin supplementation, thus providing only weak support for a protective effect. On the other hand, the limited a priori evidence suggests that a benefit from riboflavin and niacin may be more pronounced for esophageal cancer. Thus, we view the finding of lowered esophageal cancer incidence as an encouraging sign worthy of additional investigation.

Vitamin C has been suggested as protective against several cancers, particularly stomach cancer (6). Although results of experimental studies are mixed, most case-control studies of stomach and esophageal cancers have shown that adult diets of the patients typically are low in intake of vitamin C-containing foods (5). Vitamin C can inhibit endogenous formation of nitrosamines, and it has antioxidant and other biological properties that may also inhibit carcinogenesis (46). Data from the Linxian trial, however, showed no evidence of reduced cancer mortality or incidence (in fact, the RRs were above 1.0) among persons receiving daily vitamin C and molybdenum supplements at doses approximately twice the U.S. RDAs.

The failure of this trial to find significant reductions in cancer mortality among those supplemented with retinol and zinc, riboflavin and niacin, or vitamin C and molybdenum could be related to the shortness (5¼ years) of the intervention and follow-up. Indeed, if these nutrients had a protective effect on the early stages of carcinogenesis, our focus on concurrent events in adults taking the supplements would not be expected to show a mortality differential. The data suggest only that supplementation with these particular nutrients resulted in no demonstrable short-term mortality benefit. Continued monitoring of the participants will determine whether any reductions in cancer or other disease may emerge in the coming years.

Several reports have suggested that antioxidant nutrients may reduce the risk or progression of cerebrovascular disease, a common cause of death in Linxian, and perhaps lower the rate of hypertension, a strong risk factor (6,47-49). We found no significant treatment group differences, but mortality from cerebrovascular disease was 10% lower among those receiving supplements with the antioxidants beta carotene, vitamin E, and selenium. Although the effects of antioxidants on cerebrovascular disease may be caused by limiting neuronal tissue damage from cerebral ischemia, evidence is accumulating that antioxidants may inhibit atherosclerosis, especially of the coronary vessels, by reducing the oxidation of low-density lipoproteins (50). A lowered risk of cardiovascular disease has been reported among American men and women taking vitamin E supplements (51,52). Furthermore, in a randomized trial among U.S. physicians (53), beta carotene was found to reduce by 44% the risk of major coronary events in the

subset of participants with chronic angina. Elsewhere, plasma levels of carotene and vitamins E and C have been inversely related to risk of angina (54). Only 1% of the deaths among Linxian trial participants were attributed to ischemic heart disease, limiting evaluation of intervention effects, but we found little or no reduction in mortality from cardiovascular disease among those receiving beta carotene, vitamin E, and selenium.

In summary, when the Linxian trial observations are combined with the epidemiologic, experimental, and biological evidence at hand, it seems plausible that the lowered cancer rates represent a protective effect of beta carotene, vitamin E, and selenium intervention. Although pill supplementation ceased in the summer of 1991, continued follow-up of the Linxian participants over the coming years is planned. In this manner, persistence of the lowered mortality associated with beta carotene, vitamin E, and selenium and the reduced esophageal cancer incidence associated with riboflavin and niacin can be evaluated along with the potential long-term effects of each of the four nutrient combinations after intervention. Shorter-term trials are also planned in the context of a gastric screening project in another high-risk area of China to assess the effectiveness of beta carotene versus vitamin E versus selenium in inhibiting transitions from chronic atrophic gastritis to intestinal metaplasia and gastric dysplasia. Thus, while the Linxian results should be considered preliminary in nature, they offer a hopeful sign that vitamin/mineral supplementation may lower the risk of certain cancers and suggest lines of further research to evaluate the protective effects of specific micronutrients.

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Notes

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Nutrition Intervention Trials in Linxian, China: Multiple Vitamin/Mineral Supplementation, Cancer Incidence, and Disease-Specific Mortality Among Adults With Esophageal Dysplasia

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Background: A number of vitamins and minerals have been shown to influence carcinogenesis in experimental animals. In humans, epidemiologic evidence suggests that intake of fruits and vegetables may reduce risk of esophageal and other cancers. Vitamins and minerals in these foods may contribute to the reduced cancer risk. The people of Linxian, China, have persistently low intake of multiple nutrients and exhibit one of the world's highest rates of esophageal/gastric cardia cancer, with an exceptionally high risk of esophageal dysplasia. **Purpose:** To determine whether supplementation with multiple vitamins and minerals may reduce esophageal/gastric cardia cancer among persons with esophageal dysplasia, we conducted a 6-year prospective intervention trial in Linxian. **Methods:** Mortality and cancer incidence were ascertained from May 1985 through May 1991 for 3318 persons with cytologic evidence of esophageal dysplasia who were randomly assigned to receive, throughout that period, daily supplementation with 14 vitamins and 12 minerals or placebo. Doses were typically two to three times U.S. Recommended Daily Allowances. Compliance was assessed by counting unused pills monthly for all trial participants and by assaying nutrient levels in blood collected from samples of individuals randomly selected without replacement every 3 months throughout the trial. Cancers were identified through routine surveillance and by special cytology and endoscopy screenings after 2½ years and 6 years. **Results:** A total of 324 deaths occurred during the 6-year intervention period; 167 occurred in the control (placebo) group and 157 occurred in the supplement group. Cancer was the leading cause of death (54% of all deaths); 18% were due to cerebrovascular diseases and 29% to other causes. Cumulative esophageal/gastric cardia death rates were 8% lower (relative risk [RR] = 0.92; 95% confidence interval [CI] = 0.67-1.28) among individuals

receiving supplements rather than placebo, a nonsignificant ($P > .10$) difference. Risk of total mortality was 7% lower (RR = 0.93; 95% CI = 0.75-1.16; $P > .10$), total cancer 4% lower (RR = 0.96; 95% CI = 0.71-1.29; $P > .10$), cerebrovascular disease 38% lower (RR = 0.62; 95% CI = 0.37-1.06; $P = .08$), and other diseases 12% higher (RR = 1.12; 95% CI = 0.74-1.69; $P > .10$) among the treated group. Cumulative cancer incidence rates were nearly the same in the two groups. **Conclusions:** No substantial short-term beneficial effect on incidence or mortality for this type of cancer occurred following daily supplementation with multiple vitamins and minerals among adults with precancerous lesions of the esophagus. **Implications:** Although no statistically significant short-term benefits were observed, longer follow-up should be more informative about the effectiveness of this 6-year supplementation on cancer and other diseases among individuals with esophageal dysplasia. [J Natl Cancer Inst 85:1492-1498, 1993]

Rates of esophageal/gastric cardia cancer in Linxian, a rural county in Henan Province, north-central China, are among the highest in the world (1). The excess risk is especially pronounced among persons with esophageal dysplasia, a precancerous lesion affecting over 20% of adults in this area (2,3). The excess cancers occur not only as squamous cell carcinomas of the esophagus, but also as adenocarcinomas of the gastric cardia. Traditionally, both tumors have been called "esophageal cancer" in Linxian because of their proximity to one another and similarity in symptoms.

*See "Notes" section following "References."