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Baseline gastric mucosal atrophy is a risk factor associated with the development of gastric cancer after *Helicobacter pylori* eradication therapy in patients with peptic ulcer diseases

Susumu Take[1,3], Motowo Mizuno[2], Kuniharu Ishiki[3], Yasuhiro Nagahara[3], Tomowo Yoshida[3], Kenji Yokota[4], and Keiji Oguma[4]

[1]Fukuwatari Municipal Hospital, Okayama, Japan
[2]Department of Internal Medicine, Hiroshima City Hospital, 7-33 Motomachi, Naka-ku, Hiroshima 730-8518, Japan
[3]Department of Internal Medicine, Department of Internal Medicine, Nippon Kokan Fukuyama Hospital, Fukuyama, Japan
[4]Department of Bacteriology, Okayama University Graduate School of Medicine and Dentistry, Okayama, Japan

Background. We previously reported that eradication of *Helicobacter pylori* could reduce the risk of developing gastric cancer in patients with peptic ulcer diseases. In the present study, we further followed up our patient groups to identify factors associated with the development of gastric cancer. ***Methods.*** Prospective posteradication evaluations were conducted in 1342 consecutive patients (1191 men and 151 women; mean age, 50 years) with peptic ulcer disease who had received *H. pylori* eradication therapy. The patients had undergone endoscopic examination before eradication therapy to evaluate peptic ulcers, background gastric mucosa, and *H. pylori* infection. After confirmation of eradication, follow-up endoscopy was performed yearly. ***Results.*** A total of 1131 patients were followed for up to 9.5 years (mean, 3.9 years). Gastric cancer developed in 9 of 953 patients cured of infection and in 4 of 178 who had persistent infection ($P = 0.04$). The risk of developing gastric cancer after receiving *H. pylori* eradication therapy was increased according to the grade of baseline gastric mucosal atrophy ($P = 0.01$). In patients with peptic ulcer diseases, persistent infection of *H. pylori* (hazard ratio, 3.9; $P = 0.03$), the grade of baseline gastric mucosal atrophy (3.3, $P = 0.01$) and age (2.0, $P = 0.04$) were identified as significant risk factors for developing gastric cancer. ***Conclusions.*** The grade of gastric atrophy was closely related to the development of gastric cancer after receiving *H. pylori* eradication therapy. Thus, eradication of *H. pylori* before the significant expansion of atrophy is most beneficial to prevent gastric cancer.

Key words: gastric mucosal atrophy, gastric cancer, *Helicobacter pylori*, eradication therapy, peptic ulcer disease

Reprint requests to: M. Mizuno

Introduction

Accumulating evidence indicates that *Helicobacter pylori* is a necessary cause, although not a sufficient one, of developing gastric cancer,[1–6] and eradication of *H. pylori* is expected to virtually eliminate gastric cancer by eliminating the reservoir of *H. pylori* infection.[7] However, the direct effect of eradication of *H. pylori* on the development of gastric cancer in those who have already been infected with this bacterium for a long time is still under debate.[8] Eradication therapy appears to reduce the risk of developing recurrent cancer after endoscopic mucosal resection of early gastric cancer,[9,10] but it had a limited beneficial effect in a high-risk population in China.[11]

We previously reported that eradication of *H. pylori* reduces the risk of developing gastric cancer to approximately one-third in patients with peptic ulcer diseases in whom the cancer is not yet established, but gastric cancer developed in some patients even after cure of *H. pylori* infection.[12] In the present study, we further followed up our patient groups and extended our previous work to better define the effect of eradication therapy on the development of gastric cancer. In addition, we aimed to identify factors associated with the development of gastric cancer after eradication therapy in these patients with peptic ulcer diseases.

