

# Effects of Vitamin/Mineral Supplementation on the Prevalence of Histological Dysplasia and Early Cancer of the Esophagus and Stomach: Results from the General Population Trial in Linxian, China<sup>1</sup>

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## Abstract

**A randomized nutrition intervention trial was conducted among 29,584 adult residents of Linxian, China, to examine the effects of vitamin/mineral supplementation on the occurrence of esophageal/gastric cardia cancer in this high-risk population. A fractional factorial study design allowed evaluations of four different combinations of nutrients: (A) retinol and zinc; (B) riboflavin and niacin; (C) vitamin C and molybdenum; and (D)  $\beta$ -carotene, vitamin E, and selenium. During the 5.25-year intervention, significant reductions in total mortality, total cancer mortality, and stomach cancer mortality occurred among those receiving  $\beta$ -carotene, vitamin E, and selenium. At the end of intervention, an endoscopic survey was carried out in a sample of subjects to see if the nutritional supplements had affected the prevalence of clinically silent precancerous lesions and early invasive cancers of the esophagus or stomach. Endoscopy was performed on 391 individuals from two study villages. The prevalences of esophageal and gastric dysplasia and cancer were compared by nutrient factor. Cancer or dysplasia was diagnosed in 15% of the participants. No statistically significant reductions in the prevalence of esophageal or gastric dysplasia or cancer were seen for any of the four vitamin/mineral combinations. The greatest reduction in risk (odds ratio, 0.38;  $P = 0.09$ ) was seen for the effect of retinol and zinc on the prevalence of gastric cancer. Although no significant protective effects were seen in this endoscopic survey, there was a suggestion that**

**supplementation with retinol and zinc may protect against the development of gastric neoplasia in this high-risk population. Additional studies with larger numbers of endpoints will be needed to further evaluate this possibility.**

## Introduction

Previous reports have described a randomized multiple vitamin/mineral intervention trial among the general population of Linxian, a rural county in northern China which has some of the highest rates of esophageal/gastric cardia cancer in the world (1, 2). During this 5.25-year General Population Trial, significant reductions in total mortality, total cancer mortality, stomach cancer mortality, and stomach cancer incidence occurred among participants receiving daily supplementation with  $\beta$ -carotene, vitamin E, and selenium (2). To examine the effect of these and other supplements on earlier stages of esophageal and gastric neoplasia, an endoscopic survey was conducted at the end of intervention to look for clinically silent precancerous and early invasive lesions of the esophagus and stomach.

## Materials and Methods

### The General Population Trial

Details of the procedures of the General Population Trial have been previously described (1). In brief, this trial was conducted among 40-69-year-old residents from the general population of four communes in northern Linxian; 29,584 individuals were enrolled. The intervention agents were grouped into four factors: factor A (retinol and zinc); factor B (riboflavin and niacin); factor C (vitamin C and molybdenum); and factor D (vitamin E, selenium and  $\beta$ -carotene). Daily doses of the active pills, given in Table 1, were one to two times the U.S. Recommended Daily Allowances. The participants were randomized into eight treatment groups which together formed a half replicate of a  $2^4$  factorial study design (3). The eight treatment groups received the following combinations of factors: placebo; AB; AC; AD; BC; BD; CD; and ABCD. This study design enabled all of the participants to be simultaneously randomized into separate evaluations of each factor (3). We used the term "factor group" to refer to all patients who were assigned to receive or not receive a given factor. Active intervention began in March 1986 and ended in May 1991.

### 1991 Endoscopic Survey

In April and May, 1991, at the end of the 5.25-year intervention, an endoscopic survey was conducted among a

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Table 1 Daily doses of micronutrients, by treatment factor, in the General Population Trial, Linxian, China

Factor	Micronutrients	Dose
A	Retinol (as palmitate)	5000 international units
	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

sample of General Population Trial participants. For logistical reasons, the survey was limited to two villages in Ren-cun commune. All subjects in these villages under 70 years old who had no history of cancer and had completed an end-of-trial cytology examination were invited to undergo endoscopy. Overall, 391 (79%) of the 493 eligible subjects were endoscoped. Informed consent was obtained from each subject prior to the procedure.

During endoscopy, the esophagus and stomach were visually examined and one or more 2.8-mm biopsies were taken from all focal lesions and four standard sites (gastric angulus, cardia at 12:00 and 6:00, and mid-esophagus). The biopsies were oriented on filter paper, fixed in buffered formalin, embedded in paraffin, cut in 5-µm sections and stained with hematoxylin and eosin.

