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## Gastric Dysplasia and Gastric Cancer: *Helicobacter pylori*, Serum Vitamin C, and Other Risk Factors

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**Background:** Gastric cancer is generally thought to arise through a series of gastric mucosal changes, but the determinants of the precancerous lesions are not well understood. To identify such determinants, we launched a follow-up study in 1989–1990 among 3433 adults in Linq County, China, a region with very high rates of gastric cancer. **Methods:** Data on cigarette smoking, alcohol consumption, and other characteristics of the participants were obtained by interview in 1989–1990, when an initial endoscopy was taken. At study entry, antibodies to *Helicobacter pylori* were assayed in 2646 adults (77% of people screened), and levels of serum micronutrients were measured in approximately 450 adults. Follow-up endoscopic and histopathologic examinations were conducted in 1994. Antibodies to *H. pylori*, levels of serum micronutrients, and other baseline characteristics were compared between subjects whose condition showed progression to dysplasia or gastric cancer from study entry to 1994 and subjects with no change or with regression of their lesions over the same time frame. All *P* values are two-sided. **Results:** The presence of *H. pylori* at baseline was associated with an increased risk of progression to dysplasia or gastric cancer (odds ratio [OR] = 1.8; 95% confidence interval [CI] = 1.2–2.6). The risk of progression to dysplasia or gastric cancer also was moderately increased with the number of years of cigarette smoking. In contrast, the risk of progression was decreased by 80% (OR = 0.2; 95% CI = 0.1–0.7) among subjects with baseline ascorbic acid levels in the highest tertile compared with those in

the lowest tertile, and there was a slightly elevated risk in those individuals with higher levels of  $\alpha$ -tocopherol. **Conclusions:** *H. pylori* infection, cigarette smoking, and low levels of dietary vitamin C may contribute to the progression of precancerous lesions to gastric cancer in this high-risk population. [J Natl Cancer Inst 2000;92:1607–12]

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Although mortality rates for gastric cancer have been declining in many countries, no parallel trend has been observed in China (1). Linq County, a rural area in Shandong Province of northeast China, has rates of gastric cancer that are among the world's highest (2). Reasons for the exceptionally high incidence rates in this region are not entirely clear, but high intake of salt, salty food, and fermented sour pancakes, low consumption of fresh vegetables and fruits, and cigarette smoking were identified as risk factors in an earlier case-control study (2). Serum micronutrient levels were not measured in the case-control study because the values could have been influenced by the presence of cancer. In 1989–1990, population-based endoscopic screening among 3433 adults was conducted in Linq (3). Antibodies to *Helicobacter pylori* were assayed for 2646 adults at baseline (77% of people screened), and levels of serum micronutrients were measured in approximately 450 adults at baseline. In this cross-sectional study, the presence of *H. pylori* and cigarette smoking were associated with the prevalence of severe chronic atrophic gastritis, intestinal metaplasia, or dysplasia, whereas serum concentrations of vitamin C and  $\beta$ -carotene

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showed a negative relationship (4–6). Follow-up endoscopic and histopathologic examinations conducted in 1994 showed that gastric cancer risk was greatly increased in subjects with intestinal metaplasia or with moderate or severe dysplasia at baseline (7).

Herein we report the results of a 4.5-year follow-up study designed to identify factors that influence the progression of gastric precursor lesions to dysplasia and gastric cancer in this high-risk population.

## SUBJECTS AND METHODS

### Study Population

During the period from November 1989 through March 1990, a total of 3433 subjects participated in a gastric cancer-screening study, representing 83% of eligible residents aged 35–64 years in 14 villages selected at random within four townships of Linqu County, as described previously (3). The study was approved by the Institutional Review Board of both the National Cancer Institute and the Beijing Institute for Cancer Research (BICR), and all subjects gave written informed consent. In brief, after the names of all of the residents were transcribed from village population rosters, health workers visited each person, explained the study, and invited participation in a gastric cancer-screening program; willing individuals received physical and endoscopic examinations. Three experienced gastroenterologists using a fiberoptic gastroscope (Olympus) in 1989–1990 and 1994 performed the endoscopic examinations. The gastric mucosa was observed, and seven biopsy specimens were obtained from standard locations of the stomach: two in the body of the stomach, one in the angulus, and four in the antrum. After the endoscopic examination in 1989–1990, participants were followed with systematic monitoring of death and cancer occurrences. In the autumn of 1994, a repeat endoscopic examination employing the same endoscopic procedures as those used in 1989–1990 was offered to all cohort members (7).<sup>1</sup>

