

HELICOBACTER PYLORI INFECTION AND THE DEVELOPMENT OF GASTRIC CANCER

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ABSTRACT

Background Although many studies have found an association between *Helicobacter pylori* infection and the development of gastric cancer, many aspects of this relation remain uncertain.

Methods We prospectively studied 1526 Japanese patients who had duodenal ulcers, gastric ulcers, gastric hyperplasia, or nonulcer dyspepsia at the time of enrollment; 1246 had *H. pylori* infection and 280 did not. The mean follow-up was 7.8 years (range, 1.0 to 10.6). Patients underwent endoscopy with biopsy at enrollment and then between one and three years after enrollment. *H. pylori* infection was assessed by histologic examination, serologic testing, and rapid urease tests and was defined by a positive result on any of these tests.

Results Gastric cancers developed in 36 (2.9 percent) of the infected and none of the uninfected patients. There were 23 intestinal-type and 13 diffuse-type cancers. Among the patients with *H. pylori* infection, those with severe gastric atrophy, corpus-predominant gastritis, and intestinal metaplasia were at significantly higher risk for gastric cancer. We detected gastric cancers in 21 (4.7 percent) of the 445 patients with nonulcer dyspepsia, 10 (3.4 percent) of the 297 with gastric ulcers, 5 (2.2 percent) of the 229 with gastric hyperplastic polyps, and none of the 275 with duodenal ulcers.

Conclusions Gastric cancer develops in persons infected with *H. pylori* but not in uninfected persons. Those with histologic findings of severe gastric atrophy, corpus-predominant gastritis, or intestinal metaplasia are at increased risk. Persons with *H. pylori* infection and nonulcer dyspepsia, gastric ulcers, or gastric hyperplastic polyps are also at risk, but those with duodenal ulcers are not. (N Engl J Med 2001; 345:784-9.)

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SINCE the discovery of *Helicobacter pylori* in 1983,¹ the diagnosis and treatment of upper gastrointestinal disease have changed greatly. A higher risk of the development of gastric cancer has been reported in subjects with positive serologic tests for *H. pylori*.²⁻⁴ The World Health Organization and International Agency for Research on Cancer consensus group⁵ stated in 1994 that there was sufficient epidemiologic and histologic^{6,7} evidence to classify *H. pylori* as a definite carcinogen. Most but not all recent studies^{8,9} have found *H. pylori* to be associated with gastric cancer. The rates of infection in

patients with gastric cancer vary greatly among studies. These variations may be attributable to differences in the methods of detecting *H. pylori* or in the patient groups. Most prospective studies^{8,9} have used control groups “nested” within cohorts of study patients from whom blood samples were taken years before the onset of clinical gastric cancer. Various diagnostic tests for *H. pylori*^{10,11} may have false negative results, and the use of multiple tests may help to provide a more accurate diagnosis of *H. pylori* infection.¹² In Japan, where the incidence of gastric cancer is high, endoscopy is performed frequently for the early detection of gastric cancer, even as part of the examination of patients without symptoms of the disease. As a result, early-stage cancers are often discovered by endoscopy.

We conducted a prospective, long-term study of a large group of patients who were assessed for *H. pylori* infection by endoscopy and biopsy, followed by histologic examination, a rapid urease test, and serologic testing, to determine the relation between *H. pylori* infection and the development of gastric cancer.

METHODS

Patients

Between April 1990 and March 1993, we enrolled 1603 consecutive patients with active duodenal ulcers, active gastric ulcers, gastric hyperplastic polyps, or nonulcer dyspepsia. They were assessed for *H. pylori* infection and underwent endoscopic follow-up for the early detection of gastric cancer. We had previously excluded patients with severe underlying disease, including gastric cancer and adenoma, those who had undergone gastric resection, and those taking nonsteroidal antiinflammatory drugs. We then excluded 77 patients who declined a second endoscopic examination. The remaining 1526 patients (869 men and 657 women; mean age, 52 years; range, 20 to 76) were studied. Endoscopy with biopsy was performed in all patients at enrollment and between one and three years after enrollment. Follow-up data were censored because of deaths from other causes and the use of antibiotic treatment for the eradication of *H. pylori*. The mean duration of follow-up was 7.8 years (range, 1.0 to 10.6). All patients gave written informed consent. The study protocol was approved by the ethics committees of Kure Kyosai Hospital and was reviewed annually.