### Histological Categories

The biopsies were read jointly by three pathologists (S. M. D., F. S. L., K. J. L.), without knowledge of the patient's history, treatment group, or the visual endoscopic findings. The histological criteria were based on previous descriptions (4-8).

**Esophageal Categories. Normal.** A full-thickness stratified squamous epithelium was present which showed no features diagnostic of acanthosis, esophagitis, squamous dysplasia, or squamous cancer, as defined below.

**Acanthosis.** An otherwise normal epithelium was  $\geq 0.5$  mm thick.

**Esophagitis.** One or more of the following three criteria were present: elongation of lamina propria papillae into the upper third of the epithelium together with basal cell hyperplasia, defined as a basal zone thickness  $>15\%$  of total epithelial thickness; epithelial infiltration by neutrophils or eosinophils; or a dense nonfollicular infiltrate of mononuclear inflammatory cells or neutrophils in the lamina propria.

**Squamous Dysplasia.** Nuclear atypia (enlargement, pleomorphism, and hyperchromasia), loss of normal cell polarity, and abnormal tissue maturation were present in the lower third (mild), in the lower two-thirds (moderate), or in all thirds (severe) of the epithelium, without invasion.

**Squamous Cancer.** Neoplastic squamous cells were present which had invaded the basement membrane.

**Gastric Categories. Normal.** A gastric mucosa was present which showed no features diagnostic of gastritis, gastric dysplasia, or adenocarcinoma, as defined below. No inflam-

matory infiltrate was allowed in normal biopsies from the gastric fundus or body, but a mild lymphoplasmacytic infiltrate was permitted in normal biopsies from the cardia or antrum.

**Gastritis without Atrophy.** Any inflammation other than a mild lymphoplasmacytic infiltrate in biopsies from the cardia or antrum was called gastritis. For the purposes of this study, we did not separate superficial from full-thickness involvement or chronic from chronic active inflammation. No atrophy (loss of glands) or metaplasia was identified.

**Atrophic Gastritis.** There was variable inflammation and loss of normal glands, with or without intestinal or pyloric metaplasia.

**Gastric Dysplasia.** Neoplastic features, including nuclear atypia and/or architectural abnormalities, were present but confined to the gastric epithelium, without invasion. Dysplasia was categorized as low-grade or high-grade based on the severity of the neoplastic features (8).

**Adenocarcinoma.** Neoplastic gastric epithelial cells were present which had invaded through the basement membrane.

Symptoms were ascertained by interview at the time of the endoscopic examination. In this article, we report on the prevalence of dysphagia, the most common symptom associated with cancer of the esophagus and gastric cardia. The subjects were asked, "Within the last year, how often have you experienced difficulty swallowing?" (daily, often, upon occasion, or rarely/never).

### Analysis

All of the 391 subjects total in the endoscopic survey had at least one satisfactory biopsy, including 379 (97%) with satisfactory esophageal biopsies and 390 (99%) with satisfactory gastric biopsies (386 with gastric cardia biopsies and 378 with biopsies from elsewhere in the stomach). All but four of the esophageal biopsies showed squamous mucosa; these four glandular esophageal biopsies were excluded from the analysis. All of the gastric biopsies showed glandular mucosa.

For each subject, a worst esophageal diagnosis (invasive cancer  $>$  dysplasia  $>$  esophagitis  $>$  acanthosis  $>$  normal) and a worst gastric diagnosis (invasive cancer  $>$  dysplasia  $>$  atrophic gastritis  $>$  gastritis without atrophy  $>$  normal) were determined. Then a worst overall diagnosis was derived to examine the overall effect of the nutritional supplements in a population in which both esophageal and gastric cardia cancers are significant causes of mortality: normal, a worst biopsy diagnosis of normal or acanthotic squamous mucosa or normal gastric mucosa; inflammation, esophagitis or gastritis; low-grade dysplasia, mild squamous dysplasia or low-grade gastric dysplasia; high-grade dysplasia, moderate or severe squamous dysplasia or high-grade gastric dysplasia; and cancer, squamous cancer or adenocarcinoma. The distributions of the worst esophageal, worst gastric, and worst overall diagnoses were then compared for subjects who received versus those who did not receive each factor of intervention agents.

