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BRIEF COMMUNICATION

Fifteen-Year Effects of *Helicobacter pylori*, Garlic, and Vitamin Treatments on Gastric Cancer Incidence and Mortality

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In the Shandong Intervention Trial, 2 weeks of antibiotic treatment for *Helicobacter pylori* reduced the prevalence of precancerous gastric lesions, whereas 7.3 years of oral supplementation with garlic extract and oil (garlic treatment) or vitamin C, vitamin E, and selenium (vitamin treatment) did not. Here we report 14.7-year follow-up for gastric cancer incidence and cause-specific mortality among 3365 randomly assigned subjects in this masked factorial placebo-controlled trial. Conditional logistic regression was used to estimate the odds of gastric cancer incidence, and the Cox proportional hazards model was used to estimate the relative hazard of cause-specific mortality. All statistical tests were two-sided. Gastric cancer was diagnosed in 3.0% of subjects who received *H pylori* treatment and in 4.6% of those who received placebo (odds ratio = 0.61, 95% confidence interval = 0.38 to 0.96, *P* = .032). Gastric cancer deaths occurred among 1.5% of subjects assigned *H pylori* treatment and among 2.1% of those assigned placebo (hazard ratio [HR] of death = 0.67, 95% CI = 0.36 to 1.28). Garlic and vitamin treatments were associated with non-statistically significant reductions in gastric cancer incidence and mortality. Vitamin treatment was associated with statistically significantly fewer deaths from gastric or esophageal cancer, a secondary endpoint (HR = 0.51, 95% CI = 0.30 to 0.87; *P* = .014).

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The Shandong Intervention Trial (clinicaltrials.gov identifier: NCT00339768), which began in Linqu County (Shandong Province, China) in 1995, investigated interventions to reduce the prevalence of advanced precancerous gastric lesions (1). The interventions included a 2-week course of amoxicillin and omeprazole for subjects who were seropositive for *Helicobacter pylori* (*H pylori* treatment) and 7 years of oral supplementation with a mixture of garlic extract and steam-distilled garlic oil (garlic treatment) or with a mixture of vitamin C, vitamin E, and selenium (vitamin treatment). The trial demonstrated that amoxicillin and omeprazole statistically significantly reduced the prevalence and average histological severity of precancerous gastric lesions (1), whereas the garlic and vitamin treatments did not. To evaluate the long-term effects of these interventions on gastric cancer incidence and cause-specific mortality, we extended follow-up from May 1, 2003, to August 1, 2010, for a total follow-up of 14.7 years after antibiotic treatment ended and 7.3 years after garlic and vitamin treatments ended.

The rationale, trial registration, study population, informed consent, design, treatments, masking, and effects of the treatments on histopathology were described previously (1,2) (Supplementary Methods and Results, available online). New written informed consents were obtained for the extended follow-up phase from May 2, 2003, to August 1, 2010. Data from 3365 eligible participants aged 35–64 years at randomization were analyzed both in the original trial report (1) and for the extended follow-up. *Helicobacter pylori*-seropositive subjects were randomly assigned in a 2 × 2 × 2 factorial design to the three treatments or their placebos, and *H pylori*-seronegative subjects were randomly assigned in a 2 × 2 factorial design to vitamin treatments and garlic treatments or their placebos (Supplementary Figure 1, available online).

The endpoints were gastric cancer incidence and cause-specific mortality. Gastric cancer incidence was estimated from two scheduled endoscopies with biopsies of seven standard sites in 1999 and 2003 and from active clinical follow-up, and cause-specific mortality was estimated from active follow-up (Supplementary Methods and Results, available online). Conditional logistic regression was used to estimate the odds of gastric cancer incidence, and Cox regression was used to estimate cause-specific mortality hazard ratios (HRs). Both analyses were stratified on baseline gastric histopathology and adjusted for age, sex, history of ever smoking, and history of alcohol consumption (Supplementary Methods and Results, available online). Schoenfeld residuals did not identify violations of the proportional hazards assumption for treatment main effects, nor did tests for interaction of treatment with time on study. We used intention-to-treat analyses to estimate the main effects of the three treatments. All *P* values are two-sided.

Previous work (1,2) comparing the active treatment arms with their corresponding placebo arms demonstrated similar distributions of age, sex, baseline serologic results for *H pylori*, and baseline histological grade. Pill counts indicated that 99.2% of participants assigned to *H pylori* treatment and 95% of participants assigned to vitamin treatments and to garlic treatments took all of their study medications. Results of ^{13}C-urea breath tests conducted from January to March of 1996 indicated that *H pylori* treatment in 1995 eradicated *H pylori* infections in 74% of serologically positive

participants, and 47% of those given *H pylori* treatment remained breath test negative 7 years later (3).