### Pathology

Histopathologic diagnoses of gastric lesions were made in 1994 by the same three pathologists who conducted the 1989 survey at the BICR, and quality-control slides were reviewed by reference pathologists from China and the United States (7). The presence or absence of superficial gastritis, chronic atrophic gastritis, intestinal metaplasia, dysplasia, or gastric cancer was recorded for each biopsy specimen, and each subject was assigned a global diagnosis based on the most severe diagnosis among any of the biopsy specimens. Details of the pathologic procedures and classification criteria, along with photographs of superficial gastritis, chronic atrophic gastritis, intestinal metaplasia, dysplasia, and gastric cancer, and quality-control procedures are provided elsewhere (3,7). Since none of the subjects had a completely normal gastric mucosa and only 1.6% of the subjects had superficial gastritis as the most severe diagnosis, we combined superficial gastritis and chronic atrophic gastritis into one category. The

cohort was divided into three groups based on the 1989 pathology: 1) superficial gastritis or chronic atrophic gastritis ( $n = 1240$ ), 2) intestinal metaplasia ( $n = 842$ ), and 3) dysplasia ( $n = 546$ ).

### Serum Samples

During the physical examination at baseline, approximately 15 mL of blood was collected from each fasting subject. The blood specimen was allowed to clot for 30–40 minutes at room temperature in a dark place and then centrifuged at 965*g* for 15 minutes. The resulting serum was separated into nine vials, stored immediately at  $-20^{\circ}\text{C}$ , and then moved into a  $-70^{\circ}\text{C}$  freezer within 2 or 3 days. A meta-phosphoric acid solution (6%) was immediately added to the appropriate vial for the vitamin C assay. In approximately 450 randomly selected subjects of 3433 screened subjects, 13% of the total screened population, we measured serum micronutrients.

### Laboratory Analysis

**Micronutrients.** The analysis of fat-soluble vitamins was carried out at BICR, and quality-control assays were done at Rutgers University, Piscataway, NJ, in 1991–1992 on a 10% sample (5). A high-performance liquid chromatography (HPLC) method developed by Yang and Lee (8) was used on duplicate 150- $\mu\text{L}$  serum samples. Ascorbic acid concentrations were determined at Rutgers University according to the HPLC method of Zhang et al. (9). Trace elements were assayed at the Beijing Metal Institute, China, by neutron activation, and quality control was carried out at the National Toxicologic Laboratory, Quebec, Canada. Ferritin was assayed (10) at the Nutrition Department of the Beijing Medical University, and quality-control samples were assayed at the University of Washington, Seattle.

***H. pylori* antibody assay.** Details of the serologic assay are described elsewhere (5). Briefly, *H. pylori* strains cultured from gastric biopsy specimens from two patients in Linqu County were used to provide a local antigen preparation for serology. Serum *H. pylori* immunoglobulin G (IgG) and immunoglobulin A (IgA) antibody concentrations were each measured twice at baseline at BICR in 1991–1992 with the use of enzyme-linked immunosorbent assay (ELISA) procedures. Quality-control samples were assayed at Vanderbilt University, Nashville, TN. Each assay value was based on the mean of duplicate readings, and the mean of the two assay values was used to assess positivity. An individual was considered to be positive if the mean ELISA optical density reading for either the IgG or IgA was above 1.0, a cutoff based on examination of the distribution of such readings in relation to a group of *H. pylori*-negative persons and reference sera.

