Randomized Double-Blind Factorial Trial of Three Treatments To Reduce the Prevalence of Precancerous Gastric Lesions

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Background: **Randomized trials have yielded mixed results on the effects of treatment for *Helicobacter pylori* and little information on the effects of vitamins or garlic supplements on precancerous gastric lesions. We conducted a randomized trial to test the effects of one-time *H. pylori* treatment and long-term vitamin or garlic supplements in reducing the prevalence of advanced precancerous gastric lesions.** ***Methods:*** **Most of the adults aged 35–64 years in 13 randomly selected villages in Linqu County, Shandong Province, China, were identified and given baseline endoscopies in 1994. In 1995, 3365 eligible subjects were randomly assigned in a factorial design to three interventions or placebos: amoxicillin and omeprazole for 2 weeks in 1995 (*H. pylori* treatment); vitamin C, vitamin E, and selenium for 7.3 years (vitamin supplement); and aged garlic extract and steam-distilled garlic oil for 7.3 years (garlic supplement). Subjects underwent endoscopies with biopsies in 1999 and 2003, and the prevalence of precancerous gastric lesions was determined by histopathologic examination of seven standard biopsy sites. The 3365 eligible randomized subjects represented 93.5% of those with baseline endoscopy and included all baseline histologic categories except gastric cancer. Only 0.18% had normal gastric mucosa. Logistic regression was used to estimate the intervention effects on the odds of advanced precancerous gastric lesions, and *t*-tests were used to assess effects on histologic severity. All statistical tests were two-sided.** ***Results: H. pylori*** **treatment resulted in statistically significant decreases in the combined prevalence of severe chronic atrophic gastritis, intestinal metaplasia, dysplasia, or gastric cancer in 1999 (odds ratio [OR] = 0.77; 95% confidence interval [CI] = 0.62 to 0.95) and in 2003 (OR = 0.60; 95% CI = 0.47 to 0.75), and had favorable effects on the average histopathologic severity and on progression and regression of precancerous gastric lesions in 2003. *H. pylori* treatment did not reduce the combined prevalence of dysplasia or gastric cancer. However, fewer subjects receiving *H. pylori* treatment (19/1130; 1.7%) than receiving placebo (27/1128; 2.4%) developed gastric cancer (adjusted *P* = .14). No statistically significant favorable effects were seen for garlic or vitamin supplements.** ***Conclusion: H. pylori*** **treatment reduces the prevalence of precancerous gastric lesions and may reduce gastric cancer incidence, but further data are needed to prove the latter point. Long-term vitamin or garlic supplementation had no beneficial effects on the prevalence of precancerous gastric lesions or on gastric cancer incidence. [J Natl Cancer Inst 2006;98:974–83]**

Gastric cancer is the second leading cause of cancer mortality worldwide *(1)* and accounts for 42% of the cancer deaths in Linqu County, Shandong Province, China *(2)*. The prevalence of precancerous gastric lesions is very high in Linqu County *(3)*, where 67% of adults have antibodies to *Helicobacter pylori (4)*. This bacterium is found in the gastric mucous layer or adherent to the epithelial lining of the stomach and is thought to cause gastric cancer *(5)*. A longitudinal study in Linqu County *(6)* found that the relative risks for subsequent development of gastric cancer were 104 (95% confidence interval [CI] = 9.7 to 999) for subjects with moderate or severe dysplasia, 29 (95% CI = 3.9 to 219) for subjects with mild dysplasia or deep intestinal metaplasia, and 17 (95% CI = 1.5 to 202) for subjects with superficial intestinal metaplasia, all compared with subjects with superficial gastritis or chronic atrophic gastritis. These results, along with histopathologic evidence for the multistep nature of gastric carcinogenesis *(7)*, suggest that interventions that slow the progression of precancerous gastric lesions may reduce the incidence of gastric cancer.

We conducted a randomized, placebo-controlled factorial-design trial of one-time antibiotic treatment for *H. pylori* infection and/or 7.3 years oral supplementation with a vitamin preparation and/or 7.3 years oral supplementation with a garlic preparation to evaluate effects on the prevalence of advanced precancerous gastric lesions. We used the combination of amoxicillin and omeprazole to treat *H. pylori* infection because it had been proven safe and effective in a pilot study *(4)*; this treatment was administered to *H. pylori*–seropositive subjects only. We also evaluated the effect of a supplement consisting of vitamins E and C and selenium because observational data from Linqu County indicated that increasing consumption of fruits and vegetables was associated with a decreasing risk of gastric cancer *(8)* and that a higher serum level of vitamin C was associated with less advanced precancerous gastric lesions *(9)* and less chance of progression of precancerous gastric lesions *(10)*. In addition, an earlier trial in Henan Province, which also has a high incidence of gastric cancer, indicated that a

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mixture of β-carotene, vitamin E, and selenium reduced gastric cancer mortality *(11)*. Finally, we also evaluated the effect of a mixture of aqueous ethanol–aged garlic extract and steam-distilled garlic oil because increased consumption of allium-containing vegetables, especially garlic, has been associated with a decreased risk of gastric cancer in Linqu County *(12)*.

Population and Methods

Study Population

Details of the study design and population have been described previously *(4)*. Briefly, in 1994, a census of 13 randomly selected villages within four townships in Linqu County, Shandong Province, China, identified 4010 residents who were aged 35–64 years. In 1994, 3599 of these residents agreed to undergo a gastroscopy with biopsy and to provide blood for serology to detect *H. pylori* infection at baseline. In the summer of 1995, these individuals were invited to participate in the current trial and provided written informed consent. A total of 3411 subjects who were thought to be eligible were randomly assigned to treatment groups in a stratified factorial design (Fig. 1 and Table 1). Eligibility exclusions before randomization included refusal to provide informed consent, residence outside the study villages, penicillin allergy, missing baseline *H. pylori* serology, ages outside the range of 35–64 years, previous *H. pylori* treatment, previous diagnosis of cancer (except nonmelanoma skin cancer), bleeding disorder, heart failure, emphysema, renal or liver disease, or other life-threatening illness. After randomization, it was determined that 46 subjects were actually ineligible before randomization (two subjects had died, 38 subjects had been diagnosed with gastric cancer, and six subjects had had been diagnosed with another cancer), leaving 3365 subjects available for analysis (Fig. 1 and Table 1). These determinations were made independently of treatment received or outcome; although ineligible, 41 of these 46 subjects received interventions. Follow-up endoscopies with biopsies were performed between March 15, 1999, and May 3, 1999, and between March 16, 2003, and April 24, 2003. This study was approved by the institutional review boards of the Beijing Institute for Cancer Research, the U.S. National Cancer Institute, and Westat, and written informed consent to participate was obtained from each subject. This trial is registered in the U.S. National Cancer Institute PDQ database (trial number NCI-OH-95-C-N029; available at http://www.cancer.gov/clinicaltrials/).