Three participants were lost to follow-up for vital status, two during the trial and one during extended follow-up, as shown in Supplementary Figure 1 (available online), which also describes the trial design and study population. There were 106 diagnoses of incident gastric cancer, 59 during the trial and 47 during extended follow-up (Table 1). Over the entire study, 55 gastric cancers (52%) were diagnosed from histopathology at screening endoscopy (41 in the trial and 14 in extended follow-up); 47 (44%) were diagnosed from clinical and laboratory data, of which 37 had pathology data; and four (4%) were diagnosed at the time of death with pathology data. Thus, pathological confirmation was available on 96 gastric cancers (90.6%). One patient with gastric stromal tumor was not counted.

Incident gastric cancer was diagnosed in 34 (3.0%) of 1130 subjects who received *H pylori* treatment and in 52 (4.6%) of 1128 subjects who received the placebo for *H pylori* treatment (Table 1), corresponding to an absolute risk reduction of 1.6% (95% confidence interval [CI] = 0.0% to 3.2%). *Helicobacter pylori* treatment yielded a statistically significant reduction in the odds of gastric cancer incidence, both in analyses that were stratified only by baseline histopathology (odds ratio [OR] = 0.61, 95% CI = 0.39 to 0.96, $P = .034$) and in analyses that were additionally adjusted for age, sex, history of ever using alcohol, and history of ever smoking (OR = 0.61, 95% CI = 0.38 to 0.96, $P = .032$) (Table 2). The fully adjusted odds ratios for garlic and vitamin treatments were 0.80 (95% CI = 0.53 to 1.20) and 0.81 (95% CI = 0.54 to 1.22), respectively.

A total of 427 trial participants died, 47 from gastric cancer, as shown in Supplementary Table 1 (available online), which lists cause-specific numbers of deaths. The 47 deaths from gastric cancer constituted 11% of all deaths and 26% of all cancer deaths (gastric cancer, esophageal cancer, or other cancer). There were 22 deaths from esophageal cancer, which constituted 5% of all deaths and 12% of the cancer deaths. A total of 43% of deaths occurred during the trial and 57% occurred during the extended follow-up. A total of 45% of gastric cancer deaths occurred during the trial and 55% occurred during the extended follow-up (Supplementary Table 1, available online).

Table 3 presents the hazard ratios for each treatment for the gastric cancer mortality endpoint and for three secondary mortality endpoints (gastric or esophageal cancer deaths, all cancer deaths, and all deaths). The numbers of deaths differ slightly from those reported in Supplementary Table 1 (available online) because persons with missing 1994 histopathology or covariates were excluded from analyses presented in Table 3. Among those assigned to *H pylori* treatment, 17 (1.5%) of 1130 died of gastric cancer compared with 24 (2.1%) of 1128 on placebo, but neither this difference nor those for the other mortality endpoints was statistically significant. However, the fully adjusted hazard ratio of death from gastric cancer for *H pylori* treatment vs

Table 1. Numbers of incident gastric cancers by treatment group and period*

Treatment	No. of gastric cancers during trial	No. of gastric cancers during extended follow-up	Total number of gastric cancers
Helicobacter pylori treatment active (n = 1130)	19	15	34
H pylori treatment placebo (n = 1128)	28	24	52
Total in *H pylori* arms	47	39	86
Garlic active (n = 1678)	30	19	49
Garlic placebo (n = 1687)	29	28	57
Total in garlic arms	59	47	106
Vitamin active (n = 1677)	29	19	48
Vitamin placebo (n = 1688)	30	28	58
Total in vitamin arms	59	47	106

* Events during the trial included those from the date of random assignment, July 23, 1995, to May 1, 2003. The extended follow-up included events from May 2, 2003, to August 1, 2010. The 28 gastric cancers that were diagnosed during the trial among those on placebo for *H pylori* treatment is one more than was reported earlier (1) because subsequent data identified an additional event. One stromal gastric cancer was not counted. There were 59 gastric cancers diagnosed during the trial, and these fell into active or placebo treatment groups as shown in the second column. Only 47 of these gastric cancers were among the subset of subjects who were randomly assigned to *H pylori* treatment or its placebo. Likewise, 47 gastric cancers were diagnosed during extended follow-up, yielding a total of 106 gastric cancers, of which 86 were assigned to *H pylori* treatment or its placebo.

