Helicobacter pylori Eradication to Prevent Gastric Cancer in a High-Risk Region of China
A Randomized Controlled Trial

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Context Although chronic Helicobacter pylori infection is associated with gastric cancer, the effect of H pylori treatment on prevention of gastric cancer development in chronic carriers is unknown.

Objective To determine whether treatment of H pylori infection reduces the incidence of gastric cancer.

Design, Setting, and Participants Prospective, randomized, placebo-controlled, population-based primary prevention study of 1630 healthy carriers of H pylori infection from Fujian Province, China, recruited in July 1994 and followed up until January 2002. A total of 988 participants did not have precancerous lesions (gastric atrophy, intestinal metaplasia, or gastric dysplasia) on study entry.

Intervention Patients were randomly assigned to receive H pylori eradication treatment: a 2-week course of omeprazole, 20 mg, a combination product of amoxicillin and clavulanate potassium, 750 mg, and metronidazole, 400 mg, all twice daily (n=817); or placebo (n=813).

Main Outcome Measures The primary outcome measure was incidence of gastric cancer during follow-up, compared between H pylori eradication and placebo groups. The secondary outcome measure was incidence of gastric cancer in patients with or without precancerous lesions, compared between the 2 groups.

Results Among the 18 new cases of gastric cancers that developed, no overall reduction was observed in participants who received H pylori eradication treatment (n=7) compared with those who did not (n=11) (P=.33). In a subgroup of patients with no precancerous lesions on presentation, no patient developed gastric cancer during a follow-up of 7.5 years after H pylori eradication treatment compared with those who received placebo (0 vs 6; P=.02). Smoking (hazard ratio [HR], 6.2; 95% confidence interval [CI], 2.3-16.5; P<.001) and older age (HR, 1.10; 95% CI, 1.05-1.15; P<.001) were independent risk factors for the development of gastric cancer in this cohort.

Conclusions We found that the incidence of gastric cancer development at the population level was similar between participants receiving H pylori eradication treatment and those receiving placebo during a period of 7.5 years in a high-risk region of China. In the subgroup of H pylori carriers without precancerous lesions, eradication of H pylori significantly decreased the development of gastric cancer. Further studies to investigate the role of H pylori eradication in participants with precancerous lesions are warranted.


See also p 244 and Patient Page.
This report presents the follow-up re-
reduce the incidence of gastric cancer.
the relative, randomized, placebo-controlled,
risk population in China would re-
tive, randomized, placebo-controlled,
whether this is the first prospec-
tory, randomized, placebo-controlled,
population-based study to determine
whether H pylori eradication in a high-
reduce the incidence of gastric cancer.
This report presents the follow-up re-
METHODS
Participants
The study was conducted in Changle
County, Fujian Province, in southern
China, which had a standardized mor-
tality rate of gastric cancer in men of
153 per 100000 in 1988.13 In July 1994,
a total of 2423 healthy persons were re-
cruited through local health organiza-
tions under the Changle Public Health
Bureau from 7 villages. Exclusion cri-
teria included age younger than 35 years
or older than 65 years, severe concomi-
tant illness (eg, cardiac, respiratory, he-
patic, or renal insufficiency), and his-
tory of H pylori eradication treatment.
Each person received a physical ex-
amination, a detailed dietary and life-
style questionnaire, phlebotomy, and
upper endoscopy. Serum samples were
tested for anti–H pylori antibody and
anti-CagA antibody. The results of the
serology studies have been reported
elsewhere.14 Patients with proven en-
doscopic ulcers were excluded be-
cause they had a definite indication for
H pylori treatment. Part of the screen-
ing program was reported previ-
ously.13

Sample Size
The 7-year incidence rate of gastric can-
cer in the general population, without
reference to H pylori infection, based on
the age-specific incidence rate in Changle
during 1988-1991 was estimated as 0.99%.13
Among persons with H pylori infection, the odds of gastric
cancer development was increased by
2- to 4-fold.12,14 Taking an estimate of a
3-fold increase, the incidence rate of
gastric cancer in the placebo group of
H pylori carriers for 7 years was esti-
rated as 0.99% × 3 = 3%. Assuming a
reduction in the 7-year incidence rate of
gastric cancer after treatment from
3% to 0.99%, we needed to have 774
H pylori–positive participants in each
group to have a power of 80% by log-
rank test to detect a difference at an
α = .05 level of significance. Assuming
the prevalence of H pylori in the gen-
eral population is approximately 70%
in Changle and a 5% default rate, ap-
proximately 2329 persons would need to
be screened.