### Statistical Analysis

Means and/or geometric means and standard deviations for each serum element were calculated for groups defined by 1989–1990 baseline and 1994 global histologic diagnoses. Micronutrient levels and logarithms of serum levels of ascorbic acid,  $\beta$ -carotene, and ferritin were compared with the use of the Student's *t* tests. Associations of the serum tertiles of the various nutrients, the presence of *H.*

*pylori*, and other variables related to the risk of progression from baseline superficial gastritis, chronic atrophic gastritis, or intestinal metaplasia to dysplasia or gastric cancer were estimated by odds ratios (ORs). Adjusted OR and 95% confidence interval (CI) estimates were obtained by logistic regression analysis in an SAS program (SAS Institute, Inc., Cary, NC) (11). The ORs were adjusted for subjects' sex, age (34–44, 45–54, or  $\geq 55$  years), number of cigarettes smoked per day (0, 1–19, or  $\geq 20$ ), and 1989 baseline gastric status (0 = superficial or chronic atrophic gastritis or 1 = intestinal metaplasia). There was no adjustment for the number of cigarettes smoked per day in the analysis of smoking duration, however. Age was included as a categorical variable, whereas smoking and exposures classified in tertiles were coded as 0, 1, or 2 for trend tests with 1 *df*. All *P* values were two-sided and were considered to be statistically significant at the .05 level.

## RESULTS

After the exclusion of 13 subjects diagnosed with gastric cancer at the baseline survey, 3386 subjects were followed. Follow-up endoscopic examinations were completed on 2749 persons, but 121 subjects were later excluded because of insufficient tissue samples. Therefore, histopathologic diagnoses were available for 2628 subjects in 1994. During the approximately 4.5-year follow-up, 34 incident gastric cancers were diagnosed (one among 1240 subjects who were previously diagnosed with superficial gastritis or chronic atrophic gastritis, 18 among 842 diagnosed with intestinal metaplasia, and 15 among 546 diagnosed with dysplasia) [see also (7)]. The proportion of cases progressing to dysplasia or gastric cancer in 1994 among the 1240 subjects with baseline superficial or chronic atrophic gastritis and the 842 subjects with intestinal metaplasia at baseline was 6.4% and 21.0%, respectively.

Most information on baseline cigarette smoking and other variables was available for 2436 subjects, although occasional subjects with missing covariates (27 subjects missing in income and three in cigarette smoking or alcohol consumption categories) were excluded from analyses requiring covariate adjustment. Baseline and follow-up *H. pylori* antibody status was available for 1889 subjects. Because less than 15-mL blood samples were collected from a number of subjects, baseline data for specific micronutrients were available for 366 subjects for ascorbic acid, 387 subjects for copper, and from 430 to 434 subjects for other micronutrients, respectively.

Smoking duration (OR = 1.6 for  $\geq 25$

years [95% CI = 1.0–2.1]; trend test,  $P = .04$ ) and the presence of *H. pylori* at baseline (OR = 1.8 [95% CI = 1.2–2.6]) were associated with progression to dysplasia or gastric cancer during the 4.5-year follow-up (Table 1). The OR for progression to dysplasia or gastric cancer was elevated among subjects who smoked 20 or more cigarettes per day, but it was not statistically significant (OR = 1.4 [95% CI = 0.9–2.3]; trend test,  $P = .12$ ). Similar trends were obtained for duration of smoking and number of cigarettes smoked per day with adjustment for *H. pylori* in addition to age, sex, alcohol consumption, and baseline histopathology. There was no clear evidence that subjects' income, education, or alcohol consumption at baseline was related to the risk of progression to dysplasia or gastric cancer.

Table 2 presents the means of nutrient concentrations according to characteris-

tics of the subjects. Serum concentrations of retinol,  $\alpha$ -tocopherol, selenium, copper, and zinc were approximately symmetrically distributed. The distributions of  $\beta$ -carotene, ascorbic acid, and ferritin appeared skewed; thus, geometric mean values were more appropriate. The mean serum level of ascorbic acid was 40% lower among subjects with progression to dysplasia or gastric cancer than among those in whom superficial gastritis, chronic atrophic gastritis, or intestinal metaplasia did not progress ( $P < .001$ ). Although the serum levels of  $\beta$ -carotene,  $\alpha$ -tocopherol, selenium, and copper were somewhat higher among those with progression to dysplasia or gastric cancer, the values were not statistically significantly different from those without progression ( $\beta$ -carotene:  $P = .11$ ;  $\alpha$ -tocopherol:  $P = .06$ ; selenium:  $P = .50$ ; and copper:  $P = .23$ ).