CONTEXTS AND CAVEATS

Prior knowledge

The Shandong Intervention Trial showed that in a population with elevated rates of gastric cancer, 2 weeks of amoxicillin and omeprazole treatment for *Helicobacter pylori* reduced the prevalence of precancerous gastric lesions, whereas 7.3 years of oral supplementation with garlic extract and oil or vitamin C, vitamin E, and selenium did not.

Study design

An updated analysis of data from 3365 subjects in this randomized trial, with a total follow-up of 14.7 years after antibiotic treatment ended and 7.3 years after garlic and vitamin treatments ended, to evaluate the long-term effects of these interventions on gastric cancer incidence and mortality.

Contribution

Short-term treatment with amoxicillin and omeprazole statistically significantly reduced gastric cancer incidence by 39% during the period extending 14.7 years after *H pylori* treatment. A similar but non-statistically significant reduction was seen for gastric cancer mortality. Neither long-term supplementation with garlic nor with vitamin C, vitamin E, and selenium statistically significantly reduced gastric cancer incidence or mortality.

Implication

These results provide leads for prevention research in populations with elevated rates of gastric cancer.

Limitations

The individual effects of the various components of the vitamin and garlic supplements could not be determined. The results may not generalize to regions with lower incidences of gastric cancer or to non-rural regions. Endoscopic surveillance was conducted during the trial but not routinely in the extended follow-up period.

From the Editors

Table 2. Estimated odds ratios (ORs) and 95% confidence intervals (CIs) for gastric cancer incidence from logistic regression analyses for *Helicobacter pylori* treatment, garlic treatment, and vitamin treatment*

	Adjusted for baseline histology only			Fully adjusted		
Treatment	OR (95% CI)	*P*	No. of gastric cancers	OR (95% CI)	*P*	No. of gastric cancers
H pylori treatment	0.61 (0.39 to 0.96)	.034	85	0.61 (0.38 to 0.96)	.032	84
Garlic	0.83 (0.56 to 1.23)	.36	105	0.80 (0.53 to 1.20)	.28	103
Vitamin	0.85 (0.57 to 1.26)	.41	105	0.81 (0.54 to 1.22)	.32	103

* All models were stratified on baseline histopathology as described in Supplementary Methods (available online). The fully adjusted analyses were also adjusted for age (<40, 40–44, 45–54, ≥55 years), sex, history of ever using alcohol, and history of ever smoking, as described in Supplementary Methods (available online). Each of the age ranges included approximately one-quarter of the population. *Helicobacter pylori* treatment refers to short-term treatment with amoxicillin and omeprazole; Garlic and Vitamin refer to 7.3 years of supplementation with garlic extracts and with a mixture of vitamin C, vitamin E, and selenium, respectively. *P* values are two-sided (Wald test).

placebo (HR of death = 0.67, 95% CI = 0.36 to 1.28) was similar in magnitude to the odds ratio for gastric cancer incidence (OR = 0.61, 95% CI = 0.38 to 0.96). With 39 gastric cancer deaths in the fully adjusted analysis, we had only 24% power to detect a statistically significant hazard ratio of death from gastric cancer of 0.67. *Helicobacter pylori* treatment did not statistically significantly reduce mortality from gastric or esophageal cancer combined (HR of death = 0.87, 95% CI = 0.51 to 1.49).

Garlic treatment was not statistically significantly associated with any of the mortality endpoints (Table 3). Fully adjusted hazard ratios in the garlic treatment vs placebo groups were 0.65 (95% CI = 0.35 to 1.20) for gastric cancer mortality and 0.62 (95% CI = 0.37 to 1.05) for esophageal or gastric cancer mortality. The power to detect a statistically significant relative risk of 0.65 for gastric cancer mortality based on 43 events was 29%.

Vitamin treatment was associated with a nearly statistically significant reduction in gastric cancer mortality (fully adjusted HR = 0.55 with 95% CI = 0.29 to 1.03, *P* = .06). Vitamin treatment was associated with a statistically significant reduction in gastric or esophageal cancer mortality (fully adjusted HR = 0.51 with 95% CI = 0.30 to 0.87, *P* = .014). The corresponding reduction in the unadjusted 15-year percentage of subjects who died of gastric cancer, measured from the date of randomization, July 23, 1995, was 1.8% minus 1.0%, or 0.8% (95% CI = 0.0% to 1.6%), and the corresponding reduction in the unadjusted 15-year percentage of subjects who died of gastric cancer or esophageal cancer was 2.6% minus 1.5%, or 1.1% (95% CI = 0.1% to 2.0%) (Supplementary Table 1, available online). These percentages were obtained by dividing numbers of deaths in the entire study (Supplementary Table 1, available online) by the corresponding population sizes, and 95% confidence intervals were constructed from variance estimates for proportions based on binomial sampling.