Endoscopy and Histologic Examination

All endoscopic examinations were performed with only local anesthesia (lidocaine). An Olympus videoscope (model GIF-230, Olympus, Tokyo, Japan) was used. Four biopsy specimens were tak-

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en, two from the greater curvature of the antrum and two from the upper body of the stomach (when lesions suspected to be cancerous were noted, additional biopsies were performed). Of these four specimens, two were fixed in formalin and assessed for *H. pylori* (by Giemsa staining) and the degree of neutrophil infiltration and intestinal metaplasia (by staining with hematoxylin and eosin). The remaining two were used for a rapid urease test (CLO, Delta West, Bentley, Australia). The degree of neutrophil infiltration was classified according to four grades (0 denoting no infiltration, 1 mild, 2 moderate, and 3 marked) and expressed as a score by two pathologists according to the updated Sydney system.¹³ Consensus was reached through joint review of all the slides. Active gastritis was classified into four categories (no gastritis, antrum-predominant gastritis, pangastritis, and corpus-predominant gastritis). Intestinal metaplasia was classified in two grades (absent or present), because the multifocal distribution of metaplasia may lead to misclassification when only two biopsy specimens are obtained. Gastric mucosal atrophy was evaluated according to the endoscopic-atrophic-border scale described by Kimura and Takemoto,¹⁴ which correlates with the results of histologic evaluation.^{15,16} There were three classifications (1 denoting mild atrophy or none, 2 moderate, and 3 severe). The pathologists were not aware of the clinical or endoscopic data. The results were scored blindly with the use of patient codes.

The rapid urease test was monitored for up to 24 hours. Gastric cancer was defined as evident invasion of neoplastic epithelium into the lamina propria of the mucosa or beyond (i.e., category 5.1 or 5.2 according to the Vienna classification¹⁷) and was classified according to Laurén¹⁸ as intestinal or diffuse type.

Serologic Evaluation

Blood was sampled immediately before endoscopy; serum was immediately separated and cryopreserved at -20°C until it was assayed for antibodies against *H. pylori* (HM-CAP, Enteric Products, Westbury, N.Y.). A positive serologic test for *H. pylori* was defined as one with a titer of 1.8 or more.

Detection of *H. pylori* Infection

H. pylori infection was identified by histologic examination, the rapid urease test, and serologic evaluation. Patients in whom any of these assays were positive were classified as *H. pylori*-positive. Those in whom all three were negative were considered *H. pylori*-negative.

Statistical Analysis

All statistical analyses were performed with SAS software (SAS Institute, Cary, N.C.).¹⁹ The demographic and clinical characteristics of the patients were compared by Student's t-test (for age, duration of follow-up, and number of endoscopic procedures) or the chi-square test (for sex, diagnosis, grade of gastric mucosal atrophy, distribution of gastritis, and presence or absence of intestinal metaplasia). We calculated relative risks for gastric findings — such as the degree of atrophy, the pattern of distribution of gastritis, and the presence of intestinal metaplasia — using Cox proportional-hazards models. Since gastric cancer has not been demonstrated to develop in patients with duodenal ulcers or in those who are *H. pylori*-negative (with or without eradication therapy), we could not calculate the difference in the incidence of gastric cancer using the Cox proportional-hazards model. For this reason, Kaplan-Meier analysis and the chi-square test or Fisher's exact test were used to assess the difference in proportions. All P values are two-sided; significance was indicated by a P value of less than 0.05.