As a secondary outcome measure, a
post hoc analysis of gastric cancer de-
velopment was performed in partici-
pants with precancerous lesions and
participants with no precancerous le-
sions.

Endoscopic Screening
and Diagnosis of H pylori
Upper endoscopies were performed by
10 gastroenterologists using fiberop-
tic and video endoscopes (Olympus
Hong Kong Ltd and Pentax Hong Kong/
Asahi Optical [International] Ltd, Hon-
kong, China). During endoscopy, 3 an-
tral biopsy specimens (1 from the
greater and 2 from lesser curvatures 2-3
cm from the pylorus), 1 incisura bi-
opsy specimen, and 1 corpus biopsy
specimen (greater curvature at the mid
corpus) were taken. One antral biopsy
specimen was used for a rapid urease
test and the rest for histologic exami-
nation and H pylori status by hema-
toxylin-eosin stain and Warthin-
Starry silver stain. Additional biopsy
specimens were taken from patients
with gastric ulcer, suspected cancer, or
other significant pathologic findings.
Specimens were read by a single ex-
perienced pathologist (R.E.F.) who was
blinded to all clinical information,
including the rapid urease test results.
The definition of H pylori infection re-
quired both rapid urease test and his-
tologic test results to be positive.
Equivocal and negative cases were ex-
cluded. This approach has been vali-
dated in our center with an accuracy of
100%.16

Randomization and Follow-up
Patients with normal endoscopy results
and H pylori infection (n=1630) were
randomized to receive a 2-week course
of omeprazole, 20 mg (AstraZeneca,
Wilmington, Del), a combination prod-
uct of amoxicillin and clavulanate po-
tassium, 750 mg (GlaxoSmithKline, Re-
search Triangle Park, NC), and
metronidazole, 400 mg, all twice daily
(n=817); or placebo (n=813). Random-
ization was performed by drawing a
sealed envelope that contained a preas-
signed random treatment generated by
computer. All participants returned at
week 4, and unused tablets were counted.
Participants who had been random-
ized to receive triple therapy were in-
vited to receive a carbon 13 urea breath
test (13C-UBT) 6 weeks after treat-
ment by a standardized protocol.
Briefly, participants fasted for 4 hours
before the test. No test meal was given,
and a predose breath sample was ob-
tained. A total of 75 mg of 13C-urea
powder dissolved in 50 mL of water was
given orally. The second breath sample
was collected after 30 minutes. The
cutoff value used was 5%. All partici-
pants were kept in a sitting position
during the entire testing period. Col-
lected samples were analyzed by a pur-
pose-built isotope ratio mass spectrom-
ter. This protocol has been validated
in our center with a sensitivity of 96.5%
and specificity of 97.7%.17

Participants in whom eradication
treatment failed were invited to re-
ceive quadruple therapy, which con-
sisted of colloidal bismuth subcitrate, 240 mg, metronidazole, 600 mg, clarithromycin, 500 mg, and omeprazole, 20 mg, all twice daily for 1 week. The $^{13}\text{C}$-UBT was performed again 6 weeks after the second-line treatment period. Regardless of treatment results, all participants were then prospectively followed up every 6 months by a local clinical team blinded to the treatment type of the participants. Participants received biannual $^{13}\text{C}$-UBTs for H pylori status.

Five years after the first endoscopy, all randomized participants were invited to receive additional endoscopic examinations. Biopsy specimens were taken from the same sites as at the first endoscopy, and additional biopsy specimens were taken for patients with significant pathologic findings. Upper endoscopies were performed again in participants with persistent epigastric symptoms or presence of symptoms such as weight loss, anemia, dysphagia, and abdominal mass. During all endoscopic follow-up, the endoscopists were blinded to the treatment of the participants.