We previously reported that amoxicillin and omeprazole reduced the prevalence and average severity of precancerous gastric lesions (1). In this follow-up study, *H pylori* treatment reduced the odds of gastric cancer incidence overall by 39% (OR = 0.61, 95% CI = 0.38 to 0.96, *P* = .032), an effect that was present both during and after the trial; the unadjusted relative incidences were 0.68 (95% CI = 0.39 to 1.21) during the trial and 0.62 (95% CI = 0.34 to 1.19) thereafter. Our data provide the first evidence from a single trial that *H pylori*

Table 3. Estimated hazard ratios (HRs) of death and 95% confidence intervals (CIs) for *Helicobacter pylori* treatment, garlic treatment, and vitamin treatment*

	Adjusted for baseline histology only			Fully adjusted		
Treatment, cause of death	HR (95% CI)	*P*	No. of deaths	HR (95% CI)	*P*	No. of deaths
H pylori treatment						
Gastric cancer	0.66 (0.35 to 1.25)	.20	40	0.67 (0.36 to 1.28)	.22	39
Esophageal or gastric cancer	0.90 (0.54 to 1.50)	.69	59	0.87 (0.51 to 1.49)	.61	53
All cancer	0.99 (0.71 to 1.38)	.95	137	0.97 (0.68 to 1.39)	.89	121
All deaths	1.11 (0.89 to 1.40)	.36	294	1.14 (0.90 to 1.46)	.28	262
Garlic						
Gastric cancer	0.73 (0.40 to 1.32)	.30	45	0.65 (0.35 to 1.20)	.17	43
Esophageal or gastric cancer	0.72 (0.44 to 1.16)	.18	67	0.62 (0.37 to 1.05)	.07	60
All cancer	0.93 (0.70 to 1.25)	.64	179	0.87 (0.64 to 1.19)	.38	158
All deaths	0.98 (0.81 to 1.19)	.85	421	0.92 (0.75 to 1.12)	.40	374
Vitamin						
Gastric cancer	0.61 (0.34 to 1.12)	.11	45	0.55 (0.29 to 1.03)	.06	43
Esophageal or gastric cancer	0.60 (0.37 to 0.99)	.043	67	0.51 (0.30 to 0.87)	.014	60
All cancer	0.96 (0.71 to 1.28)	.76	179	0.90 (0.66 to 1.23)	.52	158
All deaths	0.88 (0.73 to 1.07)	.21	421	0.90 (0.73 to 1.10)	.31	374

* Estimates were from proportional hazards regression models on the scale of time since random assignment. All models were stratified on baseline histopathology, as described in Supplementary Methods (available online). Fully adjusted analyses were also adjusted for age (<40, 40–44, 45–54, ≥55 years), sex, history of ever using alcohol, and history of ever smoking, as described in Supplementary Methods (available online). Each of the age ranges included approximately one-quarter of the population. *Helicobacter pylori* treatment refers to short-term treatment with amoxicillin and omeprazole; Garlic and Vitamin refer to 7.3 years of supplementation with garlic extracts and with a mixture of vitamin C, vitamin E, and selenium, respectively. *P* values are two-sided (Wald test).

treatment reduces gastric cancer incidence. When we combined our data with those from other randomized trials examining the effects of *H pylori* treatment on gastric cancer incidence (Supplementary Table 2, available online), the estimated combined-study odds ratio for gastric cancer incidence was 0.66 (95% CI = 0.46 to 0.95, $P = .027$), which is similar in magnitude to the fully adjusted hazard ratio of death from gastric cancer for *H pylori* treatment vs placebo in this study of 0.67 (95% CI = 0.36 to 1.28). However, the association with death was not statistically significant ($P = .22$), possibly because of low statistical power.

Further research is needed to assess the public health potential for antibiotic-based prevention of gastric cancer. Such research is needed to evaluate the feasibility and duration of effectiveness of *H pylori* eradication programs and the balance of favorable and unfavorable effects of *H pylori* eradication. The potential benefits are considerable in a region such as Linqu County, where a 33% reduction in gastric cancer mortality from *H pylori* treatment (Table 3) would, in the absence of other effects, translate into a reduction in total cancer mortality of 12% and an overall mortality reduction of 6% in *H pylori*-seropositive people. These calculations are based on the data for cause-specific mortality among *H pylori*-seropositive people who were given placebo for *H pylori* treatment (Supplementary Table 1, available online). However, the observed the hazard ratio of death from any cancer among those who did vs did not receive antibiotic therapy for *H pylori* was 0.97 (95% CI = 0.68 to 1.39) (Table 3), partly due to a non-statistically significant excess of esophageal cancer deaths among those who received *H pylori* treatment (Supplementary Table 1, available online). In other geographical regions, the risk of esophageal adenocarcinoma is lower among persons with *H pylori* infection than in those without infection (4), raising the possibility that eradication of *H pylori* may both decrease the risk of gastric cancer and increase the risk of esophageal adenocarcinoma. Thus, more work is needed to evaluate the entire spectrum of effects of *H pylori* treatment. Moreover, *H pylori* eradication programs may not be feasible or advantageous in regions where *H pylori* is less prevalent, where more complex treatments are required to eradicate *H pylori*, where *H pylori* eradication does not persist, or where susceptibility to esophageal adenocarcinoma is high.