RESULTS

Of the 1526 patients, 1246 were *H. pylori*-positive and 280 *H. pylori*-negative. The base-line characteristics of both groups are shown in Table 1. There were no significant differences between the two groups in age, sex, or the mean number of endoscopic procedures. The *H. pylori*-positive patients included 445

with nonulcer dyspepsia (206 men and 239 women; mean age, 54 years; range, 22 to 76), 275 with duodenal ulcers (198 men and 77 women; mean age, 48 years; range, 20 to 76), 297 with gastric ulcers (226 men and 71 women; mean age, 52 years; range, 22 to 75), and 229 with gastric polyps (84 men and 145 women; mean age, 56 years; range, 26 to 76). The *H. pylori*-negative patients all had nonulcer dyspepsia. Atrophy and intestinal metaplasia of any grade were found in 4 percent and 2 percent of *H. pylori*-negative patients, respectively. Of the *H. pylori*-negative group, only 2 percent had gastritis, all antrum predominant. In the *H. pylori*-positive group, 53 percent had moderate atrophy and 17 percent had severe atrophy. Antrum-predominant gastritis was found in 56 percent, pangastritis in 27 percent, and corpus-predominant gastritis in 17 percent of *H. pylori*-positive patients. Thirty-seven percent had intestinal metaplasia. There were significant differences in these variables between the groups (P<0.001 by the chi-square test). The duration of follow-up in the *H. pylori*-positive group was significantly shorter than in the uninfected group (P<0.001), because 253 of 1246 infected patients received eradication therapy at an early stage of follow-up.

Development of Gastric Cancer

During follow-up, gastric cancer developed in 36 of 1246 *H. pylori*-infected patients (2.9 percent) but in none of the 280 uninfected patients (P<0.001). All

TABLE 1. BASE-LINE CHARACTERISTICS OF THE 1526 PATIENTS.*

CHARACTERISTIC	H. PYLORI-POSITIVE PATIENTS (N=1246)	H. PYLORI-NEGATIVE PATIENTS (N=280)
Age — yr	52.3±11.1	52.7±12.8
Sex — no.		
Male	714	155
Female	532	125
Endoscopic diagnosis — no.		
Nonulcer dyspepsia†	445	280
Active gastric ulcer	297	0
Gastric hyperplastic polyps	229	0
Active duodenal ulcer	275	0
Grade of gastric atrophy — no. (%)		
None or mild†	381 (31)	270 (96)
Moderate	657 (53)	3 (1)
Severe	208 (17)	7 (2)
Distribution of gastritis — no. (%)		
None†	0	274 (98)
Antrum-predominant gastritis	699 (56)	6 (2)
Pangastritis	337 (27)	0
Corpus-predominant gastritis	210 (17)	0
Intestinal metaplasia — no. (%)†	464 (37)	5 (2)
Duration of follow-up — yr†	7.6±2.5	8.1±2.2
Endoscopic procedures — no.	7.0±1.8	6.8±1.8

*Plus-minus values are means ±SD. There were no significant differences in age, sex, or the mean number of endoscopic procedures (by the chi-square test or Student's t-test).

†P<0.001 for the comparison between the two groups.

cancers were visible on endoscopy and were identified histologically on biopsy. In Figure 1, the risk of gastric cancer is shown to be 5 percent at 10 years by Kaplan–Meier analysis. There were 23 men and 13 women with gastric cancer (at base line: mean age, 60 years; range, 41 to 76; at the time of detection of gastric cancer: mean age, 65; range, 47 to 83). Sixteen men and seven women had intestinal-type cancers (at base line: mean age, 64 years; range, 44 to 76; at the time of detection of gastric cancer: mean age, 70; range, 53 to 83), and six men and seven women had diffuse-type cancers (at base line: mean age, 52 years; range, 41 to 68; at the time of detection of gastric cancer: mean age, 58; range, 47 to 75). The mean age at enrollment and at the time of detection of gastric cancer was significantly lower in the patients with diffuse-type cancer than in those with intestinal-type cancer ($P < 0.001$ for both comparisons).

Table 2 shows the abnormalities of the gastric mucosa at base line in all the *H. pylori*-infected patients and in the 36 patients with gastric cancer, as well as the relative risks of cancer according to the base-line abnormalities. The frequency of severe atrophy, corpus-predominant gastritis, and intestinal metaplasia was significantly higher in patients with intestinal-type gastric cancer than in those with diffuse-type cancer ($P = 0.002$, $P < 0.001$, and $P = 0.008$, respectively). Nine of the patients with diffuse-type gastric cancer had moderate atrophy, and 10 had pangastritis.

