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Clinical features of gastric cancer discovered after successful eradication of Helicobacter pylori: *results from a 9-year prospective follow-up study in Japan*

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SUMMARY

Background: Eradication of *Helicobacter pylori* is expected to prevent the development of gastric cancer. However, gastric cancer is sometimes discovered after successful eradication of *H. pylori*.

Aim: To conduct a prospective study to determine the clinical features of patients who underwent successful eradication and were later diagnosed with gastric cancer.

Methods: A total of 1787 patients (1299 males and 488 females; mean age, 58.2 years; range: 15–84) who underwent successful eradication therapy between April 1994 and March 2001 were our study subjects.

Results: Gastric cancer occurred at a rate of 1.1% (20 of 1787) during the follow-up period. Gastric cancer comprises six of 105 (5.7%) with early gastric cancer after endoscopic resection, 12 of 575 (2.1%) with gastric ulcer and two of 453 (0.4%) with atrophic gastritis. Gastric cancer did not develop in any patient with duodenal ulcer. All patients with gastric cancer had baseline severe atrophic gastritis in the corpus.

Conclusion: Careful endoscopic examination is necessary even after successful eradication of *H. pylori* in patients with early gastric cancer or gastric ulcer with severe mucosal atrophy in the corpus.

INTRODUCTION

The association between *Helicobacter pylori* infection and development of gastric cancer is well established, based on epidemiological study,[1–7] experimental carcinogenesis in Mongolian gerbils[8, 9] and prevention of gastric cancer by eradication therapy in patients shown to have early gastric cancer after endoscopic resection (ER).[10, 11]

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Uemura *et al.*[7] reported that gastric cancer developed in 36 (2.9%) of 1246 *H. pylori*-infected patients but in none of the uninfected patients at 7.8 years of follow-up. Generally, eradication of *H. pylori* is expected to prevent gastric cancer. However, gastric cancer is sometimes discovered after successful eradication of *H. pylori*. In a recent large-scale prospective study conducted in a high-incidence region of China, Wong *et al.*[12] showed that the development of gastric cancer at the population level was of similar incidence between participants receiving *H. pylori* eradication treatment and those receiving placebo.

We conducted a prospective study investigating the clinical features of patients with gastric cancer discovered after successful eradication of *H. pylori*.

PATIENTS AND METHODS

Patients

The study was conducted in the Division of Gastroenterology, Department of Internal Medicine, Kawasaki Medical School and at three other institutions from April 1994 through March 2001. We enrolled 2157 consecutive patients shown to have active duodenal ulcer, active gastric ulcer, atrophic gastritis, or early gastric cancer after ER. These patients all underwent oesophagogastroduodenal examination with biopsy and a ^{13}C-urea breath test (UBT) for *H. pylori* infection. Patients who had undergone gastric resection, those taking non-steroidal anti-inflammatory drugs, and those who underwent eradication therapy before the study period were not included in this group. Of the 2157 patients, 2124 were *H. pylori*-positive and 33 were *H. pylori*-negative. We then excluded 104 *H. pylori*-positive patients who declined a second endoscopic examination. Among the remaining 2020 *H. pylori*-positive patients who underwent eradication therapy, therapy was successful in 1787 and therapy failed in 233. The 1787 patients (1299 males and 488 females; mean age, 58.2 years; range: 15–84) in whom eradication therapy was successful were studied. Patients had duodenal ulcer ($n = 654$), gastric ulcer ($n = 575$), atrophic gastritis ($n = 453$) or early gastric cancer after ER ($n = 105$). Early gastric cancer was defined as invasion of neoplastic epithelium limited to the lamina propria of the mucosa or submucosa. Patients were followed up for a median of 4.5 years (range: 2.0–9.0). All patients provided informed consent before eradication therapy. The study protocol was approved by the Ethics Committee of the gastrointestinal unit.

Endoscopy and histological examination of stomach biopsy specimens

As a matter of principle, endoscopy with biopsy was performed before and every year after eradication therapy in all patients. An Olympus videoscope (model GIF-230, Olympus, Tokyo, Japan) was used throughout the study. Patients fasted overnight and were not premedicated. Two biopsy specimens were obtained from the lesser curvature of the mid-antrum and one each from the anterior and posterior wall of the fundus. The resected biopsy specimens were fixed in 10% buffered formalin, embedded in paraffin, cut into 4-μm sections, and treated with haematoxylin-eosin (H & E) and Giemsa stain for identification of *H. pylori*.