Patients and methods

We enrolled 1342 consecutive patients (1191 men and 151 women; mean age, 50 years; range, 17–83) with peptic ulcer disease who had visited the outpatient clinic of Nippon Kokan Fukuyama Hospital from June 1995 to March 2003 and had received *H. pylori* eradication therapy. The patients were mostly male factory workers at JFE Steel Corporation, West Japan Works (Fukuyama, Japan). We excluded patients who had pre-

viously undergone gastrectomy or were pregnant and those who had an allergy to penicillin or clarithromycin, had used a proton pump inhibitor, H_2 receptor antagonist, adrenocortical steroids, or nonsteroidal anti-inflammatory drugs within the month preceding the study, or were taking anticoagulants. The patients underwent endoscopic examination at enrollment to evaluate peptic ulcers, background gastric mucosa, and *H. pylori* infection. A total of 776 had gastric ulcer, 495 had duodenal ulcer, and 71 had both. Gastric mucosal atrophy was evaluated according to the endoscopic–atrophic border scale described by Kimura and Takemoto,[13,14] which correlates with the results of the histologic evaluation,[15,16] and was classified by degree into three grades: mild (C-1 and C-2 patterns) = 1; moderate (C-3 and O-1 patterns) = 2; or severe (O-2 and O-3 patterns) = 3. *Helicobacter pylori* infection was defined as a positive bacterial culture from endoscopic biopsy specimens taken before eradication therapy was begun.[17,18] The specimens were obtained from the greater curvature of the body and the antrum of the stomach, and cultured using Brucella agar with 7% horse blood and antibiotics. Urease activities of the specimens were tested in a modified rapid urease test (MR UREA S; Institute of Immunology, Tokyo, Japan).

Patients received *H. pylori* eradication therapy as described.[12] One to 2 months after the completion of therapy, including the cessation of maintenance therapy with acid secretion inhibitors, a ^{13}C-urea breath test and follow-up endoscopy were performed in each patient to determine the *H. pylori* status. *Helicobacter pylori* infection was considered cured when the bacterial culture, rapid urease testing, and urea breath test (cutoff value, 3.5‰[19]) were all negative. After the confirmation of eradication, follow-up endoscopy and urea breath tests were performed yearly.

Gastric cancer was defined as a malignant epithelial tumor of the stomach mucosa with glandular differentiation[20] and classified according to Lauren as intestinal or diffuse type.[21] The pathologists were not aware of the clinical data, including *H. pylori* status. The study was conducted according to the tenets of the Declaration of Helsinki. A local ethics committee approved the study protocol. The objective of the study was explained to all patients prior to their participation, and written informed consent was obtained from each patient.

Statistical differences were calculated using the Mann-Whitney *U* test, the χ-squared test, and Fisher's exact test. Survival curves were constructed by the Kaplan-Meier method, and statistical significance between curves was tested by the log-rank test. The risk of developing gastric cancer was assessed by using Cox's proportional hazards models.

Results

Two hundred and eleven patients were dropped from the study for failure to complete 1 year of follow-up. A total of 1131 patients completed more than 1 year of follow-up; they were followed for up to 9.5 years (mean, 3.9 years). *Helicobacter pylori* infection was cured in 953 and persisted in 178 patients. In the patients' baseline characteristics (Table 1), there was no significant difference between the two groups with respect to sex, location of peptic ulcers, background gastric mucosal

Table 1. Patients' demographic characteristics

	Cured	Persistent infection	
	n = 953	*n* = 178	*P* value
Sex (male/female)	849/104	163/15	0.35*
Age (years)	50.0 ± 7.9	49.0 ± 7.6	0.05**
Gastric/duodenal ulcer[a]	598/355	113/65	0.87*
Atrophic score[b]	2.01 ± 0.75	1.98 ± 0.76	0.58**
Smoking (absence/presence)	295/658	42/136	0.05*
Drinking (absence/presence)	342/611	57/121	0.35*
Duration of follow-up (years)	4.0 ± 2.3	3.2 ± 2.0	<0.0001**
Dual/triple therapy[c]	407/546	128/50	<0.0001*

[a] Endoscopic diagnosis of peptic ulcers; when patients had both duodenal and gastric ulcers, they were classified into a gastric ulcer group
[b] Background gastric mucosa at the time of eradication therapy. Gastric mucosal atrophy was evaluated according to the endoscopic–atrophic border scale described by Kimura and Takemoto[13,14] and classified by degree into three grades, mild (C-1 and C-2 patterns) = 1, moderate (C-3 and O-1 patterns) = 2, or severe (O-2 and O-3 patterns) = 3
[c] *Helicobacter pylori* eradication therapy
* Fisher's exact test
** Mann-Whitney *U* test