Histologic Assessment

The approach, methods, and assessment were designed by a team of 3 senior pathologists (S.T.X., S.Y.L., and J.H.). Biopsy samples were fixed in 10% buffered formalin, dehydrated, and paraffin embedded. At embedding, tissues were oriented on edge, positioning the mucosal plane perpendicular to the cutting surface. Histologic assessment was performed by a single histopathologist (R.E.F.) who was blinded to the treatment and any clinical information related to the patients. Random selection of cases for validation of histopathologic diagnosis was performed by the team of senior pathologists. Biopsy specimens were graded for the following variables using the modified Sydney classification (Houston): H pylori density, intensity of acute (polymorphonuclear) infiltrates, intensity of chronic (lymphoplasmacytic) infiltration, gastric atrophy, and intestinal metaplasia. Intestinal metaplasia was recognized by the presence of goblet cells and absorptive cells by hematoxylin-eosin stain and periodic acid–Schiff Alcian blue. Gastric atrophy was defined as loss of glandular tissue and fibrous replacement of the laminar propria. When metaplastic epithelium replaced the specialized epithelium (either intestinal metaplasia or pseudopyloric metaplasia) of the mucous glands in the antrum or oxyntic glands in the corpus, atrophy was considered to be present. Dysplasia was defined by the presence of cytological atypia and architectural derangement independent of the degree of inflammation.

Each participant was given a histologic diagnosis that represented the most advanced grade seen at different sites of biopsy in the following descending order: cancer, dysplasia, intestinal metaplasia, nonmetaplastic gastric atrophy, and chronic nonatrophic gastritis. The presence of gastric atrophy, intestinal metaplasia, or dysplasia was classified as precancerous lesions.

Evaluation of the Diagnosis of Cancer

All gastric cancers were diagnosed either before the scheduled follow-up endoscopy in 1999 or during clinical follow-up of the patients. All initial reports of gastric cancer were submitted to the coordinating center in Hong Kong for review. Clinical records and pathology specimens were retrieved if available and reviewed by 2 gastroenterologists (W.M.W. and K.C.L.) and 1 pathologist (R.E.F.) who were blinded to the treatment of the patients. A positive diagnosis of gastric cancer was considered confirmed when the review process was completed.

Blinding

Blinding was done at 4 levels. First, endoscopists who performed the first and second endoscopies were blinded to the treatment of the participants. Second, the local clinical team who followed up the participants was blinded to treatment. Third, pathologists who performed the histopathologic examination of the biopsy specimens were blinded to treatment. Fourth, the clinical team in Hong Kong, who reviewed the records of patients with gastric cancer, was blinded to the treatment of the patients.

Outcome Measures

The primary outcome measure was the incidence of gastric cancer during follow-up, compared between the H pylori eradication treatment and placebo groups. The secondary outcome measure was the incidence of gastric cancer in patients with or without precancerous lesions, compared between the 2 groups.

Statistical Analysis

Demographic data of the 2 groups were compared by the Fisher exact test or Wilcoxon rank sum test where appropriate. The cumulative incidences of gastric cancer in the 2 groups were calculated using the Kaplan-Meier method, with comparison between groups performed using the log-rank test. The same method was used to compare the cumulative incidences of gastric cancer between participants with positive and negative final H pylori status (at 7.5-year follow-up or last available H pylori status for patients lost to follow-up or patients with cancer). Risk factors of gastric cancer were examined by Cox regression analysis. All statistical calculations were performed with SAS statistical software, version 8.2 (SAS Institute Inc, Cary, NC). A 2-tailed $P < .05$ was considered statistically significant.

RESULTS

Baseline Demographic Data

After endoscopic examination of 2423 participants, 373 participants (15.4%) with macroscopic lesions and 420 participants (17.3%) who tested negative for H pylori were excluded (FIGURE 1). Of the remaining 1630 participants with no endoscopic lesions who were positive for H pylori infection, 817 were randomized to the treatment group and 813 to the placebo group. The treatment group, when compared with the

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placebo group, had more alcohol users (P = .048), fewer participants with frequent intake of fish sauce (P < .001), and more participants with frequent intake of fruit (P = .03) (Table 1). Overall, 62% of the study participants had no precancerous lesions (gastric atrophy, intestinal metaplasia, or dysplasia); this variable was comparable between the 2 treatment groups (60% and 63% in the treatment and placebo groups, respectively; P = .28) (Table 1). No specific treatment was given to patients with gastric dysplasia. Baseline demographics in participants with or without precancerous lesions were analyzed in relation to treatment groups (data not shown). The only significant difference was a less frequent intake of fish sauce in the treatment group compared with the placebo group in participants without precancerous lesions (P < .001).