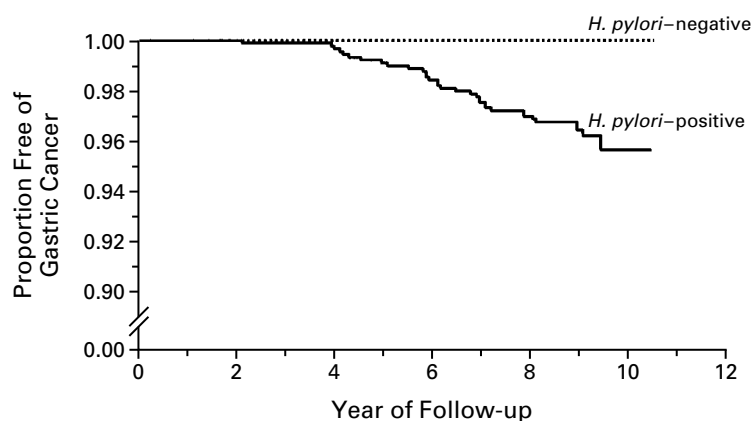
During follow-up, gastric cancer was detected in 21 of the 445 patients with nonulcer dyspepsia (4.7 percent), in 10 of the 297 with gastric ulcers (3.4 percent), and in 5 of the 229 with gastric polyps (2.2

percent) at base line (Fig. 2). No gastric cancer was detected in patients with duodenal ulcers. The frequency of gastric cancer in patients with nonulcer dyspepsia, gastric ulcers, and gastric polyps was significantly higher than in those with duodenal ulcers (Table 3). The frequency of diffuse-type cancer in patients with gastric ulcers was significantly higher than in patients with nonulcer dyspepsia and gastric polyps ($P = 0.03$ by the chi-square test). The mean age at the time of diagnosis of gastric cancer in patients with gastric ulcers (53 years) was significantly lower than in those with nonulcer dyspepsia (63 years) ($P = 0.009$ by Student's t-test). Gastric cancer did not develop in any of the 253 patients with *H. pylori* infection who received eradication therapy. The mean (\pm SD) duration of follow-up after eradication (4.8 ± 1.2 years) was shorter than the mean duration for patients who were not treated (8.5 ± 1.7 years; $P < 0.001$ by Student's t-test).

DISCUSSION

We found that gastric cancer developed in patients with *H. pylori* infection but not in uninfected patients. Our findings are consistent with those of a recent meta-analysis.⁸ In Japan, it has been reported that each year, gastric cancer develops in 300,000 (0.5 percent) of the 60 million people who are *H. pylori*-positive,²⁰ which means that gastric cancer develops in 5 percent of *H. pylori*-positive persons over 10 years. Our results support this estimate.

In previous epidemiologic studies showing a close relation between *H. pylori* infection and gastric cancer, a large number of patients with negative serologic re-



No. AT RISK	0	2	4	6	8	10
<i>H. pylori</i> -negative	280	272	251	245	213	57
<i>H. pylori</i> -positive	1246	1219	1086	907	782	258

Figure 1. Kaplan–Meier Analysis of the Proportion of *H. pylori*-Positive and *H. pylori*-Negative Patients Who Remained Free of Gastric Cancer.