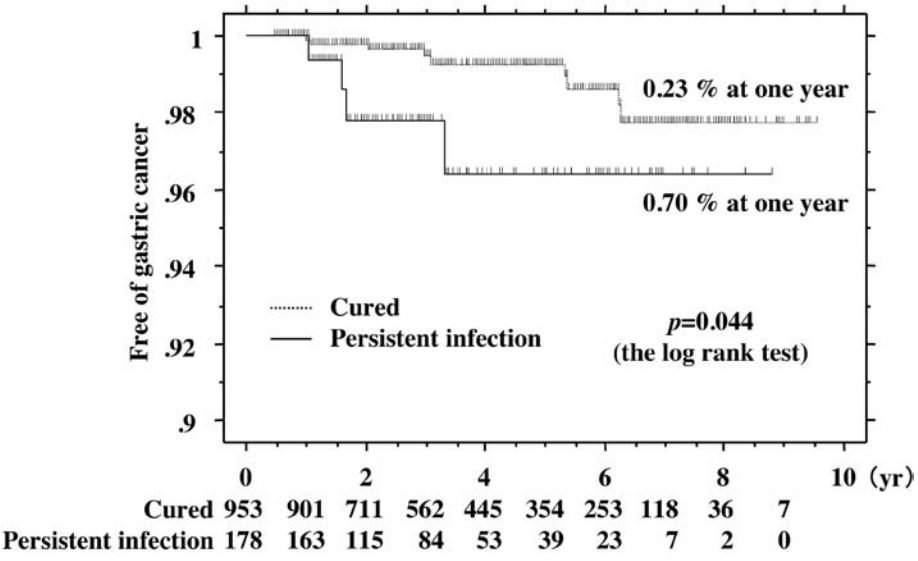

Fig. 1. Kaplan-Meier analysis of the proportion of patients cured of *Helicobacter pylori* infection and patients with persistent infection who remained free of gastric cancer in patients with peptic ulcers. During follow-up, gastric cancer developed in 9 of 953 patients cured of *H. pylori* infection and in 4 of 178 with persistent infection. The risk of developing gastric cancer in patients cured of infection (0.23% at 1 year) was significantly lower than that in patients who had persistent infection (0.70%, $P = 0.04$, log-rank test)

Table 2. Characteristics of 13 gastric cancers that developed after *H. pylori* eradication therapy

H. pylori status	Background gastric mucosal atrophy[a]	Years[b]	Histology of cancer	TNM stage[c]
Cured	Severe	1	Diffuse	IA (T1N0M0)
Cured	Severe	1.1	Diffuse	IA (T1N0M0)
Cured	Moderate	2.1	Intestinal	0 (TisN0M0)
Cured	Moderate	3	Intestinal	IA (T1N0M0)
Cured	Severe	3.1	Intestinal	0 (TisN0M0)
Cured	Severe	5.3	Diffuse	0 (TisN0M0)
Cured	Moderate	5.4	Diffuse	IIIA (T4N1M0)
Cured	Severe	6.2	Diffuse	IB (T2N0M0)
Cured	Severe	6.3	Intestinal	IA (T1N0M0)
Persistent	Severe	1.1	Intestinal	0 (TisN0M0)
Persistent	Moderate	1.6	Intestinal	IA (T1N0M0)
Persistent	Severe	1.7	Intestinal	0 (TisN0M0)
Persistent	Moderate	3.3	Intestinal	0 (TisN0M0)

[a] Background gastric mucosal atrophy at the time of eradication therapy. Gastric mucosal atrophy was evaluated according to the endoscopic–atrophic border scale
[b] Years after eradication therapy when gastric cancer developed
[c] Clinical stage

atrophy, or alcohol consumption. In the patient group with persistent infection, mean age was younger ($P = 0.05$), smokers were more frequent ($P = 0.05$), dual therapy was more often used for eradication therapy ($P < 0.0001$), and the duration of follow-up was shorter ($P < 0.0001$) than in the patient group whose infection was cured. In the patient group whose infection was cured, positive urea breath tests, suggesting possible reinfection of *H. pylori*, were noted in 19 patients 2.6 ± 1.7 years (mean ± SD) after the start of follow-up. In the patient group with persistent infection, 111 patients requested retreatment 3.0 ± 1.9 years after the start of follow-up. The analysis of these patients was stopped at the time of the possible reinfection or the start of retreatment.