**Helicobacter pylori** eradication after first-line treatment was successful in 624 (76.4%) of 817. For the patients in whom first-line treatment failed, 85 agreed to receive the second-line treatment, and successful eradication was documented in 60 patients. The overall eradication rate in the treatment group was 83.7%. One thousand eleven patients (62%) participated in the endoscopic surveillance in 1999. Those who refused the endoscopic examination were followed up every 6 months by the local clinical team. Endoscopic examination was repeated if necessary.

**Effect of Eradicating H pylori on Gastric Cancer Development**

Incidence of gastric cancer, compared between the **H pylori** eradication treatment group and the placebo group, was the primary outcome measure. Through December 31, 2001, 18 participants (1.1%) were reported as new cases of gastric cancer (147.2 per 100 000 person-years), including 7 (0.86%) in the treatment group and 11 (1.35%) in the placebo group. Five cases (all in the placebo group) were diagnosed before the endoscopic surveillance in 1999, and these 6 patients were relatively asymptomatic during the second endoscopy. Seven more cases of gastric cancer were diagnosed after the endoscopic surveillance in 1999 (2 in the treatment group and 5 in the placebo group). For the 5 placebo-group patients with cancer detected after 5 years, 1 refused endoscopic examination in 1999 and 4 participated in the endoscopic surveillance in 1999, in which 2 had chronic gastritis, 1 had gastric atrophy, and 1 had intestinal metaplasia. Among the 2 patients in the treatment group, 1 refused endoscopic examination in 1999 and 1 had intestinal metaplasia found during the endoscopic surveillance in 1999. Cumulative incidence of gastric cancer was not significantly different between the treatment and placebo groups (P = .33 by log-rank test) (Figure 2). In the Cox regression analysis, variables that were significantly different at baseline in the treatment and placebo groups, including alcohol use, frequent intake of fish sauce, and regular intake of fruit, did not show any effects on gastric cancer development (Table 2). Smoking (hazard ratio [HR], 6.2; 95% confidence interval [CI], 2.3-16.5; P < .001) and older age (HR per 1-year increment, 1.10; 95% CI, 1.05-1.15; P < .001) significantly increased the risk of developing gastric cancer (Table 2).

Among the 18 new cases of gastric cancer, 6 developed in participants without precancerous lesions, whereas the remaining 12 developed in participants with existing precancerous lesions (7 in the eradication treatment group and 5 in the placebo group) (Table 3). All except 1 were found in

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**Figure 1. Flow of Study Participants**

- 2423 Individuals Assessed for Eligibility
- 793 Excluded
  - 373 Had Macroscopic Lesions on Upper Endoscopy
  - 137 Duodenal Ulcer
  - 82 Gastric Ulcer
  - 22 Gastric Carcinoma
  - 132 Other
  - 48 Gastric Erosion
  - 12 Duodenal Erosion
  - 17 Gastric Polyp
  - 5 Coexisting Gastric and Duodenal Ulcer
  - 48 Postgastrectomy
  - 2 Carcinoma of Esophagus
- 420 Had Negative Test Result for **H pylori** and Normal Upper Endoscopy
- 1630 Randomized
- 817 Assigned to Receive Active Treatment
- 813 Assigned to Receive Placebo
- 19 Died
  - 10 Deaths Due to Cancers Other Than Gastric Cancer
  - 9 Noncancer Causes
- 63 Lost to Follow-up
- 26 Withdrew
- 37 Moved
- 735 Followed up at 7.5 Years
- 817 Included in Primary Analysis
- 17 Died
  - 8 Deaths Due to Cancers Other Than Gastric Cancer
  - 9 Noncancer Causes
- 93 Lost to Follow-up
- 16 Withdrew
- 77 Moved
- 703 Followed up at 7.5 Years
- 813 Included in Primary Analysis

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the distal aspect of the stomach and were adenocarcinomas. In participants for whom full surgical specimens were available, all of the lesions were intestinal. In the remaining 9 participants, surgery was never performed, only endoscopic biopsy specimens were available for diagnosis of cancer, and histologic subtyping could not be reliably performed. Up to December 31, 2001, 9 patients had died of gastric malignancy (3 in the treatment group and 6 in the placebo group) after a median follow-up of 11 months (range, 2.3-25 months).