Compared with subjects assigned to placebo, subjects assigned to vitamin treatment had lower risks of dying from gastric cancer (fully adjusted HR = 0.55, 95% CI = 0.29 to 1.03, $P = .06$) and from gastric or esophageal cancer (fully adjusted HR = 0.51, 95% CI = 0.30 to 0.87, $P = .014$) (Table 3). This finding was surprising because vitamins did not reduce the prevalence or severity of precancerous gastric lesions after 7.3 years of supplementation (1) and hardly reduced gastric cancer incidence during the trial (Table 1). Moreover, the overall reduction in gastric cancer incidence was not statistically significant (fully adjusted OR = 0.81, 95% CI = 0.54 to 1.22, $P = .32$). Data in Supplementary Table 1 (available online) suggest that vitamin treatment reduced mortality for gastric cancer during the trial, when there was little effect on gastric cancer incidence, and during extended follow-up, raising the possibility that vitamins lower the rate of mortality after the onset of gastric cancers.

Previous studies have examined the effects of vitamin supplements on gastric cancer incidence and mortality. An intervention trial in Linxian County (Henan Province, China) demonstrated that a mixture of vitamin E, β-carotene, and selenium was associated with a 21% (95% CI = 1% to 36%) reduction in gastric cancer mortality after 5 years (5) and with an 11% (95% CI = 0% to 21%) reduction after 16 years (6). There was no convincing evidence of an effect on esophageal cancer mortality. A systematic literature review of randomized intervention studies yielded no evidence of protective effects of vitamin E, β-carotene, or combinations that included vitamin C on gastric cancer incidence (7). However, the combined data from five randomized studies of selenium supplements yielded non-statistically significant reductions in the risk of gastric cancer incidence compared with the incidence without selenium supplements (relative risk = 0.76, 95% CI = 0.44 to 1.31) (7). In Linqu County, the mean serum levels of vitamin C and selenium (8) were well below reference ranges (9), and diets changed little during the Shandong Intervention Trial (10). Thus, the reductions in gastric cancer mortality and in gastric or esophageal cancer mortality associated with vitamins in the Shandong Intervention Trial may not generalize to regions with higher dietary intakes of vitamin C and selenium.

The strengths of this study include its randomized factorial design, high compliance to treatments, blinded assessment of pathology and endoscopy data, long duration, and high completeness of follow-up. The trial also had certain limitations. The trial design does not allow one to separate out the effects of the various components of the vitamin and garlic supplements. Because the trial was conducted in a rural region with a high incidence of gastric cancer, its conclusions may not generalize to regions with lower incidences of gastric cancer or to non-rural regions. Because endoscopic surveillance was conducted during the trial but not routinely in the extended follow-up period, some endoscopically detectable incident gastric cancers would not have been diagnosed during extended follow-up. One would not expect such underascertainment to bias the estimated odds ratios associated with treatments, however. Statistical significance levels for secondary endpoints (gastric or esophageal cancer deaths, all cancer deaths, and all deaths) were not adjusted for multiple comparisons; thus, findings such as the preventive effect of vitamin supplements on gastric or esophageal cancer mortality rates need to be confirmed.

In summary, short-term treatment with amoxicillin and omeprazole statistically significantly reduced the incidence of gastric cancer by 39% during the period extending 15.0 years after randomization and 14.7 years after *H pylori* treatment in the Shandong Intervention Trial, and similar, but non-statistically significant, reductions were seen for gastric cancer mortality. Long-term supplementation with a mixture of vitamin C, vitamin E, and selenium was also statistically significantly associated with reduced mortality from gastric cancer and esophageal cancer combined, which was a secondary endpoint. Garlic and vitamin supplements were associated with non-statistically significant reductions in gastric cancer incidence and gastric cancer mortality. These results offer compelling leads for prevention research in populations with elevated rates of gastric cancer.

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Notes

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