Table 3 shows the adjusted ORs of progression to dysplasia or gastric cancer in the 1994 follow-up, according to tertile levels of each serum micronutrient. The highest tertile of serum concentration of ascorbic acid of greater than 5.52  $\mu\text{g/mL}$  (geometric mean: 9.76  $\mu\text{g/mL}$ ) was associated with a reduced risk of progression to dysplasia or gastric cancer (OR = 0.2 [95% CI = 0.1–0.7]; trend test,  $P = .006$ ) compared with those with the lowest level of less than 1.84  $\mu\text{g/mL}$  (geometric mean: 0.99  $\mu\text{g/mL}$ ). Similar trends were obtained with adjustment for *H. pylori* status in addition to age, sex, number of cigarettes smoked per day, and baseline histopathology. Risk of dysplasia or gastric cancer was elevated in the middle and upper tertiles of  $\alpha$ -tocopherol, compared with lowest levels, but the trend test was not statistically significant ( $P = .07$ ). Increasing serum concentrations of retinol (trend test,  $P = .54$ ),  $\beta$ -carotene (trend test,  $P = .33$ ), selenium (trend test,  $P = .16$ ), zinc/copper ratio (trend test,  $P = .91$ ), and ferritin (trend test,  $P = .18$ ) were not associated with risk of progression to dysplasia or gastric cancer.

## DISCUSSION

In this rural area of China with one of the world's highest rates of gastric cancer, we found previously that the risk of gastric cancer and advanced precursor lesions over a 4.5-year follow-up was strongly related to the severity of the lesions diagnosed at the start of follow-up (7). We, therefore, controlled for baseline histopathology in this study. Controlling for baseline histopathology of precursor lesions as well as for age, sex, and smoking status, we found that the presence of *H. pylori* is a risk factor for progression to dysplasia or gastric cancer. Since at least 70% of this population acquires *H. pylori*, approximately 32.9% (95% CI = 10.9%–52.8%) of the cases progressing to dysplasia or gastric cancer in Linqu in this 4.5-year period may be attributable to the presence of *H. pylori* (6). The finding that *H. pylori* is a risk factor for progression to dysplasia or gastric cancer is consistent with the findings obtained in other prospective studies of gastric cancer (12–15) and with the association between the presence of *H. pylori* and the prevalence of dysplasia in Linqu (6) and in Cangshan, a neighboring county with a much lower mortality from gastric cancer (16). Thus, our findings suggest that the presence of *H. pylori* influences gastric carcinogene-

**Table 1.** Odds ratio for progression to dysplasia and gastric cancer according to selected variables at follow-up

1989 baseline	1994 follow-up: progression to dysplasia or gastric cancer			
	No. with no progression	No. with progression	OR (95% CI)*	$P^{\dagger}$
Schooling $\ddagger$				
No	892	110	1.0 (referent)	
Yes	1279	155	0.9 (0.6–1.2)	.44
Income, Yan $\ddagger$				
<300	982	116	1.0 (referent)	
$\geq$ 300	1164	147	1.1 (0.8–1.4)	.56
No. of cigarettes smoked per day $\S$				
None	1208	115	1.0 (referent)	
1–19	323	44	1.2 (0.7–1.9)	
$\geq$ 20	637	106	1.4 (0.9–2.3)	.12
Years of smoking $\S$				
None	1211	116	1.0 (referent)	
1–24	582	64	1.1 (0.7–1.7)	
$\geq$ 25	378	85	1.6 (1.0–2.7)	.04
Alcohol consumption, mL/wk $\parallel$				
Never	1255	124	1.0 (referent)	
1–399	558	84	1.3 (0.9–1.9)	
$\geq$ 400	355	57	1.4 (0.9–2.1)	.14
Smoking and alcohol consumption $\parallel\parallel$				
Both no	1455	147	1.0 (referent)	
Both yes	713	118	1.4 (1.0–2.0)	.04
Presence of <i>Helicobacter pylori</i> $\ddagger$				
No	443	35	1.0 (referent)	
Yes	1247	164	1.8 (1.2–2.6)	.003

\*OR = odds ratio; CI = confidence interval.