Histological interpretation was based on the updated Sydney System.[13] Graded histological variables included glandular atrophy, chronic inflammation, activity and intestinal metaplasia; mucosal atrophy was defined as the loss of glandular tissue, inflammation of the gastric mucosa was defined as the presence of inflammatory infiltrates composed of lymphocytes and plasma cells, and activity of the gastric mucosa was defined as the presence of neutrophils in the superficial or deep layers. Mucosal atrophy, inflammation, activity and intestinal metaplasia were classified by degree into four categories: none = 0, mild = 1, moderate = 2, severe = 3. All H & E and Giemsa-stained biopsy specimens were reviewed by two pathologists who were blinded to the subjects' symptoms and laboratory data. Consensus was reached through joint review of all slides. We evaluated histological gastritis before and 1 year after eradication in patients with gastric cancer discovered and not discovered after successful eradication of *H. pylori*.

Gastric cancer was defined as evident invasion of neoplastic epithelium into the lamina propria of the mucosa or beyond, and tumours were classified according to the Lauren classification system[14] as an intestinal or diffuse type. We determined the time to discovery of gastric cancer and the incidence of gastric cancer after successful eradication of *H. pylori*. In addition, we investigated location, size, stage, and macroscopic and histological types of tumour.

^{13}C-urea breath test, eradication therapy and assessment of H. pylori

Helicobacter pylori infection was diagnosed in all patients by ^{13}C-UBT as previously described (sensitivity, 100%; specificity, 96%).[15]

All patients were given omeprazole (40 mg) or lansoprazole (60 mg), amoxicillin (1500 mg) and clarithromycin (600 mg) for 7 days. Adequate compliance was defined as consumption of more than 90% of the scheduled drug. *Helicobacter pylori* infection status was determined by histological examination and by ^{13}C-UBT. Patients were considered to be infected by *H. pylori* if the results of at least one of the two

assessment methods were positive. Patients were considered not to be infected if results of both methods were negative. Repeat endoscopy with biopsy and ^{13}C-UBT were performed at least 8 weeks after the completion of therapy. The success of eradication therapy was evaluated by histological examination and by ^{13}C-UBT, with *H. pylori* eradication being considered successful if both methods yielded negative results.

Statistical analysis

All statistical calculations were performed with SAS statistical software (SAS Institute Inc, Cary, NC, USA). The cumulative incidences of gastric cancer were calculated by the Kaplan–Meier method. The atrophy, inflammation, activity and intestinal metaplasia scores before and 1 year after eradication in patients with gastric cancer are shown as mean ± s.d. A two-tailed Wilcoxon signed rank test was used for paired comparisons before and after eradication. $P < 0.05$ was considered significant.

RESULTS

Discovery of gastric cancer after successful eradication of H. pylori

During follow-up, gastric cancer was discovered in 20 (17 men, three women; mean age, 64 years; range: 35–73) of 1787 patients (1.1%) after successful eradication therapy. None of the gastric cancers was visible endoscopically before eradication therapy, but all were visible endoscopically after eradication and were identified histologically on biopsy specimens. The risk of gastric cancer after successful eradication was shown by Kaplan–Meier analysis to be 2.2% at 9 years. Gastric cancer was discovered between 13 and 78 months (mean, 39 months) after successful eradication. Detection was within 48 months after eradication in 16 of the 20 patients (80%) and later than 48 months after eradication in the remaining four (Figure 1).

Clinicopathological features of gastric cancer discovered after successful eradication of H. pylori

Clinicopathological features of the gastric cancers discovered after eradication of *H. pylori* are shown in Table 1. With respect to location, 16 were non-cardiac cancers and four were cardiac cancers. Of the 16 non-cardiac cancers, eight were in the antrum, five were in the angulus and three were in the corpus. With respect to stage, 19 were early cancers and one was advanced cancer. Macroscopic types were ulcers type ($n = 18$) and polypoid type ($n = 2$), and histological types were intestinal type ($n = 15$) and diffuse type ($n = 5$).