We examined the potential for selection bias in the interpretation of treatment effects in a number of ways and found that the number of subjects excluded from eligibility for the endoscopic examination because of death or incident cancer, the refusal rates among eligible subjects, and the prevalence of dysphagia in the endoscoped subjects did not differ significantly by factor group. In addition, the prevalence of

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Table 2 Linxian general population trial endoscopic survey esophageal biopsy results

Treatment factor received <sup>a</sup>	No. of subjects endoscoped <sup>b</sup>	Worst esophageal biopsy diagnosis							Cancer
		Normal	Acanthosis	Esophagitis	Dysplasia			Total	
					Mild	Mod <sup>c</sup>	Sev <sup>c</sup>		
A	192	147 (76.6) <sup>d</sup>	12 (6.3)	12 (6.3)	6 (3.1)	5 (2.6)	2 (1.0)	13 (6.8)	8 (4.2)
No A	187	147 (78.6)	6 (3.2)	15 (8.0)	10 (5.4)	1 (0.5)	1 (0.5)	12 (6.4)	7 (3.7)
B	188	146 (77.7)	8 (4.3)	13 (6.9)	8 (4.3)	3 (1.6)	2 (1.1)	13 (6.9)	8 (4.3)
No B	191	148 (77.5)	10 (5.2)	14 (7.3)	8 (4.2)	3 (1.6)	1 (0.5)	12 (6.3)	7 (3.7)
C	201	152 (75.6)	12 (6.0)	14 (7.0)	9 (4.5)	3 (1.5)	2 (1.0)	14 (7.0)	9 (4.5)
No C	178	142 (79.8)	6 (3.4)	13 (7.3)	7 (3.9)	3 (1.7)	1 (0.6)	11 (6.2)	6 (3.4)
D	173	139 (80.4)	8 (4.6)	9 (5.2)	9 (5.2)	1 (0.6)	2 (1.2)	12 (6.9)	5 (2.9)
No D	206	155 (75.2)	10 (4.9)	18 (8.7)	7 (3.4)	5 (2.4)	1 (0.5)	13 (6.3)	10 (4.9)
Total	379	294 (77.6)	18 (4.8)	27 (7.1)	16 (4.2)	6 (1.6)	3 (0.8)	25 (6.6)	15 (4.0)

<sup>a</sup> Factor A, retinol and zinc; Factor B, riboflavin and niacin; Factor C, vitamin C and molybdenum; Factor D,  $\beta$ -carotene, vitamin E, and selenium.

<sup>b</sup> Twelve subjects had no satisfactory esophageal biopsies.

<sup>c</sup> Mod, moderate dysplasia; Sev, severe dysplasia.

<sup>d</sup> Number of subjects (row %).

dysphagia among those eligible for endoscopy did not differ between those who accepted and those who refused endoscopy.

Differences in the prevalence of risk factors between the total trial population and the endoscopy subjects and differences in risk factors between nutrient factor groups in the endoscoped cohort were tested with *t* tests for mean age and  $\chi^2$  tests for gender, smoking, and alcohol use. Factor group differences in the overall distributions of the esophageal, gastric, and worst overall biopsy diagnoses were also tested using  $\chi^2$  tests. OR<sup>3</sup> and CI for treatment effects were estimated using SAS PROC LOGIST (9) with adjustment for age, gender, smoking status and alcohol use.

## Results

The mean age of the endoscopy participants was 53 years. Fifty % were males, 36% were smokers, and 37% reported alcohol use. Compared with the total trial population, the endoscopy cohort was younger (mean age 53 *versus* 57 years in 1991;  $P < 0.001$ ) and included more males (50 *versus* 45%;  $P = 0.048$ ), more smokers (36 *versus* 30%;  $P = 0.013$ ), and more subjects who used alcohol (37 *versus* 23%;  $P < 0.001$ ). There were no significant differences in any of these characteristics, however, between factor groups in the endoscoped cohort.

Cumulative pill disappearance rates, a measure of intervention compliance, were 96–97% for the endoscoped subjects in each factor group. High compliance was also indicated by quarterly biochemical assessments of a sample of the total General Population Trial population which showed significant improvements in blood levels of retinol, riboflavin, ascorbic acid, and  $\beta$ -carotene in subjects who received *versus* those who did not receive these intervention agents (1).

Tables 2–4 show the esophageal, gastric, and worst overall biopsy diagnoses from the endoscopy survey, by factor group (those who received *versus* those who did not receive the nutritional supplements in each factor). In all tables, the overall distributions of diagnoses were not significantly different by factor group for any of the vitamin/mineral combinations ( $P > 0.10$  for all comparisons).