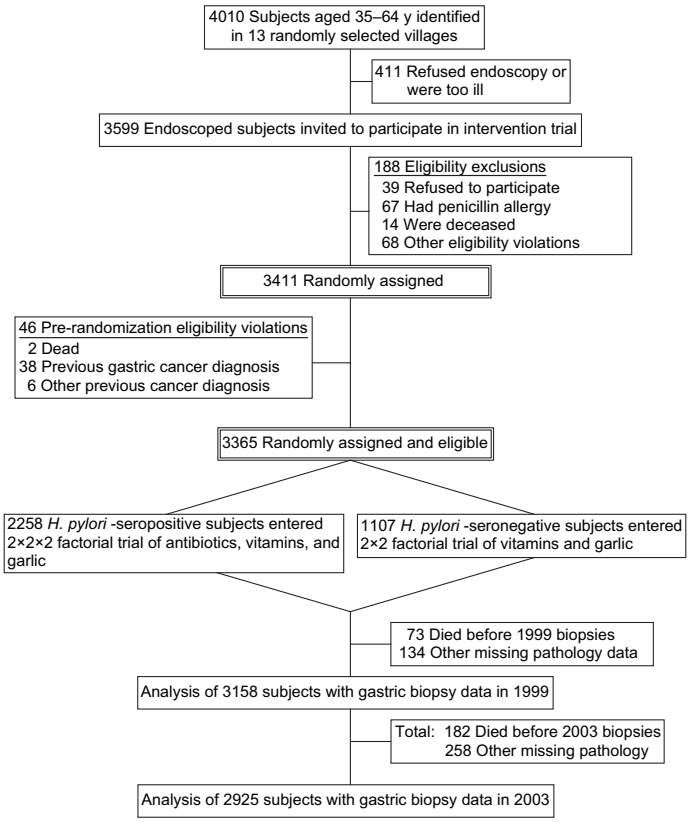

Fig. 1. Participant flow diagram.

Study Design and Randomization

Subjects were stratified on the basis of their *H. pylori* antibody status at baseline in 1994 (*H. pylori*–seropositive versus *H. pylori*–seronegative) *(4)*. *H. pylori*–seropositive subjects were randomly assigned to three interventions (antibiotics and/or garlic supplements and/or vitamin supplements) or their placebos in a 2 × 2 × 2 factorial design (Fig. 1 and Table 1). *H. pylori*–seronegative subjects were randomly assigned to vitamin supplements and/or garlic supplements in a 2 × 2 factorial design; these subjects also received placebo for the initial *H. pylori* treatment to protect blinding (Fig. 1 and Table 1). To ensure treatment balance with respect to sex and age, subjects were ordered by age within four groups defined by sex and by *H. pylori* serostatus in 1994. Among *H. pylori*–seropositive males and *H. pylori*–seropositive females, the ordered subjects were assigned at random, in blocks of eight, to the eight treatment combinations (Table 1), and among *H. pylori*–seronegative males and *H. pylori*–seronegative females, the subjects were assigned at random, in blocks of four, to the four treatment combinations (Table 1). Both the participants and the investigators were masked to treatment assignment *(4)*. Randomized treatment assignments were generated at Westat in the United States after eligibility was determined. Pill bottles bearing codes corresponding to those assignments were then distributed to the study participants in Linqu County.

Treatments

From September 15 to November 29, 1995, eligible *H. pylori*–seropositive subjects were given capsules containing amoxicillin (1 g) and omeprazole (20 mg) ($N = 1130$) or placebo ($N = 1128$) to take twice daily for 2 weeks. The 2-week course of active treatment was offered again to the 382 subjects for whom the initial course of active therapy did not eradicate *H. pylori*, as determined by results of [^{13}C]urea breath tests (CUBT) (which detect the activity of urease, an enzyme produced by *H. pylori*) that were conducted from January to March 1996. To preserve masking, 383 subjects in the placebo group who were matched on village, age, and sex were offered re-treatment with placebo. Vitamins and garlic supplementation began on November 30, 1995, and continued until March 31, 2003, for a total of 7.3 years. The vitamin supplement ($N = 1677$) was a capsule that contained vitamin C (250 mg), vitamin E (100 IU), and selenium from yeast (37.5 μg) or placebo ($N = 1688$); it was to be taken twice daily. (We refer to this combination as "vitamins," even though it included selenium.) The garlic supplement ($N = 1678$) was a capsule that contained 200 mg of aged garlic extract (known as

Table 1. Numbers of randomly assigned and eligible subjects and data on age, sex, and histologic severity by *H. pylori* infection status at baseline in 1994*

Intervention			No. of subjects randomly assigned	Eligible subjects						
							Histologic severity score in 1999 (%)		Histologic severity score in 2003 (%)	
Antibiotics	Garlic	Vitamins		No.	Mean age (y)	Male (%)	≥6	≥3	≥6	≥3
IgG or IgA* H. pylori *seropositive in 1994										
A	A	A	286	283	46.8	49.5	16.0	74.3	34.6	66.7
A	A	P	285	283	46.8	49.1	19.9	75.2	41.1	74.3
A	P	A	286	281	46.7	48.8	17.1	76.4	36.8	72.4
A	P	P	285	283	46.8	50.2	14.5	67.7	30.3	66.1
P	A	A	285	279	46.7	50.2	16.4	75.2	34.4	78.4
P	A	P	286	282	46.8	50.7	13.5	75.6	31.8	75.7
P	P	A	286	283	46.9	50.2	17.3	81.6	38.9	82.1
P	P	P	286	284	47.0	50.0	15.4	79.3	33.3	77.5
IgG and IgA* H. pylori *seronegative in 1994										
P	A	A	282	274	47.6	53.6	10.0	60.4	21.8	51.7
P	A	P	281	277	47.6	54.2	5.70	50.6	23.4	48.1
P	P	A	281	277	47.6	54.2	8.05	57.1	21.7	46.3
P	P	P	282	279	47.7	54.1	10.7	50.2	25.3	47.3
Total			3411	3365	47.1	51.3	13.7	68.7	31.2	65.8

*A severity score of ≥6 corresponds to dysplasia or gastric cancer. A severity score of ≥3 corresponds to severe chronic atrophic gastritis, intestinal metaplasia, dysplasia, or gastric cancer. The mean age, percent male, and percentage of subjects with severity scores were computed among the eligible randomized subjects. A = active intervention; P = corresponding placebo; IgG = immunoglobulin G; IgA = immunoglobulin A.