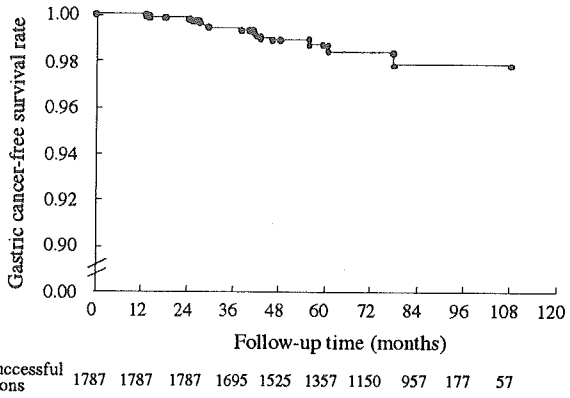

Figure 1. Kaplan–Meier analysis of gastric cancer-free survival after eradication of *Helicobacter pylori*. During follow-up, gastric cancer was discovered in 20 of 1787 (1.1%) patients who underwent successful eradication therapy.

Table 1. Clinicopathological features of gastric cancer discovered after successful eradication of *Helicobacter pylori*

	Incidence
Location	
Cardiac/non-cardiac	4 (20)/16 (80)
Size (mm)	
<10/11–20/>21	10 (50)/8 (40)/2 (10)
Tumour stage	
Early/advanced	19 (95)/1 (5)
Macroscopic type	
Polypoid/ulcerative	2 (10)/18 (90)
Histological type	
Intestinal/diffuse	15 (75)/5 (25)

Number and percentage of cases are shown.

Incidence of gastric cancer discovered after eradication of H. pylori *in relation to endoscopic diagnoses before eradication*

The 20 patients in whom gastric cancer developed comprises six of a total 105 (5.7%) with early gastric cancer after ER, 12 of 575 (2.1%) with gastric ulcer and two of 453 (0.4%) with atrophic gastritis. Gastric cancer did not develop in any patient with duodenal ulcer (Table 2).

Table 2. Incidence of GCa discovered after eradication of *Helicobacter pylori* according to endoscopic diagnoses before eradication

	DU	GU	AG	GCa after ER
Number of patients	654	575	453	105
Male/female ratio	488/166	400/175	290/163	83/22
Mean age (years)	47.1	58.1	62.4	68.3
Mean observation period (months)	48.4	49.6	45.6	44.3
Incidence of GCa (%)	0	12 (2.1)	2 (0.4)	6 (5.7)

DU, duodenal ulcer; GU, gastric ulcer; AG, atrophic gastritis; GCa, gastric cancer; ER, endoscopic resection.

Mean scores of histological gastritis before and 1 year after eradication in patients who later discovered gastric cancer and not discovered gastric cancer

All patients with gastric cancer discovered after eradication had baseline histological gastritis. Histological gastritis was found not only in the antrum but also in the corpus in these patients, and all had severe baseline atrophic gastritis in the corpus. In the 20 patients in whom *H. pylori* was successfully eradicated, atrophy scores for the antrum and corpus were significantly decreased at 1 year after eradication in comparison with pre-treatment scores (antrum: 1.4 ± 0.4 vs. 1.9 ± 0.7, $P < 0.05$; corpus: 1.6 ± 0.4 vs. 2.1 ± 0.6, $P < 0.05$). Both inflammation and activity scores for the antrum and corpus were significantly decreased at 1 year after eradication in comparison with pre-treatment scores (inflammation score; antrum: 0.7 ± 0.3 vs. 1.4 ± 0.6, $P < 0.01$; corpus: 0.5 ± 0.3 vs. 1.4 ± 0.6, $P < 0.01$; activity score: 0.2 ± 0.3 vs. 1.4 ± 0.7, $P < 0.01$; corpus: 0.2 ± 0.3 vs. 1.6 ± 0.7, $P < 0.01$). However, there was no significant improvement in intestinal metaplasia scores after eradication. On the contrary, in patients who not discovered gastric cancer, both inflammation and activity scores for the antrum and corpus were significantly decreased at 1 year after eradication in comparison with pre-treatment scores, but there was no significant improvement in atrophy and intestinal metaplasia scores after eradication of *H. pylori*. There was not difference in the baseline histological gastritis between the patients who discovered gastric cancer and not discovered gastric cancer (Table 3).