Table 2 shows the esophageal biopsy diagnoses. All factor groups had similar proportions of normal subjects and subjects with esophageal dysplasia. Subjects receiving factor C (vitamin C + molybdenum) had more cancers and subjects receiving factor D ( $\beta$ -carotene + vitamin E + selenium) had fewer cancers at endoscopy than those not receiving these supplements.

All seven cases of gastric dysplasia and 14/16 (88%) of the gastric cancers were found in the gastric cardia. Factor group comparisons of the distributions of diagnoses were similar for the cardia and noncardia gastric biopsies, so only the combined data are shown. Table 3 shows the gastric biopsy diagnoses. All factor groups had similar proportions of normal subjects and subjects with gastritis. Subjects receiving factor A (retinol + zinc) had fewer cancers at endoscopy than those not receiving these supplements, while subjects receiving factor B (riboflavin + niacin) or factor C (vitamin C + molybdenum) had more cancers than those who were not given these agents.

Table 4 shows the worst overall diagnoses from the endoscopy survey. The prevalences of dysplasia did not differ substantially by nutrient factor group. Subjects receiving factor A or factor D had fewer cancers and those receiving factor B or factor C had more cancers than did the subjects not taking these supplements.

Odds ratios for finding dysplasia or cancer at endoscopy, by treatment factor (those receiving *versus* those not receiving that factor), are shown in Table 5. Factors A and D had odds ratios consistently near or below 1.0, while the odds ratios for factors B and C were uniformly above 1.0.

<sup>3</sup> The abbreviations used are: OR, odds ratio; CI, confidence interval.

Table 3 Linxian general population trial endoscopic survey gastric biopsy results

Treatment factor received <sup>a</sup>	No. of subjects endoscoped <sup>b</sup>	Worst gastric biopsy diagnosis						
		Normal	Gastritis without atrophy	Atrophic gastritis	Dysplasia			Cancer
					Low grade	High grade	Total	
A	196	63 (32.1) <sup>c</sup>	74 (37.8)	50 (25.5)	4 (2.0)	0 (0.0)	4 (2.0)	5 (2.6)
No A	194	63 (32.5)	64 (33.0)	53 (27.3)	2 (1.0)	1 (0.5)	3 (1.5)	11 (5.7)
B	193	63 (32.6)	70 (36.3)	47 (24.4)	3 (1.6)	0 (0.0)	3 (1.6)	10 (5.2)
No B	197	63 (32.0)	68 (34.5)	56 (28.4)	3 (1.5)	1 (0.5)	4 (2.0)	6 (3.1)
C	205	67 (32.7)	77 (37.6)	44 (21.5)	4 (2.0)	1 (0.5)	5 (2.4)	12 (5.9)
No C	185	59 (31.9)	61 (33.0)	59 (31.9)	2 (1.1)	0 (0.0)	2 (1.1)	4 (2.2)
D	176	55 (31.3)	67 (38.1)	45 (25.6)	1 (0.6)	1 (0.6)	2 (1.1)	7 (4.0)
No D	214	71 (33.2)	71 (33.2)	58 (27.1)	5 (2.3)	0 (0.0)	5 (2.3)	9 (4.2)
Total	390	126 (32.3)	138 (35.4)	103 (26.4)	6 (1.5)	1 (0.3)	7 (1.8)	16 (4.1)

<sup>a</sup> Factor A, retinol and zinc; Factor B, riboflavin and niacin; Factor C, vitamin C and molybdenum; Factor D,  $\beta$ -carotene, vitamin E, and selenium.

<sup>b</sup> One subject had no satisfactory gastric biopsies.

<sup>c</sup> Number of subjects (row %).