$\dagger$ Two-sided  $P$  values for number of cigarettes smoked per day, years of smoking, and alcohol consumption are the trend test of ORs. For schooling, income, and presence of *H. pylori*,  $P$  value is from chi-square test.

$\ddagger$ OR adjusted for sex, age, number of cigarettes smoked per day, and baseline histopathology (superficial gastritis or chronic atrophic gastritis versus intestinal metaplasia).

$\S$ OR adjusted for sex, age, alcohol consumption, and baseline histopathology (superficial gastritis or chronic atrophic gastritis versus intestinal metaplasia).

$\parallel$ OR adjusted for sex, age, smoking, and baseline histopathology (superficial gastritis or chronic atrophic gastritis versus intestinal metaplasia).

$\parallel\parallel$ OR adjusted for sex, age, and baseline histopathology (superficial gastritis or chronic atrophic gastritis versus intestinal metaplasia).

**Table 2.** Baseline levels of serum nutrient concentrations (mean ± standard deviation) categorized by 1994 follow-up gastric pathology\*

	Retinol, µg/mL	β-Carotene, † µg/mL	Ascorbic acid, † µg/mL	α-Tocopherol, µg/mL	Ferritin, † µg/mL	Selenium, µg/dL	Zinc, µg/dL	Copper, µg/dL
<i>1989–1990 baseline serum nutrient concentrations</i>								
All subjects	0.54 (0.38–0.70) n = 430	0.28 (0–0.93) n = 425	3.16 (2.15–4.17) n = 366	9.65 (6.78–12.52) n = 430	36.0 (35.01–36.99) n = 431	3.01 (2.05–3.97) n = 434	92.7 (74.13–111.27) n = 434	102.1 (84.26–119.9) n = 387
<i>Micronutrient levels by pathology at follow-up in 1994</i>								
No progression	0.54 (0.37–0.71) n = 368	0.27 (0–0.91) n = 363	3.40 (2.40–4.40) n = 311	9.54 (6.71–12.37) n = 367	36.6 (35.59–37.61) n = 369	2.99 (2.01–3.97) n = 368	92.7 (74.58–110.78) n = 368	101.7 (84.21–119.11) n = 327
Progression to dysplasia ‡	0.54 (0.39–0.68) n = 62	0.31 (0–0.97) n = 62	2.09 (1.15–3.03) n = 55	10.3 (7.21–13.35) n = 63	32.9 (32.00–33.84) n = 62	3.08 (2.21–4.66) n = 66	92.8 (71.70–113.92) n = 66	104.7 (84.67–124.69) n = 60
<i>P</i> §	.70	.11	.0009	.059	.44	.50	.96	.23

\*Values in columns = means (ranges of standard deviations).

†For β-carotene, ascorbic acid, and ferritin, geometric means (ranges of standard deviations) are given.

‡Including progression to gastric cancer.

§Based on two-tailed *t* test comparing those with and without progression to dysplasia.