DISCUSSION

Our study revealed that careful follow-up endoscopic examination for possible gastric cancer is necessary even after successful eradication of *H. pylori* in patients with early gastric cancer or gastric ulcer because such patients can have severe baseline mucosal atrophy in the corpus.

Among our 1787 patients who underwent eradication therapy for *H. pylori*, 20 gastric cancers were discovered during follow-up after successful eradication. Of these 20 gastric cancers, 16 (80%) were detected within 48 months after eradication, and the number of gastric cancers detected within 48 months after eradication was substantially greater than the number discovered after 48 months. It is well known that *H. pylori* infection causes endoscopic gastritis with persistent infection, presenting as erythema, erosion, haemorrhagic and large gastric folds.[16] Several studies[17–19] have shown that eradication of *H. pylori* improves *H. pylori*-related endoscopic gastritis as well as histological gastritis. Therefore, improvement in endoscopic gastritis with eradication of *H. pylori* might have contributed to the detection of potential gastric cancer within 48 months after eradication in our

Table 3. Mean scores of histological gastritis before and 1 year after eradication in patients who later discovered gastric cancer (GCa) and not discovered GCa

	Discovered GCa				Not discovered GCa			
	Antrum		Corpus		Antrum		Corpus	
	Before	After	Before	After	Before	After	Before	After
Atrophic score	1.9 ± 0.7	1.4 ± 0.4*	2.1 ± 0.6	1.6 ± 0.4*	1.9 ± 0.5	1.6 ± 0.4	1.8 ± 0.5	1.6 ± 0.4
Inflammation score	1.4 ± 0.6	0.7 ± 0.3**	1.4 ± 0.6	0.5 ± 0.3**	1.4 ± 0.5	0.5 ± 0.3**	1.6 ± 0.5	0.6 ± 0.3**
Activity score	1.4 ± 0.7	0.2 ± 0.3**	1.6 ± 0.7	0.2 ± 0.3**	1.5 ± 0.5	0.2 ± 0.3**	1.8 ± 0.5	0.2 ± 0.3**
Intestinal metaplasia score	1.6 ± 0.7	1.5 ± 0.6	1.0 ± 0.6	0.9 ± 0.5	1.5 ± 0.5	1.3 ± 0.5	0.9 ± 0.5	0.8 ± 0.4

*$P < 0.05$ vs. before eradication, **$P < 0.01$ vs. before eradication.

study. Although we could not evaluate changes in endoscopic gastritis after eradication, our study showed that eradication of *H. pylori* improves histological gastritis. Thus, early endoscopic examination after successful eradication of *H. pylori* is very important for detecting gastric cancer.

In our study, the incidence of gastric cancer after eradication of *H. pylori* in patients with early gastric cancer after ER, gastric ulcer, or atrophic gastritis was higher than in those with duodenal ulcer. Uemura *et al.*[7] reported that during 8 years of follow-up, gastric cancer developed in 36 of 1246 *H. pylori*-infected patients (2.9%) but in none of 280 uninfected patients. In their study, the incidence of gastric cancer was significantly higher in patients with non-ulcer dyspepsia, gastric ulcer, or gastric polyps than in those with duodenal ulcer. In patients with duodenal ulcer who have excessive acid secretion, a high density of *H. pylori* and histological gastritis are found primarily in the antrum. In contrast, both high density of *H. pylori* and histological gastritis occur mainly in the gastric body in patients with gastric ulcer, atrophic gastritis, or early gastric cancer with hypochlorhydria. The distribution of *H. pylori* together with histological gastritis is closely related to gastric acid secretion. Because patients with gastric ulcer and early gastric cancer have severe baseline atrophy in the corpus, endoscopic examination is necessary even after successful eradication of *H. pylori* in these patients. In our study, all patients with gastric cancer discovered after eradication had severe baseline mucosal atrophy in the corpus, and the gastric cancers were mainly early non-cardiac cancers of the intestinal type with ulcers. Atrophic gastritis and gastric cancer are common in Japan,[16, 20, 21] and this highlights need for careful endoscopic follow-up.