**Post Hoc Analysis**

In participants without precancerous lesions, active treatment of *H pylori* caused a significant reduction in incidence of gastric cancer compared with placebo, by Kaplan-Meier analysis (P = .02 by log-rank test). Cumulative gastric cancer incidence in the 2 treatment subgroups is shown in **FIGURE 3**. The incidence in the treatment and placebo groups was identical for the first 34 months. The incidence in the placebo group increased rapidly after a follow-up of only 72 months. For participants with precancerous lesions on presentation, eradication of *H pylori* had no effect on the incidence of gastric cancer (P = .67 by log-rank test).

**Effect of Final *H pylori* Status on Incidence of Gastric Cancer**

Final *H pylori* status (at 7.5-year follow-up or last available *H pylori* status for patients lost to follow-up or patients with cancer) was available for 1332 participants (81.7%). In the treatment and placebo groups, 625 (82.5%) of 758 and 47 (8.2%) of 574 participants tested negative for *H pylori* infection, respectively (P < .001). No significant difference in overall cumulative gastric cancer incidence was found between patients with positive and negative final *H pylori* status (P = .06). However, for patients with no precancerous lesions on presentation, the cumulative gastric cancer incidence was significantly higher in *H pylori*-positive participants when analyzed according to their final *H pylori* status (P = .01 by log-rank test) (**FIGURE 4**).

**Other Cancers and Mortality**

Twenty-six cases of new cancers other than gastric cancer were identified during the study. They included cancer of the liver (n = 8), lung (n = 5), thyroid (n = 4), esophagus (n = 3), colon (n = 2), breast (n = 2), nasopharynx (n = 1), and brain (n = 1). The distribution of these other cancers was similar between the treatment and placebo groups (data not shown). All esophageal cancers were squamous cell carcinoma (1 in the placebo group and 2 in the treatment group). Eighteen of the 26 patients died of their underlying malignancy. Another 18 participants died of noncancer-related causes, including stroke syndrome (n = 4), motor vehicle crash (n = 4), cirrhosis of the liver (n = 3), and other miscellaneous causes (n = 7). A total of 156 participants (9.6%) de-

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**Table 1. Baseline Characteristics of the Study Participants**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Active Treatment (n = 817)</th>
<th>Placebo (n = 813)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>42.1 (9.0)</td>
<td>42.4 (9.1)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>440</td>
<td>440</td>
</tr>
<tr>
<td>Women</td>
<td>377</td>
<td>373</td>
</tr>
<tr>
<td>Daily smoking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspepsia symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dietary intake ≥2 times/wk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Green tea</td>
<td>205 (25)</td>
<td>181 (22)</td>
</tr>
<tr>
<td>Preserved vegetables</td>
<td>144 (18)</td>
<td>132 (16)</td>
</tr>
<tr>
<td>Salty fish</td>
<td>361 (45)</td>
<td>372 (46)</td>
</tr>
<tr>
<td>Fish sauce</td>
<td>172 (21)</td>
<td>241 (30)</td>
</tr>
<tr>
<td>Fruit</td>
<td>112 (14)</td>
<td>83 (10)</td>
</tr>
<tr>
<td>Fresh vegetables</td>
<td>275 (34)</td>
<td>253 (31)</td>
</tr>
<tr>
<td>Histopathologic test results</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic active gastritis</td>
<td>485 (59.4)</td>
<td>503 (61.9)</td>
</tr>
<tr>
<td>Gastric atrophy</td>
<td>72 (8.8)</td>
<td>57 (7.0)</td>
</tr>
<tr>
<td>Intestinal metaplasia</td>
<td>243 (29.7)</td>
<td>234 (28.8)</td>
</tr>
<tr>
<td>Gastric dysplasia</td>
<td>4 (0.5)</td>
<td>5 (0.6)</td>
</tr>
<tr>
<td>Unclassified†</td>
<td>13 (1.6)</td>
<td>14 (1.7)</td>
</tr>
</tbody>
</table>

*Data are expressed as No. (%) of participants unless otherwise indicated.†Histology slides were uninterpretable or no definite conclusions could be drawn.