**Table 3.** Odds ratio for progression to dysplasia or gastric cancer according to serum nutrient tertiles at follow-up

1989 baseline nutrients	1994 follow-up: progression to dysplasia or gastric cancer			<i>P</i> †
	No. with no progression	No. with progression	OR (95% CI)*	
Ascorbic acid, µg/mL				
Low, <1.84	96	24	1.0 (referent)	.006
Medium, 1.84–5.52	97	25	1.0 (0.5–2.0)	
High, >5.52	118	6	0.2 (0.1–0.7)	
Retinol, µg/mL				
Low, <0.6	121	20	1.0 (referent)	.54
Medium, 0.6–1.12	122	21	1.0 (0.5–2.1)	
High, >1.12	125	21	1.3 (0.6–2.7)	
β-Carotene, µg/mL				
Low, <0.21	122	18	1.0 (referent)	.33
Medium, 0.21–0.38	119	22	1.4 (0.7–2.8)	
High, >0.38	122	22	1.4 (0.7–2.9)	
α-Tocopherol, µg/mL				
Low, <8.30	127	14	1.0 (referent)	.07
Medium, 8.30–10.32	119	24	1.9 (0.9–2.8)	
High, >10.32	121	25	2.0 (1.0–4.0)	
Ferritin, µg/mL				
Low, <26.2	116	24	1.0 (referent)	.18
Medium, 26.2–58.0	124	22	0.8 (0.4–1.5)	
High, >58.0	129	16	0.6 (0.3–1.3)	
Selenium, µg/dL				
Low, <2.48	124	18	1.0 (referent)	.16
Medium, 2.48–3.29	120	25	1.7 (0.9–3.4)	
High, >3.29	124	23	1.7 (0.8–3.4)	
Zinc/copper ratio				
Low	107	19	1.0 (referent)	.91
Medium	103	24	1.3 (0.6–2.6)	
High	114	16	1.0 (0.5–2.2)	

\*OR = odds ratio; CI = confidence interval. OR adjusted by sex, age, number of cigarettes smoked per day, and baseline histopathology (coded in model as 0 = superficial gastritis or chronic atrophic gastritis versus 1 = intestinal metaplasia).

†Two-sided *P* values for trend test based on coding for tertiles as 0, 1, or 2.

sis, although the prevalence of *H. pylori* is lower in the subjects with dysplasia or gastric cancer than in those with severe chronic atrophic gastritis (6). While our study provided no information on the age at *H. pylori* acquisition in this population,

we found that the prevalence of *H. pylori* was statistically significantly higher among 3- to 12-year-old children in Linqu County (69%) than among children of similar ages in Cangshan County (29%) (You WC, Zhang L, Pan KF, Gail MH,

Pereza-Pereza G, Blaser MJ, et al.: unpublished data), which suggests that acquisition of *H. pylori* infection in early life is an important initiating event (17). Taken together, our findings linking the presence of *H. pylori* to subsequent risk of gastric cancer (18–20) suggest that eradication of *H. pylori* in subjects with superficial gastritis, chronic atrophic gastritis, or intestinal metaplasia may inhibit disease progression to dysplasia or gastric cancer.

This study was designed to evaluate the association of baseline *H. pylori* status with risk of progression of precancerous gastric lesions. *H. pylori* prevalence was measured only in 1989 and 1994. A study with multiple *H. pylori* measurements between 1989 and 1994 could evaluate repeated *H. pylori* values as risk predictors. In our study, the *H. pylori* prevalence fell from 71.9% in 1989–1990 to 67.1% in 1994. Thus, some individuals who had positive serology at baseline became seronegative. These serum conversions do not change substantially the nearly two-fold increases in risk associated with baseline seropositivity, however.

Our follow-up study also indicated that cigarette smoking is a risk factor for progression to dysplasia or gastric cancer, whereas there was no clear evidence implicating alcohol consumption. Although not all epidemiologic studies of gastric cancer have found an association with cigarette smoking, a preponderance of evidence indicates that the risk of gastric cancer is moderately increased among smokers (21–23). In our case-control study of gastric cancer in Linqu (2), smoking at least one pack of cigarettes

per day increased the risk of gastric cancer by 50%.

In addition, our cohort study revealed an inverse association between serum vitamin C levels and the subsequent risk of progression to dysplasia or gastric cancer. This finding is consistent with the results of our earlier studies of gastric cancer and precursor lesions in Linqu (2,5) as well as studies in other countries (24). In case-control studies in the U.K., plasma ascorbic acid concentrations were statistically significantly lower in patients with intestinal metaplasia than in control subjects (25), whereas gastric juice concentrations of vitamin C were markedly lower in subjects with chronic atrophic gastritis than in subjects with normal gastric mucosa, especially when intestinal metaplasia also was present (26). In Colombia, however, serum vitamin C levels differed only minimally between subjects with chronic atrophic gastritis/intestinal metaplasia or dysplasia and those with normal or superficial gastritis mucosa (27). To our knowledge, the only prospective study that has been reported on the relation of dietary vitamin C intake to gastric cancer ( $n = 26$ ) (24) suggested a protective effect of vitamin C intake after more than 7 years of follow-up. Although deficiencies in vitamin C were observed in the population from Linqu (5), the highest tertile level in our study was close to that reported for the U.S. population (28) based on measurements of serum micronutrients. This finding suggests that vitamin C, or the specific foods that provide this micronutrient, may reduce the risk of dysplasia and gastric cancer.