Kyolic and produced by Wakunaga Pharmaceutical Co., Osaka, Japan) and steam-distilled garlic oil (1 mg) or placebo (N = 1687); two such capsules were to be taken twice daily. Bottles containing the placebo capsules for the garlic supplement contained trace amounts of steam-distilled garlic oil to preserve masking. The placebos are described in detail elsewhere *(4)*.

Gastroscopy and Histopathology

Gastroscopy procedures, including biopsy samples taken at seven standard sites in the stomach, and histopathologic criteria have been described elsewhere *(3,6)*. The gastroenterologists and pathologists were blinded to the subjects' interventions. Quality-control studies were conducted during the trial by Dr. J.-y. Li and by two outside advisors, Drs. P. Correa of Vanderbilt University and P. Sipponen of Helsinki University Central Hospital, to assess agreement among readers and comparability of the Chinese histopathology grading criteria with those of the updated Sydney System (USS) *(13)*. The Chinese criteria, which were used in this study, corresponded to the USS grading system, with the following exceptions: superficial intestinal metaplasia in the Chinese system corresponded to mild intestinal metaplasia in USS, deep intestinal metaplasia to moderate or marked intestinal metaplasia in USS, mild dysplasia to low-grade dysplasia in USS, and severe dysplasia to high-grade dysplasia in USS. Before the trial began, Drs. Li and Correa analyzed 270 baseline biopsy samples. They assigned the same histopathologic classification in 267 cases and differed only as to whether dysplasia was mild or borderline in three cases *(6)*.

Endpoints and Statistical Analysis

At baseline (in 1994) and in 1999 and 2003, each biopsy site was assigned a severity score according to its histopathologic diagnosis in the Chinese system: 0 for normal, 1 for superficial gastritis, 2 for mild/moderate chronic atrophic gastritis, 3 for severe chronic atrophic gastritis, 4 for superficial intestinal metaplasia), 5 for deep intestinal metaplasia, 6 for mild dysplasia, 7 for moderate dysplasia, 8 for severe dysplasia, and 9 for gastric cancer. Each subject was assigned a global severity score in 1999, defined as the highest severity score in any biopsy site in 1999; a global severity score was again assigned in 2003. The global severity score was upgraded to 9 (gastric cancer) if a subject had a diagnosis of gastric cancer that was documented in a cancer abstract that was based on clinical or pathologic data obtained other than at the scheduled endoscopies in 1999 and 2003. A cancer abstract form was filed to document all incident cancers and included diagnostic code, basis of diagnosis, date and place of diagnosis, and location in the stomach if the cancer was a stomach cancer. Hereafter, we refer to the global severity score simply as the severity score. The three endpoints specified in the study protocol for analysis in 1999 and 2003 were 1) prevalence of dysplasia or gastric cancer (i.e., severity score ≥6); 2) prevalence of severe chronic atrophic gastritis, intestinal metaplasia, dysplasia, or gastric cancer (i.e., severity score ≥3); and 3) average severity score.

This study was designed to achieve a statistical power of 0.96 (for the garlic and vitamin interventions) and of 0.88 (for the antibiotic intervention) to detect a 5% decrease in the prevalence of dysplasia or gastric cancer (i.e., the prevalence of a severity score ≥6). Although this trial was not designed to detect an effect on gastric cancer incidence, it nonetheless yielded more information on gastric cancer incidence than all previously published trials of *H. pylori* treatments. We therefore also analyzed gastric cancer incidence. Except for one case, gastric cancer incidence was diagnosed from findings based on endoscopies with biopsies in 1999 and 2003 and from other pre-mortem clinical or pathologic data documented on a cancer abstract. We counted one person with a death abstract indicating gastric cancer but no pre-mortem data on a cancer abstract.

Conditional logistic regression analysis was used to adjust analyses for endpoints 1 and 2 (prevalence of severity score ≥6

and of severity score ≥3, respectively). Our analyses focused on the main effects of the interventions, as is customary for studies with factorial designs. However, we also examined interactions among the interventions. For conditional logistic regression analyses of subjects who were *H. pylori*–seropositive in 1994 (Table 1), we used the following main effects, coded as indicator variables: 1994 histologic severity score (0–2, 3–4, 5, and 6–8), age in 1994 (35–39, 40–44, 45–54, and ≥55), sex, and the three interventions. The categories for severity score (see Table 3) and age were chosen to yield adequate numbers in each group. Subjects who were *H. pylori*–seronegative in 1994 were analyzed in a similar fashion except that the indicator for the amoxicillin/omeprazole intervention was omitted. Other analyses also included interaction terms among the treatment indicators. We performed separate analyses of subjects who were *H. pylori*–seropositive and –seronegative in 1994 and computed the weighted average of the separately estimated treatment main effects (log odds ratio [OR]) with weights inversely proportional to the stratum-specific main-effect variances. After we tested for null treatment effects and computed 95% confidence intervals on the log odds scale, we exponentiated to produce 95% confidence intervals for the odds ratios. To allow the reader to examine the intervention data in detail, we have presented the prevalences of severity scores of 3 or more and of 6 or more in 1999 and 2003 for each of the eight treatment combinations among subjects who were *H. pylori*–seropositive in 1994 and for each of the four treatment combinations among subjects who were *H. pylori*–seronegative in 1994 (Table 1). Categorical distributions were analyzed by omnibus chi-square and stratified Cochran–Armitage–Mantel trend tests. All *P* values are two-sided, and $P<.05$ was considered statistically significant. Intention-to-treat analyses were performed on the 3365 eligible subjects. To examine whether the success and/or the duration of *H. pylori* eradication influenced the histologic severity score in 2003, we used an *F* test for a nonrandomized comparison among *H. pylori*–treated subjects in three groups: CUBT-positive in 1996; CUBT-negative in 1996 and CUBT-positive in 2003; and CUBT-negative in 1996 and in 2003. To analyze data on gastric cancer incidence, we used a stratified Cox proportional hazards model to adjust treatment relative hazards for 1994 histopathology strata and for main effects of age, sex, and other treatments. We could not test the proportional hazards assumptions over time because there were too few incident gastric cancers within strata defined by 1994 histopathology.