Gastric cancer developed in 9 of 953 patients cured of *H. pylori* infection and in 4 of 178 with persistent infection. By Kaplan-Meier analysis (Fig. 1), the risk of developing gastric cancer in the patients cured of infection (0.23% at 1 year) was significantly lower than that in the patients who had persistent infection (0.70%, $P = 0.04$, log-rank test). In total, gastric cancer developed in 13 of 1131 patients after *H. pylori* eradication therapy. Characteristics of the 13 gastric cancers are presented in Table 2. Most gastric cancers were in the early TNM stages (stage 0, six; stage IA, five; stage IB, one; and stage IIIA, one). Histologically, five of the gastric cancers were of the diffuse type, and these developed in patients cured of infection. The other eight cancers were intestinal types.

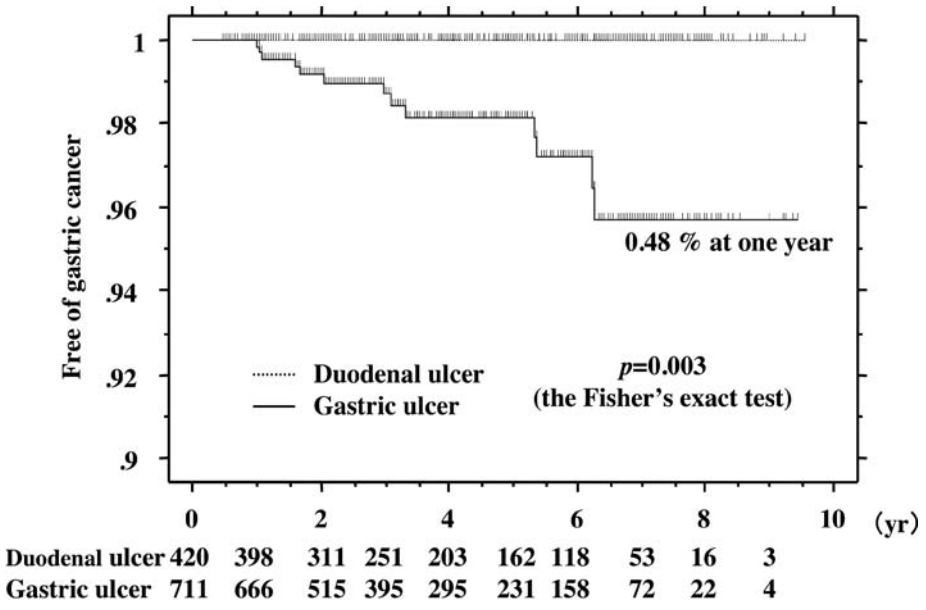

Fig. 2. Kaplan-Meier analysis of the proportion of patients with gastric ulcer and patients with duodenal ulcer who remained free of gastric cancer. During follow-up, gastric cancer developed in 13 of 711 patients with gastric ulcer (0.48% at one year) and in none of 420 with duodenal ulcer ($P = 0.003$, Fisher's exact test)

Table 3. Univariate analysis of factors associated with the development of gastric cancer in patients with peptic ulcers after *H. pylori* eradication therapy

	Total ($n = 1131$)	Development of gastric cancer		P value
		+ ($n = 13$)	– ($n = 1118$)	
Gastric/duodenal ulcer[a]	711/420	13/0	698/420	0.003*
Atrophy (mild/moderate/severe)[b]	316/492/323	0/5/8	316/487/315	0.01***
H. pylori status (cured/persistent)	953/178	9/4	944/174	0.13*
Smoking (absence/presence)	337/794	1/12	336/782	0.12*
Drinking (absence/presence)	399/732	2/11	397/721	0.16*
Age (years)	49.9 ± 7.9	53.5 ± 8.6	49.8 ± 7.9	0.26**
Sex (male/female)	1012/119	13/0	999/119	0.38*

[a] Endoscopic diagnosis of peptic ulcers; when patients had both duodenal and gastric ulcers, they were classified into the gastric ulcer group
[b] Background gastric mucosal atrophy at the time of eradication therapy. Gastric mucosal atrophy was evaluated according to the endoscopic–atrophic border scale
* Fisher's exact test
** Mann-Whitney U test
*** χ-squared test