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**Figure 2. Kaplan-Meier Analysis of Gastric Cancer Development With Respect to Treatment**

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faulted because of emigration, change of address, or withdrawal from the study (Figure 1).

**COMMENT**

We report herein a prospective, randomized, placebo-controlled study of the effect of *H pylori* eradication on prevention of gastric cancer development in a high-incidence region of China. After a follow-up of 7.5 years, gastric cancer developed in 7 and 11 participants in the *H pylori*—treated group and placebo group, respectively (*P* = .33). However, among participants with no precancerous lesions (gastric atrophy, intestinal metaplasia, and dysplasia) at presentation, 6 patients in the placebo group developed gastric cancer, whereas no patient in the *H pylori*—treated group developed gastric cancer (*P* = .02).

It has been shown that *H pylori* eradication can prevent development of a second gastric cancer after endoscopic mucosal resection of early gastric cancer in a nonrandomized study. However, whether the findings could be applied to patients with no history of early gastric cancer remains uncertain. Recently, Correa et al reported a randomized, placebo-controlled trial of 852 participants in Colombia and showed that anti-*H pylori* therapy and antioxidant supplementation with ascorbic acid and/or beta carotene all significantly increased the rates of regression of gastric atrophy and intestinal metaplasia compared with placebo, but only up to 15% to 30%. Most participants showed no disease regression. In addition, mutations of the APC gene, telomere reduction, rearrangement of the met oncogene, increased cripto expression, and *k-ras* are present as early as the intestinal metaplasia stage. Although a proportion of intestinal metaplasia may regress after *H pylori* eradication, it remains to be determined whether these molecular changes, which predispose patients to cancer, are reversible or not—in other words, at the point of no return. Our study suggests that *H pylori* eradication in high-risk areas is beneficial for a subgroup of patients with no precancerous lesions shown on first endoscopy. Two participants in the placebo group had gastric cancer detected at 12 and 22 months, respectively, during follow-up. One may argue that they may have had premalignant lesions or even early malignant lesions on presentation. In fact, these 2 participants had intestinal metaplasia on presentation, and their gastric cancers were not detected during the first endoscopy. It is unknown whether they had rapidly progressing diseases or the initial gastric biopsies failed to sample early malignant lesions.

Disappearance of *H pylori* infection occurred in 8% of the placebo group without a history of documented anti-*H pylori* therapy. One might speculate that *H pylori* was inadvertently

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**Table 2. Risk Factors for Development of Gastric Cancer**

<table>
<thead>
<tr>
<th>Variables</th>
<th>HR (95% CI)</th>
<th><em>P</em> Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age per 1-year increment</td>
<td>1.10 (1.05-1.15)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Female sex (vs male)</td>
<td>0.45 (0.16-1.26)</td>
<td>.13</td>
</tr>
<tr>
<td>Daily smoking*</td>
<td>6.18 (2.32-16.47)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Alcohol use*</td>
<td>1.35 (0.48-3.77)</td>
<td>.57</td>
</tr>
<tr>
<td>Dietary intake ≥2 times/wk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Green tea</td>
<td>1.55 (0.58-4.14)</td>
<td>.38</td>
</tr>
<tr>
<td>Preserved vegetables</td>
<td>0.28 (0.04-2.10)</td>
<td>.22</td>
</tr>
<tr>
<td>Salty fish</td>
<td>1.22 (0.49-3.08)</td>
<td>.67</td>
</tr>
<tr>
<td>Fish sauce</td>
<td>1.27 (0.45-3.57)</td>
<td>.65</td>
</tr>
<tr>
<td>Fruit</td>
<td>0.90 (0.21-3.93)</td>
<td>.89</td>
</tr>
<tr>
<td>Fresh vegetables</td>
<td>1.62 (0.64-4.10)</td>
<td>.31</td>
</tr>
<tr>
<td>Active treatment (vs placebo)</td>
<td>0.63 (0.24-1.62)</td>
<td>.34</td>
</tr>
<tr>
<td>Atrophy, intestinal metaplasia, or dysplasia</td>
<td>2.97 (0.94-9.42)</td>
<td>.06</td>
</tr>
</tbody>
</table>