Results

Compliance and *H. pylori* Eradication

As previously reported *(14)*, pill counts through February 28, 1999, indicated that approximately 95% of study participants took all of their vitamin and garlic supplements. In addition, analyses of blood samples that were collected on a quarterly basis from randomly selected subjects ($N = 80$) revealed that serum levels of vitamins C and E and of S-allyl cysteine, a marker for garlic supplements, were increased statistically significantly in the active treatment groups compared with the respective placebo groups *(14)*. These compliance patterns continued through March 31, 2003. From November 30, 1995, to May 31, 1996, the vitamin supplement also contained β-carotene (7.5 mg twice daily), which was discontinued after May 31, 1996, because of concerns about possible increased lung cancer risk that were raised by results of other trials *(15,16)*. Garlic and vitamin supplements were not given in June and July 1999, and garlic supplements were not given in September 2002 because of interruptions in the availability of the supplements. Histopathology was available from 95.9% of the living eligible subjects in 1999 and from 91.9% of the living eligible subjects in 2003 (Fig. 1).

The initial treatment with amoxicillin and omeprazole successfully eradicated *H. pylori* infections in 703 (62%) of the 1130 eligible subjects who were *H. pylori*–seropositive at baseline, as determined by CUBT; the combined eradication rate was 73% (827/1130) after re-treatment with amoxicillin and omeprazole. In 2003, 46% of the amoxicillin/omeprazole group remained free of *H. pylori* infection, and 10% of the corresponding placebo group were also free from *H. pylori* infection (as determined by CUBT).

Intervention Effects

From baseline in 1994 to 2003, the percentage of subjects with at least mild dysplasia (i.e., severity score ≥6) more than doubled, regardless of treatment (Table 2). At baseline, there were no statistically significant differences in the distributions of histopathology categories between the active treatments and their respective placebos. However, in 1999 and 2003 the distribution of histopathology categories in the *H. pylori* treatment group differed statistically significantly from that in the placebo group ($P = .009$ and $P = .0001$, respectively) (Table 2). In particular, compared with the placebo arm, the *H. pylori* treatment arm had higher proportions of subjects with mild chronic atrophic gastritis in 1999 and 2003 and with superficial gastritis in 2003. There was correspondingly less deep intestinal metaplasia in the *H. pylori* treatment arm than in the placebo arm in 1999 and 2003. No such differences were seen for the vitamin or garlic treatment arms. Data in Table 2 allow one to gauge the absolute magnitude of intervention effects. For example, in 2003, 69.9% of those treated for *H. pylori* had severity score ≥3, compared to 78.4% in the placebo group. For severity score ≥6, the corresponding results were 35.7% compared to 34.6%.

After adjustment for age, baseline histology, sex, and the other interventions, the odds of the combined endpoint of dysplasia or gastric cancer (severity score ≥6) were not statistically significantly affected by any treatment, either in 1999 or in 2003 (Table 3). *H. pylori* treatment statistically significantly decreased the odds ratio for the second endpoint, an advanced lesion (i.e., severe chronic atrophic gastritis, intestinal metaplasia, dysplasia, or gastric cancer [severity score ≥3]) to 0.77 (95% CI = 0.62 to 0.95) in 1999 and to 0.60 (95% CI = 0.47 to 0.75) in 2003. No statistically significant effects on this endpoint were seen for garlic treatment in 1999 or 2003 or for vitamin treatment in 2003. The odds ratio for a severity score of 3 or higher was transiently increased in 1999 in the active vitamin arm to 1.32 (95% CI = 1.12 to 1.57). We examined interactions among interventions for endpoints 1 and 2 in 1999 and 2003, separately among subjects who were seropositive or seronegative for *H. pylori* in 1994. None of the interactions were consistent or large, and only two of the 16 two-way interactions were nominally statistically significant without adjustment for multiple comparisons (data not shown). Among subjects in the *H. pylori* intervention group, those who received active treatment had statistically significantly lower average severity scores than those who received placebo in 2003 (4.45 versus 4.69; difference = −0.24 [95% CI = −0.40 to −0.09],

Table 2. Distribution of histologic severity score by year and treatment group

Year, treatment group	Normal (0), %	Superficial gastritis (1), %	Mild/moderate chronic atrophic gastritis (2), %*	Severe chronic atrophic gastritis (3), %	Superficial intestinal metaplasia (4), %	Deep intestinal metaplasia (5), %	Mild dysplasia (6), %	>Mild dysplasia (7–9), %†	No. of subjects‡	*P*§
1994 (Baseline)										
H. pylori treatment										
Active	0.09	1.61	33.7	5.27	9.12	35.1	14.0	1.07	1119	
Placebo	0.00	1.25	34.5	4.90	10.1	34.2	14.2	0.98	1123	.89
Vitamins										
Active	0.06	2.52	41.6	4.08	8.71	29.4	13.2	0.48	1665	
Placebo	0.30	2.32	40.7	3.99	8.87	30.1	12.2	1.49	1679	.07
Garlic										
Active	0.12	2.10	41.7	3.84	7.98	30.6	12.5	1.14	1666	
Placebo	0.24	2.74	40.6	4.23	9.59	29.0	12.8	0.83	1678	.45
1999										
H. pylori treatment										
Active	0	0.28	26.4	9.38	7.49	39.6	15.6	1.33	1055	
Placebo	0	0.66	21.4	12.6	6.85	42.8	13.5	2.16	1065	.009
Vitamins										
Active	0	0.57	28.5	12.3	7.50	36.9	12.8	1.33	1574	
Placebo	0	0.75	32.8	10.8	6.91	35.4	12.0	1.32	1591	.25
Garlic										
Active	0	0.89	30.6	10.8	7.56	36.6	12.2	1.40	1574	
Placebo	0	0.44	30.7	12.3	6.85	35.8	12.6	1.26	1591	.54
2003										
H. pylori treatment										
Active	0	3.71	26.4	2.11	1.00	31.1	31.7	4.01	997	
Placebo	0	2.01	19.6	3.51	1.20	39.1	30.8	3.81	997	<.001
Vitamins										
Active	0	4.16	29.4	2.25	1.16	31.5	27.6	3.82	1465	
Placebo	0	5.63	29.2	2.21	1.07	30.8	27.6	3.35	1491	.69
Garlic										
Active	0	4.91	29.1	2.46	1.09	31.2	27.7	3.62	1466	
Placebo	0	4.90	29.6	2.01	1.14	31.2	27.6	3.56	1490	.99

*None of the subjects had moderate chronic atrophic gastritis.

†Includes moderate dysplasia (severity score = 7), severe dysplasia (severity score = 8), and gastric cancer (severity score = 9).