Recent studies showed that eradication of *H. pylori* contributes to the chemoprevention of gastric cancer. Uemura *et al.*[10] showed that eradication of *H. pylori* improves neutrophil infiltration and intestinal metaplasia in the gastric mucosa and inhibits the development of new cancers after ER of gastric cancer. Additionally, Correa *et al.*[11] showed in a very high-risk population that eradication of *H. pylori* may have interfered with the precancerous process and may thus be an effective strategy for preventing gastric cancer. Wong *et al.*[12] showed however that development of gastric cancer at the population level was of similar incidence in participants receiving *H. pylori* eradication drugs (0.86%) and those receiving placebo (1.35%). However, they reported that in the subgroup of *H. pylori* carriers without precancerous lesions, eradication of *H. pylori* significantly decreased the development of gastric cancer. The frequency at which gastric cancer was discovered after eradication in our study is high in comparison with their reported frequency. The difference in endoscopic surveillance and baseline atrophic gastritis of patients between their study and ours might have contributed to the difference in detection rates. In our recent study,[22] histological corpus gastritis was found with high frequency in young *H. pylori*-positive patients. Therefore, we recommend that eradication of *H. pylori* should be attempted to prevent gastric cancer in young *H. pylori*-positive patients. Our study was a non-randomized study. We will need to perform a randomized, placebo-controlled study to establish whether eradication of *H. pylori* prevents development of gastric cancer.

In conclusion, gastric cancers discovered after successful eradication of *H. pylori* were characterized clinicopathologically as early non-cardiac cancers of the intestinal type with ulcers. Our findings showed that, even after successful eradication of *H. pylori*, careful endoscopic examination should be performed in cases of early gastric cancer or gastric ulcer with severe baseline mucosal atrophy in the corpus.

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GASTRIC CANCER

Predicting the development of gastric cancer from combining *Helicobacter pylori* antibodies and serum pepsinogen status: a prospective endoscopic cohort study

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Background and aim: *Helicobacter pylori* infection and gastric atrophy are both risk factors for gastric cancer. We aimed to elucidate the natural history of gastric cancer development according to *H pylori* infection and gastric atrophy status.

Subjects and methods: A total of 9293 participants in a mass health appraisal programme were candidates for inclusion in the present prospective cohort study: 6983 subjects revisited the follow up programme. Subjects were classified into four groups according to serological status at initial endoscopy. Group A (n = 3324) had "normal" pepsinogen and were negative for *H pylori* antibody; group B (n = 2134) had "normal" pepsinogen and were positive for *H pylori* antibody; group C (n = 1082) had "atrophic" pepsinogen and were positive for *H pylori* antibody; and group D (n = 443) had "atrophic" pepsinogen and were negative for *H pylori* antibody. Incidence of gastric cancer was determined by annual endoscopic examination.

Results: Mean duration of follow up was 4.7 years and the average number of endoscopic examinations was 5.1. The annual incidence of gastric cancer was 0.04% (95% confidence interval (CI) 0.02–0.09), 0.06% (0.03–0.13), 0.35% (0.23–0.57), and 0.60% (0.34–1.05) in groups A, B, C, and D, respectively. Hazard ratios compared with group A were 1.1 (95% CI 0.4–3.4), 6.0 (2.4–14.5), and 8.2 (3.2–21.5) in groups B, C, and D, respectively. Age, sex, and "group" significantly served as independent valuables by multivariate analysis.

Conclusions: The combination of serum pepsinogen and anti-*H pylori* antibody provides a good predictive marker for the development of gastric cancer.