We were unable to confirm the suggestion from our earlier baseline study (6) that high levels (the top tertile) of serum  $\beta$ -carotene are negatively associated with the prevalence of intestinal metaplasia or dysplasia (6). Although four cohort studies showed an inverse association between serum  $\beta$ -carotene levels and the subsequent risk of gastric cancer, no protective effect was found in two intervention trials [reviewed in (24)]. It is possible that other components of  $\beta$ -carotene-containing food, such as vitamin C, may protect against gastric cancer and its precursors because estimated vitamin C and  $\beta$ -carotene contents in food are highly correlated ( $r = .6$ ;  $P < .01$ ) (2). There was a suggestion of increased risk of progression of precancerous gastric lesions with elevated vitamin E levels, although the association was not statistically significant.

Although vitamin E has been shown to inhibit forestomach carcinogenesis in rats, most epidemiologic studies of gastric cancer, including an intervention trial, have not shown a protective effect of vitamin E (24,25).

Our earlier baseline study (6) noted an inverse association between serum concentrations of ferritin and the prevalence of intestinal metaplasia or dysplasia. Although our cohort study indicated a trend in the same direction, the risks were not statistically significant. In reports from Japan (29) and Hawaii (30), the risk of gastric cancer also was inversely related to prediagnostic serum ferritin levels, but the possible effects of blood loss from gastric lesions, other confounding variables, and limited sample size need to be considered.

A strength of our follow-up study is that the sampling of 14 villages at random from Linqu County ensured a representative population, while the cohort design permitted the study of factors that influence transition rates. Although the availability of baseline histopathology, *H. pylori* status, and serum micronutrient concentrations provided important advantages over previous studies, the fact that fewer than 500 subjects had micronutrient assays limited the power to evaluate specific relationships with dysplasia and gastric cancer and statistical interactions between variables, such as vitamin C and the presence of *H. pylori* (31).

In conclusion, our gastroscopy-based cohort study in Linqu County, an area with a high incidence of gastric cancer, revealed that *H. pylori* infection and cigarette smoking are risk factors for the progression of precursor lesions to dysplasia and gastric cancer, whereas high levels of serum ascorbic acid are protective. In our ongoing randomized, multi-intervention trial in Linqu (32), it will be possible to evaluate whether the eradication of *H. pylori* and/or the use of a supplement that contains vitamins C and E plus selenium will inhibit the progression of precancerous gastric lesions.

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## NOTES

<sup>1</sup>The disinfection procedures in 1989–1990 included soaking the endoscopes and forceps in 2.4% alkaline glutaraldehyde (Cidex; Johnson & Johnson, Arlington TX) in water for 10 minutes. The disinfection procedures in 1994 involved wiping the endoscopes with Cidex, as recommended by an expert panel of Chinese gastroenterologists and approved by Chinese authorities, and soaking the forceps in 2.4% alkaline glutaraldehyde in water for 10 minutes. In 1995, an intervention trial was initiated (32). Approximately two thirds of the trial participants were members of the current study. From 1994 through 1996, an unexpectedly large number of *H. pylori* seroconversions occurred among initially seronegative trial participants; data indicate continuing seroconversions from 1997 through 1999. Possible causes for these seroconversions are under investigation; however, in any case, they could have no effect on the results in this study because the final endoscopy in 1994 for this study took place before those seroconversions. As noted in this report, the prevalence of positive serology decreased from 71.9% at baseline in 1989–1990 to 67.1% in 1994, just before the 1994 endoscopies.

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