‡The number of subjects for 1994 (3344) is less than 3365 because 21 randomly assigned eligible subjects lacked 1994 histopathologic data. The number of subjects for 1999 (3165) and for 2003 (2956) are slightly greater than the corresponding numbers in Fig. 1 because some gastric cancer diagnoses were not based on the endoscopic and histopathologic examinations in 1999 and 2003, but rather on other documentation of gastric cancer diagnoses.

§The *P* value is based on a chi-square test with degrees of freedom equal to one less than the number of histopathology categories with nonzero sums.

P = .002); the average severity score was not reduced by the garlic or vitamin interventions in 1999 or 2003 (Table 3).

We analyzed the proportions of the study population for whom the severity score had decreased (indicating disease regression), stayed the same (no change in disease), or increased (indicating disease progression) from 1994 to 1999 and from 1994 to 2003 (Table 4). Compared with placebo, active *H. pylori* treatment increased the proportion of subjects with disease regression (17% versus 12%) and decreased the proportion of subjects with disease progression (45% versus 49%) in 2003 (P_{trend} = .006) but not in 1999 (22% versus 21% and 36% versus 36%, respectively; P_{trend} = .63). The garlic intervention had no effect on disease progression or regression from 1994 to either 1999 or 2003. The vitamin intervention had no statistically significant effects on disease progression or regression from 1994 to 2003, but it led to a slight increase in the proportion of subjects with progressing disease in 1999 compared with placebo (38% versus 34%; P_{trend} = .043).

To investigate whether specific types of precancerous gastric lesions were affected by *H. pylori* treatment, we examined changes in the distribution of histopathology categories from 1994 to 1999 and to 2003 (Table 5). Among the subjects who had less than severe chronic atrophic gastritis (severity score 0–2) in 1994, 60.0% of those in the active treatment arm and 47.2% of those in the placebo arm remained in this category in 2003; in 1999, 48.3% of subjects in the active arm and 45.7% of subjects in the placebo arm remained in this category (Table 5). Among the subjects who had severe chronic atrophic gastritis in 1994 (severity score 3), 48.0% of those in the active arm and 25.0% of those in the placebo arm had severe chronic atrophic gastritis or a less severe histopathology (severity score 0–3) in 2003; in 1999, 62.5% of subjects in the active arm and 58.0% of subjects in the placebo arm were in this category. Among the subjects who had intestinal metaplasia in 1994, there was little evidence of favorable treatment-induced shifts in histology in 1999 or 2003 (Table 5). Indeed, of the subjects with intestinal metaplasia in 1994, 49.3% of those receiving the active *H. pylori* treatment and 57.7% of those receiving placebo had intestinal metaplasia or a less severe histopathology (severity score 0–5) in 2003. Among subjects who had dysplasia in 1994, six (4.2%) progressed to gastric cancer with the active *H. pylori* treatment and 10 (6.6%) progressed to gastric cancer with placebo in 2003; the respective numbers were five (3.3%) and six (3.7%) in 1999. *H. pylori* treatment also had greater favorable effects on the average severity score (i.e., the difference between the average severity score on the placebo arm minus that on the active arm was greater) in subgroups with less severe baseline histopathology, including nonsmokers, women, and subjects younger than age 45 (data not shown).

Table 3. Effects of treatment on the odds of dysplasia or gastric cancer (severity score ≥6); the odds of severe chronic atrophic gastritis, intestinal metaplasia, dysplasia, or gastric cancer (severity score ≥3); and the average severity score*

Year, treatment group	Dysplasia or gastric cancer		Severe chronic atrophic gastritis, intestinal metaplasia, dysplasia, or gastric cancer		Average severity score			
	OR (95% CI)	*P*	OR (95% CI)	*P*	Active	Placebo	Difference (95% CI)	*P*†
1999								
H. pylori treatment	1.13 (0.89 to 1.44)	.32	0.77 (0.62 to 0.95)	.016	4.14	4.22	−0.08 (−0.21 to 0.05)	.22
Vitamins	1.10 (0.89 to 1.37)	.39	1.32 (1.12 to 1.57)	.001	3.97	3.87	0.10 (−0.01 to 0.21)	.068
Garlic	0.98 (0.79 to 1.22)	.86	0.99 (0.84 to 1.18)	.94	3.93	3.92	0.01 (−0.10 to 0.12)	.84
2003								
H. pylori treatment	1.07 (0.88 to 1.31)	.49	0.60 (0.47 to 0.75)	<.001	4.45	4.69	−0.24 (−0.40 to −0.09)	.002
Vitamins	1.03 (0.87 to 1.23)	.71	1.14 (0.96 to 1.37)	.14	4.29	4.23	0.06 (−0.08 to 0.20)	.38
Garlic	1.02 (0.86 to 1.21)	.83	1.08 (0.90 to 1.29)	.40	4.26	4.25	0.01 (−0.12 to 0.15)	.83

*We analyzed the 1994 *H. pylori*–seropositive and –seronegative strata separately and computed the weighted average of the separately estimated treatment main effects (log relative odds) with weights inversely proportional to the stratum-specific variances. After we tested for null treatment effects and computed confidence intervals on the logit scale, we exponentiated to produce the tabulated results. Within the *H. pylori*-seropositive stratum, we used the following main effects in a conditional logistic regression analysis: 1994 histologic severity score (0–2, 3–4, 5, and 6–8), age in 1994 (35–39, 40–44, 45–54, and ≥55 years), sex, and the three interventions. The analysis of the *H. pylori*–seronegative stratum was similar except that only the vitamin and garlic interventions were included. OR = odds ratio; CI = confidence interval.

†Two-sided *t* test.

To examine whether the success and/or the duration of *H. pylori* eradication would influence treatment effects on average severity score, we conducted a nonrandomized comparison among *H. pylori*–treated subjects who fell into three categories: CUBT-positive in 1996; CUBT-negative in 1996 and CUBT-positive in 2003; and CUBT-negative in 1996 and in 2003. These three groups had average severity scores in 2003 of 4.71 (95% CI = 3.94 to 4.42), 4.44 (95% CI = 4.24 to 4.64), and 4.18 (95% CI = 4.00 to 4.36), respectively. These average severity scores are ordered as one would expect if successful and durable eradication is more effective than transient eradication in reducing histologic severity. An *F* test indicated that the differences in severity among these three groups was statistically significant (*P* = .0016). Thus, more effective *H. pylori* eradication was associated with a lower average severity score in 2003.