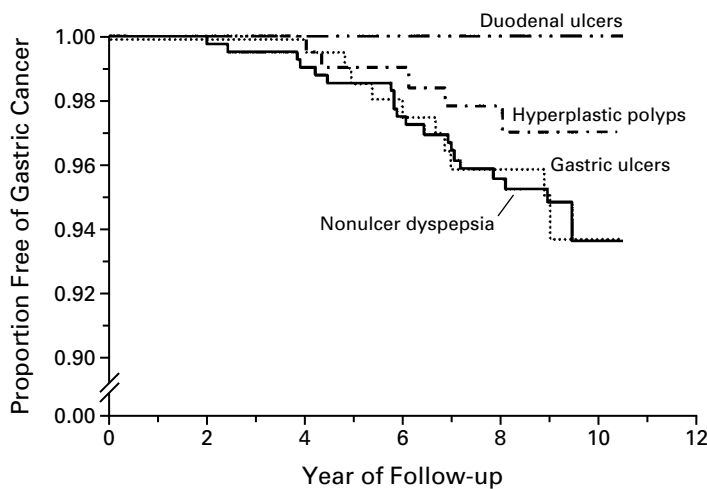
During follow-up, gastric cancer developed in 36 of the 1246 *H. pylori*-infected patients (2.9 percent) but in none of the 280 uninfected patients ($P < 0.001$).

TABLE 2. THE DEVELOPMENT OF GASTRIC CANCER IN *H. PYLORI*-POSITIVE PATIENTS ACCORDING TO ABNORMALITIES AT BASE LINE.

ABNORMALITIES AT BASE LINE	ALL <i>H. PYLORI</i> -POSITIVE PATIENTS (N=1246)	<i>H. PYLORI</i> -POSITIVE PATIENTS WITH GASTRIC CANCER (N=36)	RELATIVE RISK (95% CI)*	<i>H. PYLORI</i> -POSITIVE PATIENTS WITH INTESTINAL-TYPE CANCER (N=23)	<i>H. PYLORI</i> -POSITIVE PATIENTS WITH DIFFUSE-TYPE CANCER (N=13)
	no.	no. (%)		no.	no.
Grade of atrophy					
None or mild†	381	3 (0.8)	1.0	0	3
Moderate	657	18 (2.7)	1.7 (0.8–3.7)	9	9
Severe	208	15 (7.2)	4.9 (2.8–19.2)	14	1
Distribution of gastritis					
Antrum predominant†	699	2 (0.3)	1.0	0	2
Pangastritis	337	14 (4.2)	15.6 (6.5–36.8)	4	10
Corpus predominant	210	20 (9.5)	34.5 (7.1–166.7)	19	1
Intestinal metaplasia					
Absent†	782	6 (0.8)	1.0	1	5
Present	464	30 (6.5)	6.4 (2.6–16.1)	22	8

*CI denotes confidence interval.

†Patients in this category served as the reference group.



NO. AT RISK	0	2	4	6	8	10
Duodenal ulcers	275	265	229	186	160	58
Hyperplastic polyps	229	223	206	169	144	43
Gastric ulcers	297	290	253	181	158	49
Nonulcer dyspepsia	445	441	398	371	320	108

Figure 2. Kaplan–Meier Analysis of the Proportion of Patients Who Had Nonulcer Dyspepsia, Duodenal Ulcers, Gastric Ulcers, and Hyperplastic Gastric Polyps at the Time of Enrollment Who Remained Free of Gastric Cancer.

During follow-up, gastric cancer was detected in 21 of the 445 patients with nonulcer dyspepsia (4.7 percent), in 10 of the 297 patients with gastric ulcers (3.4 percent), and in 5 of the 229 patients with gastric polyps (2.2 percent) at base line. The rates of development of gastric cancer in patients with nonulcer dyspepsia, gastric ulcers, and gastric polyps were significantly higher than the rates in those with duodenal ulcers ($P<0.001$, $P=0.002$, and $P=0.02$, respectively, by Fisher’s exact test).

TABLE 3. THE DEVELOPMENT OF GASTRIC CANCER IN *H. PYLORI*-POSITIVE PATIENTS ACCORDING TO ENDOSCOPIC FINDINGS.*

ENDOSCOPIC FINDING	ALL <i>H. PYLORI</i> - POSITIVE PATIENTS (N=1246)	<i>H. PYLORI</i> - POSITIVE PATIENTS WITH GASTRIC CANCER (N=36)	P VALUE	HISTOLOGIC FINDING	
				INTESTINAL TYPE	DIFFUSE TYPE
	no.	no. (%)		no.	
No findings (nonulcer dyspepsia)	445	21 (4.7)	<0.001	16	5
Active gastric ulcer	297	10 (3.4)	0.002	3	7
Gastric hyperplastic polyps	229	5 (2.2)	0.02	4	1
Active duodenal ulcer	275	0		0	0