All 13 gastric cancers developed in patients with gastric ulcer, and none in patients with duodenal ulcer (Fig. 2). The locations of the gastric cancers were different from those of the preceding gastric ulcers. In the univariate analysis, an ulcer present in the stomach was identified as a factor associated with the development of gastric cancer ($P = 0.003$) (Table 3). In the background gastric mucosa at enrollment, all patients had moderate or severe atrophy of the gastric mucosa (Table 2). Gastric cancer developed in 5 of 492 patients with moderate atrophy (0.26% at 1 year), in 8 of 323 patients with severe atrophy (0.66%), and in none of 316 patients with mild atrophy (Fig. 3); the risk of developing gastric cancer after receiving *H. pylori* eradication therapy was increased according to the background gastric mucosal atrophy (Table 3, $P = 0.01$, χ-squared test).

Analysis with Cox's proportional hazards model (Table 4) identified persistent infection [hazard ratio, 3.9; 95% confidence interval (CI), 1.2–12.9; $P = 0.03$], baseline gastric mucosal atrophy (hazard ratio, 3.3; 95% CI, 1.3–8.6; $P = 0.01$), and age (hazard ratio, 2.0; 95% CI, 1.0–3.9; $P = 0.04$) as significant factors for the risk of developing gastric cancer in patients with peptic ulcer diseases in whom the cancer was not yet established.

Discussion

In this study, we confirmed our previous findings that successful eradication therapy for *H. pylori* infection could reduce the risk of developing gastric cancer in patients with peptic ulcer disease in whom the cancer

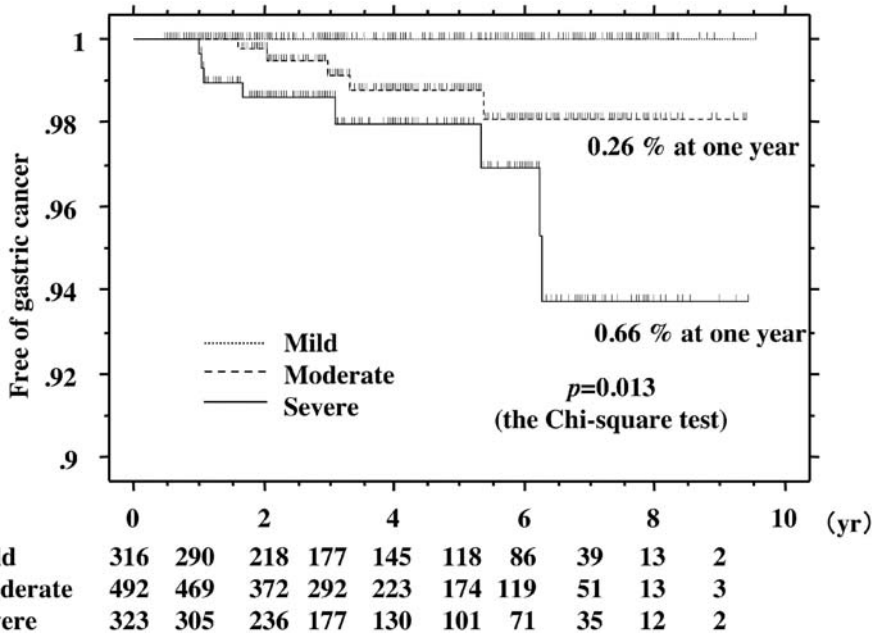

Fig. 3. Kaplan-Meier analysis of the proportion of patients with mild atrophy, patients with moderate atrophy, and patients with severe atrophy who remained free of gastric cancer in patients with peptic ulcers. During follow-up, gastric cancer developed in 5 of 492 patients with moderate atrophy (0.26% at 1 year), in 8 of 323 patients with severe atrophy (0.66%), and in none of 316 patients with mild atrophy. The risk of developing gastric cancer after receiving *H. pylori* eradication therapy was increased according to background gastric mucosal atrophy ($P = 0.01$, χ-squared test)

Table 4. Analysis of factors associated with the development of gastric cancer in patients with peptic ulcers (Cox's proportional hazards model)