A total of 46 eligible subjects who were *H. pylori*–seropositive in 1994 were diagnosed with gastric cancer by 2003 (Table 6): 19 (1.68%) of 1130 subjects in the active *H. pylori* treatment arm and 27 (2.39%) of 1128 subjects in the placebo arm (*P* = .23). For subjects in each of the 1994 histopathology categories except "missing," those in the active *H. pylori* treatment group had fewer incident gastric cancers than those in the placebo group (Table 6). The unadjusted relative risk of gastric cancer for these subjects, 0.70 (95% CI = 0.39 to 1.27), was similar to the relative hazards for gastric cancer, 0.64 (95% CI = 0.35 to 1.15; *P* = .14), which was determined from a Cox proportional hazards model that was stratified on histopathology in 1994 (severity scores of 0–2, 3–4, 5, and 6–8) and adjusted with main effects for age in 1994 (35–39, 40–44, 45–54, and ≥55 years), sex, and garlic and vitamin treatments. The 58 incident gastric cancers among all eligible subjects were nearly evenly divided between the subjects who were assigned to the vitamin interventions and their placebo control subjects and between those assigned to the garlic interventions and their placebo control subjects (Table 6). The relative hazards for gastric cancer were 1.03 (95% CI = 0.61 to 1.73; *P* = .91) for the vitamin intervention and 1.06 (95% CI = 0.63 to 1.78; *P* = .84) for the garlic intervention. These analyses were stratified into 12 categories defined by 1994 histopathology (severity score 0–2, 3, 4–5, and 6–8) and by the combination of 1994 serology for *H. pylori* with treatment for *H. pylori* (seronegative for *H. pylori*, seropositive for *H. pylori* with amoxicillin/omeprazole treatment, and seropositive for *H. pylori* with placebo for amoxicillin/omeprazole), and adjusted with main effects for age, sex, and either garlic or vitamin treatment.

Table 4. Progression and regression of 1994 histopathology in 1999 and 2003 by treatment

Treatment	1994–1999				1994–2003			
	Regression, *N* (%)	No change, *N* (%)	Progression, *N* (%)	P_{trend}*	Regression, *N* (%)	No change, *N* (%)	Progression, *N* (%)	P_{trend}*
H. pylori treatment								
Active	230 (22)	440 (42)	375 (36)		165 (17)	383 (39)	440 (45)	
Placebo	222 (21)	453 (43)	385 (36)	.63	120 (12)	388 (39)	486 (49)	.006
Vitamins								
Active	305 (20)	669 (43)	590 (38)		210 (14)	630 (43)	619(42)	
Placebo	327 (21)	724 (46)	531 (34)	.043	259 (17)	582 (39)	642 (43)	.40
Garlic								
Active	321 (21)	693 (44)	549 (35)		236 (16)	602 (41)	622 (43)	
Placebo	311 (20)	700 (44)	572 (36)	.46	233 (16)	610 (41)	639 (43)	.78

*Cochran–Armitage–Mantel trend test stratified by sex and age (35–39, 40–44, 45–54, and ≥55 years). Scores for regression, no change, and progression were −1, 0, and 1, respectively.

Table 5. Distribution of histopathology in 1999 and 2003 among subjects who were *H. pylori*–seropositive in 1994 by baseline 1994 histopathology, stratified by active versus placebo *H. pylori* treatment*

H. pylori treatment group, 1994 histopathology†	1999 histopathology (severity scores), No. (%)					2003 histopathology (severity scores), No. (%)				
	<Severe CAG (0–2)	Severe CAG (3)	IM (4–5)	DYS (6–8)	GC (9)	<Severe CAG (0–2)	Severe CAG (3)	IM (4–5)	DYS (6–8)	GC (9)
Active										
<Severe CAG	183 (48.3)	55 (14.5)	122 (32.2)	18 (4.7)	1 (0.3)	221 (60.0)	6 (1.6)	90 (24.5)	50 (13.6)	1 (0.3)
Severe CAG	22 (39.3)	13 (23.2)	14 (25.0)	7 (12.5)	0 (0)	21 (42.0)	3 (6.0)	18 (36.0)	8 (16.0)	0 (0)
IM	64 (13.9)	26 (5.7)	276 (60.1)	90 (19.6)	3 (0.6)	47 (11.0)	7 (1.6)	157 (36.7)	207 (48.4)	10 (2.3)
DYS	10 (6.6)	3 (2.0)	81 (53.6)	52 (34.4)	5 (3.3)	8 (5.6)	4 (2.8)	53 (37.3)	71 (50.0)	6 (4.2)
Placebo										
<Severe CAG	172 (45.7)	76 (20.2)	110 (29.3)	17 (4.5)	1 (0.3)	169 (47.2)	24 (6.7)	113 (31.6)	50 (14.0)	2 (0.6)
Severe CAG	13 (26.0)	16 (32.0)	19 (38.0)	0 (0)	2 (4.0)	9 (18.8)	3 (6.2)	20 (41.7)	14 (29.2)	2 (4.2)
IM	41 (8.7)	32 (6.8)	305 (64.8)	87 (18.5)	6 (1.3)	30 (6.9)	5 (1.1)	217 (49.7)	172 (39.4)	13 (3.0)
DYS	8 (4.9)	10 (6.1)	93 (57.1)	46 (28.2)	6 (3.7)	6 (4.0)	3 (2.0)	51 (33.8)	81 (53.6)	10 (6.6)

*CAG = chronic atrophic gastritis; IM = intestinal metaplasia; DYS = dysplasia; CG = gastric cancer.

†The four histopathology categories in this column correspond to severity scores of 0-2, 3, 4–5, and 6–8 respectively.

We observed no statistically significant differences in the numbers of deaths between any of the active treatment groups and their respective placebo groups. In the *H. pylori* treatment arm, eight subjects died from gastric cancer, 24 from other cancers, and 35 from other causes, compared with 10, 21, and 27 subjects, respectively, in the placebo group. In the vitamin arm, nine subjects died from gastric cancer, 32 from other cancers, and 41 from other causes compared with 12, 30, and 59 subjects, respectively, in the placebo group. In the garlic arm, 12 subjects died from gastric cancer, 31 from other cancers, and 52 from other causes compared with nine, 31, and 48 subjects, respectively, in the placebo group. As previously reported *(4,14)*, apart from rashes seen on the amoxicillin/omeprazole arm, no statistically significant toxicities were noted.

Discussion

The purpose of this trial was to examine whether one-time treatment with amoxicillin/omeprazole or long-term supplementation with vitamin or garlic preparations could impede the development of advanced precancerous gastric lesions in a population with high prevalences of *H. pylori* infection and precancerous gastric lesions and high gastric cancer mortality rates. Despite excellent treatment compliance, there was no evidence that either vitamin or garlic supplements favorably altered the distribution of precancerous gastric lesions or any of the three main endpoints, namely the proportion of subjects with dysplasia or gastric cancer, the proportion of subjects with severe chronic atrophic gastritis, intestinal metaplasia, dysplasia, or gastric cancer, or the average severity score. In addition, there was no evidence that either vitamin or garlic supplements favorably altered the histopathologic progression or regression rates.