**Table 3. Development of Gastric Cancer in Study Participants According to Baseline Histologic Test Results**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Atrophy, Intestinal Metaplasia, or Dysplasia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No (n = 6)</td>
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<tr>
<td>Age, mean (SD), y</td>
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</tr>
<tr>
<td>Sex</td>
<td></td>
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<tr>
<td>Men</td>
<td>6</td>
</tr>
<tr>
<td>Women</td>
<td>0</td>
</tr>
<tr>
<td>Last Helicobacter pylori status</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>6</td>
</tr>
<tr>
<td>Negative</td>
<td>0</td>
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<tr>
<td>Baseline histologic finding</td>
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</tr>
<tr>
<td>Chronic gastritis</td>
<td>6</td>
</tr>
<tr>
<td>Gastric atrophy</td>
<td>0</td>
</tr>
<tr>
<td>Intestinal metaplasia</td>
<td>0</td>
</tr>
<tr>
<td>Dysplasia</td>
<td>0</td>
</tr>
<tr>
<td>Treatment group</td>
<td></td>
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<td>Active</td>
<td>0</td>
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<tr>
<td>Placebo</td>
<td>6</td>
</tr>
<tr>
<td>Location of cancer</td>
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<tr>
<td>Proximal</td>
<td>0</td>
</tr>
<tr>
<td>Distal</td>
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</tr>
<tr>
<td>Histologic finding</td>
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</tr>
<tr>
<td>Intestinal</td>
<td>3</td>
</tr>
<tr>
<td>Uncertain</td>
<td>3</td>
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</table>

* Data are expressed as number of participants unless otherwise indicated.
eradicated by the use of antibiotics for the treatment of other infection or that these patients lost the infection naturally due to increasing mucosal atrophy and intestinal metaplasia with advancing age.21-23

We failed to identify any particular dietary factors that are related to gastric cancer development in this prospective study. Our results support the recent report26 of no effect of green tea consumption on risk of gastric cancer.

Three limitations exist in our study. First, the intervention was not double-blinded to offer second-line treatment to participants in whom first-line triple therapy failed. This approach is closer to clinical practice in this population-based study. However, blinding was maintained during the clinical follow-up, endoscopy, histopathologic examination, and gastric cancer review process of the study participants. Second, we were not able to provide evidence of whether the intestinal or diffuse types of gastric cancer are preventable because of the small number of cancers and the limited availability of surgical treatment for cancer patients. Third, the sample size calculation was based on assumptions that may be too optimistic. The follow-up period may be too short to observe the reduction in risk of gastric cancer in participants with precancerous lesions after \textit{H pylori} eradication.

Furthermore, the rate of gastric cancer development in the placebo group is only slightly higher for participants with precancerous lesions compared with participants with no precancerous lesions (1.7% vs 1.2%). However, such a difference represents a 42% added risk when compared with participants with no precancerous lesions. We speculate that the concept of “point of no return” applied here,27 in which the benefit of \textit{H pylori} eradication diminished after the intestinal metaplasia stage was reached (in which many molecular changes had been detected)21,22 (i.e., these are irreversible changes). Additional data from the continued follow-up of the participants in this study or later studies specifically aimed at investigating the role of \textit{H pylori} eradication in preventing gastric cancer in participants with precancerous lesions will be useful.

Our data suggest that upper endoscopy and histologic assessment of \textit{H pylori}–positive patients may be indicated in high-risk populations. Eradication of \textit{H pylori} in patients with no precancerous lesions in high-risk areas is beneficial. However, whether our data can be applied to low-risk areas is unknown. Further studies are warranted in this area. Data from Uemura et al12 suggested that \textit{H pylori}–infected participants with normal findings on upper endoscopy and no precancerous lesions on histologic analysis are still at risk of gastric cancer development. Our data correlate with their findings. Therefore, in high-risk populations, all patients with \textit{H pylori} infection with no precancerous lesions should consider the use of \textit{H pylori} eradication treatment for gastric cancer prevention.

In summary, we found that the incidence of gastric cancer development at the population level was similar between participants receiving \textit{H pylori} eradication treatment and those receiving placebo for 7.5 years in a high-risk region. In the subgroup of \textit{H pylori} carriers without precancerous lesions, eradication of \textit{H pylori} significantly decreased the development of gastric cancer.

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cancer. Longer follow-up is needed to examine the effect of eradication in participants with precancerous lesions.

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