*P values were calculated by Fisher's exact test for the comparison with patients with duodenal ulcers.

sults were found to have cancer.^{8,9} Recent studies¹⁰⁻¹² have shown that false negative results occur with the serum antibody assay, so it is possible that the rate of *H. pylori* infection has been underestimated in patients with gastric cancer. Tabata et al.¹² concluded from their study of this issue that a biopsy specimen should be taken from the greater curvature of the upper gastric body because this procedure results in fewer false negatives. Enomoto et al.²¹ performed an immunohistologic study of biopsy specimens from the greater curvature of the upper gastric body and antibodies against *H. pylori*; they found that 98 percent of patients with gastric cancer were *H. pylori*-positive. Their results and our findings suggest that there are very few patients with gastric cancer who are not infected with *H. pylori*. It has previously been shown that in *H. pylori*-negative patients, histologic evidence of gastritis, especially neutrophil infiltration, is rare, and little gastric mucosal atrophy occurs.^{22,23} This is what we found as well. Thus, the onset of gastric cancer may be related to histologic evidence of gastritis or atrophic gastritis associated with *H. pylori* infection.

Our findings suggest that patients with *H. pylori* infection and severe atrophic gastritis, corpus-predominant gastritis, or both, along with intestinal metaplasia are at high risk for intestinal-type gastric cancer. It has been shown that intestinal-type gastric cancer develops in patients who have severe atrophic gastritis in association with intestinal metaplasia.²⁴ Progression of atrophic gastritis can be caused by *H. pylori* infection.²⁵ Our results confirm the hypothesis of Correa²⁴ that severe atrophic gastritis accompanying intestinal metaplasia caused by persistent *H. pylori* infection is closely related to the development of intestinal-type gastric cancer.

Since atrophic changes are not severe in diffuse-type gastric cancer,^{25,26} it was previously considered

to have little relation to *H. pylori* infection. However, epidemiologic and histopathological studies^{27,28} have shown that the development of diffuse-type cancer is also closely related to *H. pylori* infection. In our study, many of the patients with diffuse-type gastric cancer had moderate atrophic changes and pangastritis. Our results support the hypothesis of Sipponen et al.²⁵ and Solcia et al.²⁶ that diffuse-type gastric cancer develops during the progression of atrophic gastritis in patients with *H. pylori* infection and is associated particularly with active gastritis.

In our study, gastric cancer developed in patients with nonulcer dyspepsia, active gastric ulcers, and hyperplastic gastric polyps, but no gastric cancers developed during follow-up in patients with active duodenal ulcers. Hansson et al.²⁹ have shown that gastric ulcer is associated with a high risk of gastric cancer, whereas duodenal ulcer is associated with a low risk. Patients with gastric ulcers typically have atrophic gastritis and corpus-predominant gastritis. Patients with duodenal ulcers have few atrophic changes and have antrum-predominant gastritis.³⁰⁻³² Thus, there should be a higher rate of gastric cancer in patients with gastric ulcers than in those with duodenal ulcers. Diffuse-type gastric cancer is predominant in patients with gastric ulcers, many of whom are relatively young. In young patients with gastric ulcers, it is therefore necessary to perform careful follow-up to detect diffuse-type gastric cancer even after ulcers have healed. No gastric cancer developed after eradication of *H. pylori* in 253 infected patients in our study, although the duration of follow-up was relatively short. We have previously shown that in patients with early gastric cancer that is treated by endoscopic mucosal resection, eradication of *H. pylori* prevents the development of new cancer or the continued growth of occult cancer (i.e., cancer undetectable by endoscopy at the time of initial treatment).³³

In conclusion, we found that *H. pylori* infection is associated with the development of both intestinal-type and diffuse-type gastric cancer. Among infected patients, those with severe atrophy accompanying intestinal metaplasia, corpus-predominant gastritis, or both are at particularly high risk.

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