In contrast to the negative findings for vitamin and garlic supplements, *H. pylori* treatment at the start of the trial reduced the prevalence of severe chronic atrophic gastritis, intestinal metaplasia, dysplasia, and gastric cancer combined and the average severity score for precancerous gastric lesions and induced more regression and less progression of precancerous gastric lesions than placebo. However, *H. pylori* treatment did not induce statistically significant reductions in the prevalence of dysplasia and gastric cancer combined. The favorable effects on all endpoints were more pronounced at 7.3 years after *H. pylori* treatment than at 3.3 years after treatment. Favorable changes in the distributions of precancerous gastric lesions were found among subjects who had less than severe chronic atrophic gastritis (severity score 0–2), who had severe chronic atrophic gastritis or less severe histopathology (severity score 0–3), and who had dysplasia (severity score 6–8) in 1994, but not among those who had intestinal metaplasia (severity score 4–5) in 1994. The effects of *H. pylori* on the average severity score tended to be greater in subgroups with less severe histopathology at

Table 6. Number of gastric cancers diagnosed through 2003 by 1994 histopathology and treatment group*

Treatment group	No. of subjects diagnosed with GC/total no. of subjects (%) by 1994 histopathology (severity code)					
	Missing	<Severe CAG (0–2)	Severe CAG (3)	IM (4–5)	DYS (6–8)	Total
H. pylori treatment						
Active	1/11 (9.1)	1/396 (0.25)	0/59 (0.0)	10/495 (2.0)	7/169 (4.1)	19/1130 (1.68)
Placebo	0/5 (0.0)	2/401 (0.50)	2/55 (3.6)	13/497 (2.6)	10/170 (5.9)	27/1128 (2.39)
Vitamins						
Active	0/12 (0.0)	3/735 (0.41)	2/68 (2.9)	16/635 (2.5)	8/227 (3.5)	29/1677 (1.73)
Placebo	1/9 (11.1)	2/728 (0.28)	0/67 (0.0)	12/655 (1.8)	14/229 (6.1)	29/1688 (1.72)
Garlic						
Active	1/12 (8.3)	3/732 (0.41)	1/64 (1.6)	15/643 (2.3)	10/227 (4.4)	30/1678 (1.79)
Placebo	0/9 (0.0)	2/731 (0.27)	1/71 (1.4)	13/647 (2.0)	12/229 (5.2)	28/1687 (1.66)

*Gastric cancer was diagnosed if it was found by examination of scheduled biopsies in 1999 or 2003 or if it was detected clinically and documented before May 1, 2003. One cancer was documented only on the death abstract; this subject received active *H. pylori* treatment, active vitamin treatment, and active garlic treatment. CAG = chronic atrophic gastritis; IM = intestinal metaplasia; DYS = dysplasia; GC = gastric cancer.

baseline, including nonsmokers, women, and subjects younger than 45 years.

Five previous randomized trials of *H. pylori* treatment have reported mixed results for precancerous gastric lesions. In a 2 × 2 × 2 factorial trial in Narino, Columbia, of *H. pylori* triple therapy (metronidazole, amoxicillin, and bismuth subsalicylate), vitamin C, and β-carotene, Correa et al. *(17)* found that treatment for 6 years with any combination of the active factors increased the regression rate of precancerous gastric lesions compared with treatment with placebos only. However, our subsequent analysis of data from this trial provided by the authors *(18)* showed that *H. pylori* treatment had no statistically significant main effect on the distribution of histopathology categories, on the odds of developing advanced precancerous gastric lesions, on the average severity score, or on the rates of progression or regression of precancerous gastric lesions. All subjects in this trial were offered *H. pylori* treatment after 6 years on trial *(19)*. Despite the fact that some members of the control group received *H. pylori* treatment after 6 years, an analysis of main effects at 12 years showed that *H. pylori* treatment at baseline statistically significantly reduced the histologic severity of precancerous gastric lesions, whereas treatment with β-carotene or vitamin C did not *(19)*, in agreement with our findings.

A randomized trial from The Netherlands of 231 *H. pylori*–positive subjects with gastroesophageal reflux compared *H. pylori* treatment for 1 week with omeprazole, amoxicillin, and clarithromycin versus treatment with omeprazole alone on changes in gastric histology 2 years later *(20)*. The authors compared subjects in the triple therapy group who were uninfected at the end of the trial with subjects in the omeprazole control group who remained infected at the end of the trial; thus the intention-to-treat principle was not used. These 2-year comparisons indicated statistically significant reductions in inflammation and atrophy but not in intestinal metaplasia in the triple therapy arm compared with omeprazole alone.

Another randomized trial of subjects with CagA-positive strains of *H. pylori* in Mexico *(21)* revealed that those treated with omeprazole, amoxicillin, and clarithromycin had a greater decrease in a severity score (defined as a weighted combination of the numbers of sites with various histopathologies) from 6 weeks to 1 year after treatment than those treated with placebo. However, the treatment effect was not statistically significant in a comparison of changes in histology from baseline to 1 year after treatment, and analyses of the proportions with worsening, stable, or improving histology did not differ statistically significantly between the treated and placebo groups, either from 6 weeks to 1 year after treatment or from baseline to 1 year after treatment.

Sung et al. *(22)* conducted a randomized trial to compare the effects of omeprazole, amoxicillin, and clarithromycin versus placebo on changes in precancerous gastric lesions. Their analyses were restricted to subjects in the active treatment arm who were *H. pylori*–negative 1 year after treatment and to subjects in the placebo arm who remained *H. pylori*–positive 1 year after treatment; thus, the intention-to-treat principle was not used. The authors concluded that the anti-*Helicobacter* therapy did not change either intestinal metaplasia or glandular atrophy. Subsequent 5-year follow-up data from that trial *(23)* indicated improvement in the degree of gastric atrophy and intestinal metaplasia among the subjects who received *H. pylori* therapy.

Wong et al. *(24)* described results of a randomized trial of omeprazole, amoxicillin/clavulanate, and metronidazole versus placebo among subjects in Changle County, Fujian Province, China. In this trial, subjects in the active treatment arm had less progression of gastric atrophy in the antrum and corpus and less progression of intestinal metaplasia in the corpus 5 years after treatment than subjects in the placebo arm.