Table 4 Linxian general population trial endoscopic survey worst overall biopsy results

Treatment factor received <sup>a</sup>	No. of subjects endoscoped	Worst overall biopsy diagnosis					
		Normal	Inflammation	Dysplasia			Cancer
				Low grade	High grade	Total	
A	197	51 (25.9) <sup>b</sup>	118 (59.9)	8 (4.1)	7 (3.6)	15 (7.6)	13 (6.6)
No A	194	55 (28.4)	107 (55.2)	11 (5.7)	3 (1.6)	14 (7.2)	18 (9.3)
B	194	56 (28.9)	104 (53.6)	11 (5.7)	5 (2.6)	16 (8.2)	18 (9.3)
No B	197	50 (25.4)	121 (61.4)	8 (4.1)	5 (2.5)	13 (6.6)	13 (6.6)
C	206	57 (27.7)	112 (54.4)	10 (4.9)	6 (2.9)	16 (7.8)	21 (10.2)
No C	185	49 (26.5)	113 (61.1)	9 (4.9)	4 (2.2)	13 (7.0)	10 (5.4)
D	177	48 (27.1)	104 (58.8)	9 (5.1)	4 (2.3)	13 (7.3)	12 (6.8)
No D	214	58 (27.1)	121 (56.5)	10 (4.7)	6 (2.8)	16 (7.5)	19 (8.9)
Total	391	106 (27.1)	225 (57.5)	19 (4.9)	10 (2.6)	29 (7.4)	31 (7.9)

<sup>a</sup> Factor A, retinol and zinc; Factor B, riboflavin and niacin; Factor C, vitamin C and molybdenum; Factor D,  $\beta$ -carotene, vitamin E, and selenium.

<sup>b</sup> Number of subjects (row %).

Odds ratios for a worst overall diagnosis of dysplasia or cancer were 0.83 (95% CI, 0.47–1.46) for both factor A and factor D. The greatest reduction in risk (OR, 0.38; 95% CI, 0.13–1.15;  $P = 0.088$ ) was observed for the effect of factor A (retinol and zinc) on the prevalence of gastric cancer.

Nearly all of the endoscoped subjects who were interviewed were asymptomatic with respect to dysphagia, the primary symptom of esophageal and gastric cardia cancers. Only 4/390 (1.0%) reported dysphagia (daily or often *versus* occasional or rare/never), including 1 of 25 (4.0%) with esophageal dysplasia, 1 of 15 (6.7%) with esophageal cancer, 0 of 7 with gastric dysplasia, and 0 of 16 with gastric cancer.

## Discussion

This endoscopic survey was conducted to complement the cancer incidence and mortality results of the total General Population Trial (2) by examining the effects of the Trial's nutrient supplements on the prevalence of clinically silent early stages of esophageal and gastric neoplasia. The factorial study design allowed simultaneous evaluation of the effects of four different combinations of vitamins and minerals.

The esophageal biopsy results showed no convincing evidence that any of the vitamin/mineral supplements decreased the prevalence of esophageal dysplasia or cancer. The greatest reduction in the prevalence of neoplastic

Table 5 Linxian general population trial endoscopic survey odds ratios for active treatment on esophageal and gastric cancer and precursor lesions<sup>a</sup>

Cancer	Treatment factor received	Esophageal diagnoses		Gastric diagnoses		Worst overall diagnoses	
		Dysplasia or cancer (n = 39) <sup>b</sup>	Cancer (n = 15)	Dysplasia or cancer (n = 23)	Cancer (n = 16)	Dysplasia or cancer (n = 59) <sup>b</sup>	Cancer (n = 31)
5 (2.6)	A <sup>c</sup>	1.12 (0.57-2.20) <sup>d</sup>	1.02 (0.36-2.91)	0.58 (0.24-1.39)	0.38 (0.13-1.15)	0.83 (0.47-1.46)	0.61 (0.29-1.31)
11 (5.7)	B	1.12 (0.58-2.19)	1.19 (0.42-3.39)	1.32 (0.56-3.14)	1.67 (0.58-4.76)	1.39 (0.79-2.44)	1.46 (0.68-3.11)
10 (5.2)	C	1.31 (0.67-2.57)	1.32 (0.46-3.83)	2.64 (1.01-6.93)	2.75 (0.86-8.84)	1.61 (0.91-2.86)	1.99 (0.90-4.41)
6 (3.1)	D	0.80 (0.40-1.57)	0.58 (0.19-1.76)	0.83 (0.35-2.01)	1.05 (0.37-2.92)	0.83 (0.47-1.46)	0.79 (0.36-1.69)

<sup>a</sup>Odds ratios adjusted for age, gender, smoking, and alcohol use.

<sup>b</sup>One case of dysplasia deleted due to missing covariate information.

<sup>c</sup>Factor A, retinol and zinc; Factor B, riboflavin and niacin; Factor C, vitamin C and molybdenum; Factor D,  $\beta$ -carotene, vitamin E, and selenium.