	Hazard ratio	95% CI	*P* value
H. pylori infection			
Cured	1		
Persistent	3.9	1.2–12.9	0.03
Gastric mucosal atrophy[a]	3.3	1.3–8.6	0.01
Age (per 10-year increment)	2.0	1.0–3.9	0.04

CI, confidence interval
[a] Background gastric mucosal atrophy at the time of eradication therapy. Gastric mucosal atrophy was evaluated according to the endoscopic–atrophic border scale

was not yet established.[12] In addition, we revealed here that the grade of gastric mucosal atrophy before eradication therapy was closely related to the development of gastric cancer after *H. pylori* eradication therapy. We evaluated the grade of gastric atrophy endoscopically by identifying an atrophic border,[13,14] which has been shown to correlate with the histologic evaluation of gastric atrophy.[15,16] In this study, gastric cancer developed in 13 patients after they received *H. pylori* eradication therapy, and all cancers developed in patients whose gastric atrophy was moderate or severe, that is, whose atrophic border expanded beyond the cardia of the stomach. In contrast, no gastric cancer developed in patients whose gastric atrophy was classified as mild (C-1 or C-2 patterns, i.e., whose gastric atrophy was confined in the antrum or whose gastric border did not expand to the gastric cardia).

Helicobacter pylori-induced gastritis is usually acquired in childhood and involves the non-acid-secreting gastric antrum. Then, the inflammation and mucosal atrophy gradually expands to the gastric body, involving the lesser curvature more rapidly than the greater curvature and which can be endoscopically identified as an advancing atrophic border.[13,22] Our results indicate that if *H. pylori* is eradicated before gastric atrophy expands over the lesser curvature of the gastric body, then the risk of developing gastric cancer is minimal after eradication therapy. Thus, eradication of *H. pylori* before significant expansion of gastric atrophy has occurred is most beneficial to prevent gastric cancer.

Cure of *H. pylori* infection has been shown to be associated with several molecular and physiological changes that are important for gastric cancer prevention: normalization of alterations in cell-cycle control[23] and genomic instability,[24] reduction in cyclooxygenase-2 expression and NO-related compounds,[25] and an increase in gastric acid in patients with corpus atrophy.[26] With regard to gastric atrophy, beneficial effects from *H. pylori* eradication have been shown in experimental animal models, where gastric atrophy and intestinal metaplasia were reversed.[27–29] In human studies, gastric atrophy and metaplasia did not progress,[30–33] and sometimes even regressed[24,26,34–41] in patients who had *H. pylori* eradicated. These data and the results of this study suggest that *H. pylori* eradication may help to reduce the gastric cancer risk in patients whose gastric atrophy has already expanded, although the impact of eradication is variable among patients according to the extent of gastric atrophy.

Although we have confirmed our previous finding that cure of *H. pylori* infection may reduce their risk of developing gastric cancer in patients with peptic ulcer disease, our present study was a prospective cohort study, and patients were limited to those who had peptic ulcer diseases. The best way to confirm the effect of *H. pylori* eradication therapy on gastric cancer prevention would be a prospective randomized clinical trial in various populations, including patients who do not have peptic ulcer disease. Several prospective randomized trails have been performed, but a study in a high-risk population in China showed a limited beneficial effect.[11] Most other studies met with profound problems. Because of the strong evidence that *H. pylori* infection is a cause of gastric cancer, few are prepared to enter a placebo arm, and recruitment of a statistically significant number of patients, with follow-up over a decade, has been very difficult if development of gastric cancer is taken as the end point.[8] In addition, the placebo arm itself cannot be allowed ethically in future studies. Taking these problems into account, it is unlikely that a definitive conclusion based on prospective randomized trials will be forthcoming.

At least, gastric atrophy, a strong risk factor for developing gastric cancer, does not progress or may even regress in patients who have had *H. pylori* eradicated, resulting in a significant reduction in gastric cancer risk as shown in our previous[12] and present studies. Of course, eradication of *H. pylori* will not immediately eliminate gastric cancer, but it will definitely eliminate the reservoir of *H. pylori* infection. This should eliminate new infection with *H. pylori* and the consequent gastric atrophy, which, in turn, could eventually lead to gastric cancer becoming a rare disease.[7] In conclusion, our findings strongly support the notion that eradication of *H. pylori* will prevent and may virtually eliminate gastric cancer.

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