Thus, the previous randomized controlled trials have yielded mixed results on the effects of *H. pylori* treatment on precancerous gastric lesions. Two of the three previous reports on effects at 5 or more years after treatment only appeared as abstracts *(23,24)*, and the estimated treatment effects in the other report *(19)* were potentially attenuated by treatment of the comparison group after 6 years. Nonetheless, these three studies support the strong evidence from the present trial for the long-term effect of one-time *H. pylori* treatment in reducing the prevalence of advanced precancerous gastric lesions. This result is also supported by several nonrandomized clinical studies that have reported favorable changes in histopathology after successful eradication of *H. pylori* *(25–27)*. Likewise, in our study, more effective *H. pylori* eradication was associated with lower average severity scores.

Although this trial was not designed to detect the effects of treatment on gastric cancer incidence, favorable trends were seen. Considering that three previously published randomized trials of treatment for *H. pylori* reported a total of only 33 gastric cancers, the 46 incident gastric cancers in our study (19 among 1130 subjects in the active *H. pylori* treatment arm and 27 among 1128 subjects in the placebo arm) add substantially to the evidence from randomized trials that *H. pylori* eradication may reduce gastric cancer incidence. Correa et al. *(17–19)* reported three incident gastric cancers among 321 subjects receiving *H. pylori* antibiotic treatment versus two incident gastric cancers among 309 subjects receiving a placebo during the 6 placebo-controlled years of the study. The largest previous study *(28)* reported seven gastric cancers among 817 subjects receiving antibiotic treatment versus 11 cancers among 813 subjects receiving a placebo, whereas the third study *(29)* reported four gastric cancers among 220 subjects receiving antibiotics versus six gastric cancers among 215 subjects receiving a placebo. Pooling the data from all four studies yields ratios of incident gastric cancer cases to populations at risk of 33/2488 or 0.0133 for the active group versus 46/2465 or 0.0187 with a placebo, for a corresponding relative risk of 0.71 (95% CI = 0.45 to 1.11; $P = 0.134$). This combined relative risk is similar to the relative risks reported in the present trial: 0.70 (unadjusted) and 0.64 (adjusted). The estimate of the protective effect of *H. pylori* treatment on gastric cancer incidence from the combined data is suggestive but not statistically significant. Despite similar findings from many observational studies *(5,30–32)*, new randomized studies or additional follow-up of ongoing trials will be required to determine whether *H. pylori* treatment reduces gastric cancer incidence. If such an effect can be shown, additional studies would be needed to evaluate the risks and benefits of programs to screen for and treat *H. pylori* infection in particular geographic regions. In Linqu County, where there was little toxicity to the omeprazole/amoxicillin regimen *(4,14)*, where the prevalence of *H. pylori* is 67%, where nearly half of those treated remained free of *H. pylori* infection for 7.5 years, and where gastric cancer mortality rates are among the highest in the world, it is likely that the benefits would outweigh the risks.

Despite the long duration of and the high compliance with the vitamin intervention, no beneficial effects on the prevalence of precancerous gastric lesions were seen. In fact, the vitamin intervention had transient adverse effects on precancerous gastric lesions at 3.3 years after treatment began, although those effects

disappeared by 7.3 years after treatment began. Correa et al. *(17)* reported favorable effects of vitamin C in combination with other ingredients, but our re-analysis of the 6-year vitamin C data *(18)* did not reveal statistically significant main effects on the odds of dysplasia or gastric cancer combined or on the odds of intestinal metaplasia, dysplasia, or gastric cancer combined; moreover, a subsequent analysis after 12 years of follow-up *(19)* revealed no long-term main effect on histologic severity. We are unaware of any other randomized trial that has evaluated the effect of vitamin C on the prevalence of precancerous gastric lesions. However, data from observational studies have suggested that vitamin C is associated with reduced prevalence of intestinal metaplasia *(9)* and reduced progression to dysplasia or gastric cancer *(10)*. A meta-analysis of randomized trials that examined the effect of vitamin supplements on gastric cancer incidence or mortality found no evidence that either vitamin C in combination with β-carotene and/or vitamin E nor vitamin E alone can prevent gastric cancer *(33)*. In a trial in Henan Province, China *(11)*, a combination of vitamin E, selenium, and β-carotene was associated with reduced gastric cancer mortality, whereas supplementation with a combination of vitamin C and molybdenum was not.

To our knowledge, no other randomized trials of the effect of long-term garlic supplementation on the prevalence of precancerous gastric lesions has been reported. We found no effect for a combination of aged garlic extract with steam-distilled garlic oil. A randomized trial *(34)* in Qixia County, Shandong Province, China, compared the effect of a combination of the garlic-derived organosulfide diallyl trisulfide ("allitridum") and sodium selenite against placebo, each given for 1 month each year for 3 consecutive years. Incident gastric cancers were found in 23 of 2526 subjects given the active intervention, compared with 30 of 2507 subjects receiving a placebo ($P = .32$).

This study has several potential limitations. First, one can question some of the choices made in designing and analyzing this trial, such as the agents and doses studied. For example, other garlic preparations, such as garlic powder or raw or cooked garlic, or other vitamin supplements or doses might have been effective. Second, variability in biopsy sampling and reading of the histopathology may have reduced the power to detect intervention effects of garlic and vitamin supplementation. However, the decisive results for amoxicillin/omeprazole treatment, which were based on smaller samples than the garlic and vitamin comparisons, demonstrate that our methods for histopathologic classification are informative. We might have chosen other ways to combine and analyze the histopathologic data from the various biopsy sites. The present analyses were based on prespecified endpoints set out in the protocol, but further analyses based on other features of the histopathology may be useful.

In summary, we conducted a large, long-term randomized trial that included most of the adults aged 35–64 years in 13 randomly selected villages in Linqu County. One-time *H. pylori* treatment with amoxicillin and omeprazole induced statistically significant reductions in the combined prevalence of severe chronic atrophic gastritis, intestinal metaplasia, dysplasia, or gastric cancer, in histologic severity, and in the progression of precancerous gastric lesions, but not in the combined prevalence of dysplasia or gastric cancer. There were also favorable but non–statistically significant trends in gastric cancer incidence with *H. pylori* treatment. Supplementation for 7.3 years with vitamin or garlic preparations had no such effects. Thus, a safe and simple *H. pylori* treatment retarded the progression of precancerous gastric lesions. We are continuing to follow the study population to obtain information on gastric cancer incidence and cause-specific mortality, and we are offering annual endoscopic examinations to those with moderate or severe dysplasia or any dysplasia in two or more biopsy sites.

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NOTES

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