<sup>d</sup>Odds ratio (95% confidence interval).

esophageal biopsies was a 42% decrease in esophageal cancer seen in subjects receiving factor D ( $\beta$ -carotene + vitamin E + selenium), but this result did not approach statistical significance ( $P = 0.339$ ).

The gastric biopsy results also showed no significant reductions in the prevalence of dysplasia or cancer with any of the treatments. There was a suggestion, however, that supplementation with retinol and zinc might have given some protection against the development of gastric neoplasia. Subjects receiving this supplement (factor A) showed a 62% reduction in the prevalence of gastric cancer ( $P = 0.088$ ) and a 42% reduction in the prevalence of gastric dysplasia or cancer compared with subjects not receiving these nutrients. An additional and unexpected finding, contrary to our *a priori* hypothesis, was an increased prevalence of gastric dysplasia and cancer in subjects taking factor C (vitamin C and molybdenum). The fact that multiple comparisons were made in testing four separate treatments should be considered in evaluating the apparent effects of any of the supplements.

The protective effect of retinol and zinc on gastric neoplasia which was suggested in this endoscopic survey was not observed in the overall cancer incidence and mortality data from the General Population Trial (2), which showed a 3% greater risk of gastric cancer death among individuals taking these intervention agents. Because all of the gastric lesions identified in the endoscopic survey were asymptomatic, while nearly all cancer cases in the overall trial were symptomatic (*i.e.*, later stage), it is possible that retinol and/or zinc preferentially affect early stages of gastric neoplasia, and the trial was not long enough to see this benefit in the symptomatic cancer incidence and mortality rates. Although nutritional supplementation in this population has now ended, the trial participants will be followed for future trends in symptomatic cancer incidence and mortality.

Several points should be considered in interpreting the findings of this study. Although this was a relatively large endoscopy survey and the overall prevalence of dysplasia and cancer (15%) was extraordinary for asymptomatic adults from a general population, the analysis of treatment effects was still limited by the relatively small number of dysplasia and cancer events, and small but worthwhile benefits of intervention may not have been detected. Small sample size is a general problem in endoscopy surveys because of the invasiveness of the procedure and the large amount of time and work required for each subject. In addition to sample size considerations, the nutrients may have been given for

an insufficient length of time, in insufficient doses, or too late in the lives of the subjects for major effects to be seen.

The ability of the biopsy protocol used in this survey to identify esophageal dysplasia and cancer is supported by recent studies showing that most of these histological abnormalities in Linxian are associated with endoscopically visible focal lesions similar to the ones targeted in the 1991 examinations (10) and that a protocol similar to the present one achieved a high correlation between biopsy diagnoses of squamous dysplasia and subsequent development of invasive esophageal cancer.<sup>4</sup> The ability of the current protocol to identify gastric neoplasia in this population has not yet been evaluated.

Only one previous study in China has reported esophageal biopsy results from a prospective randomized trial of nutritional supplements of the type used in the current study (11). In that trial, conducted in Huixian, a county near Linxian with similar high rates of esophageal/gastric cardia cancer, 610 adults were randomized to supplementation with riboflavin (200 mg/week), retinol (50,000 international units/week), and zinc (50 mg/week) or placebo. After 13.5 months, no difference was found in the distribution of esophageal diagnoses in the two groups. This study was limited by its few cases of squamous dysplasia ( $n = 14$ ) and squamous cancer ( $n = 5$ ). Even with our larger numbers of such cases, however, our esophageal results were still inconclusive. To our knowledge, there are no previous reports of gastric biopsy surveys after randomized nutritional intervention trials.

In summary, this endoscopic survey showed no significant protective effects for any of the four vitamin/mineral combinations on dysplasia or early cancer of the esophagus or stomach. There was a suggestion, however, that 5.25 years of daily supplementation with retinol and zinc may protect against the development of gastric neoplasia in this population. It is also possible that some of the other supplements may have had beneficial effects which could not be detected by biopsying this limited number of subjects. Additional studies with larger numbers of endpoints will be needed to further evaluate these possibilities.

<sup>4</sup>S. M. Dawsey, K. J. Lewin, G. Q. Wang, F. S. Liu, R. K. Nieberg, Y. Yu, J. Y. Li, W. J. Blot, B. Li, and P. R. Taylor. Squamous esophageal histology and subsequent risk of squamous esophageal cancer: a prospective follow-up from Linxian, China, submitted for publication.

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