The pathogenic role of *Helicobacter pylori* for gastric cancer has been documented in a large number of epidemiological studies[1–5] and basic research investigations.[6–9] In earlier epidemiological studies using *H pylori* antibody as a marker of infection, various risk ratios of *H pylori* infection for gastric cancer were reported, ranging widely from none to 10 or above.[1 5 10 16]

Recently, a follow up study by Uemura *et al* showed that gastric cancer developed only in patients infected with *H pylori* when using a full set of diagnostic tests for *H pylori* infection.[5] They also reported in the same study that subjects with severe gastric atrophy, corpus predominant gastritis, or intestinal metaplasia were at increased risk for gastric cancer.[5]

We also confirmed that gastric atrophy status was essential for cancer development in our previous cross sectional study.[17] In that study, gastric atrophy was estimated by serum pepsinogen levels, which were determined in serum samples.[17] Pepsinogen I and II, the two main precursors of pepsin, are both produced by chief cells and mucous neck cells of the stomach.[18 19] Pepsinogen II is also produced by pyloric gland cells. Chief cells are replaced by pyloric glands, leading to a decrease in pepsinogen I as gastric atrophy develops. However, a decrease in pepsinogen II is minimal. Therefore, both low serum pepsinogen I and a low pepsinogen I/II ratio are recognised as serological markers of gastric atrophy.[20–22]

The combination of serum pepsinogen and *H pylori* antibody served as a useful marker for the prevalence of gastric cancer in a cross sectional setting.[17] This modality is much simpler and less invasive than those using endoscopy, and therefore suitable for a large general population. On the basis of this premise, we conducted the present prospective study in participants in our health check programme without any specific symptoms. We aimed to estimate the incidence rate of gastric cancer in the general population. The role of *H pylori* infection and gastric atrophy in cancer development was evaluated in terms of these serological markers.

METHODS

Enrolment

Between March 1995 and February 1997, participants in health examination programmes held by Kameda General Hospital and Makuhari Clinic who underwent upper endoscopy were consecutively enrolled. Blood samples were obtained from each subject. Excluding those with gastric cancer, peptic ulcer, or a past history of surgical resection of the stomach, a total of 9293 participants were candidates for inclusion in this study. Some of these subjects were analysed in a previous cross sectional study.[17] Proton pump inhibitors or H_2 blockers had not been prescribed within one month prior to the examination. None had undergone eradication therapy for *H pylori*. Patients were encouraged to undergo endoscopic examination annually to check for the development of gastric cancer, and 6983 revisited the programme for follow up endoscopy during the observation period. Data of these participants were analysed in this study.

The protocol was approved by the ethics committees of the respective institutions, and informed consent was obtained from each subject according to the Declaration of Helsinki.

Serum *H pylori* antibody

Serum anti-*H pylori* antibody was measured using a commercial ELISA kit (GAP-IgG kit; Biomerica Inc., California, USA). Seropositivity for *H pylori* antibody was defined by optical density values according to the manufacturer's protocol. Sensitivity and specificity for *H pylori* infection in Japanese were reported to be 95% and 83%, respectively, compared with the results of specific culture.[23]

Serum pepsinogen level

Serum pepsinogen was measured using a commercial RIA kit (pepsinogen I/II RIA bead kit; Dainabot Co., Tokyo, Japan). Serum pepsinogen status was defined as "atrophic" when the criteria of both serum pepsinogen I level $\leqslant 70$ ng/ml and a pepsinogen I/II ratio (serum pepsinogen I (ng/ml)/serum pepsinogen II (ng/ml)) $\leqslant 3.0$ were simultaneously fulfilled, as proposed by Miki and colleagues.[22] All other cases were classified as "normal". A sensitivity of 70.5% and specificity of 97.0% for atrophic gastritis compared with histology have been reported in Japan.[24] These criteria have been widely applied to mass screening for gastric cancer in Japan.[17 22 24]

Classification by anti-*H pylori* antibody and serum pepsinogen status

Subjects were classified into four groups according to serum pepsinogen status and *H pylori* status antibody at enrolment. Group A had "normal" pepsinogen and were negative for *H pylori* antibody. Group B had "normal" pepsinogen and were positive for *H pylori* antibody. Group C had "atrophic" pepsinogen and were positive for *H pylori* antibody. Group D had "atrophic" pepsinogen and were negative for *H pylori* antibody.

Endoscopic and clinicopathological examinations

Gastrointestinal endoscopy was performed with electronic panendoscopes (type XQ200 or P230; Olympus, Tokyo, Japan), carefully observing the bulbar portion of the duodenum, the entire stomach, and the oesophagus. Experienced endoscopists performed each examination without knowledge of the serological data of the study subjects. Histopathological assessment of gastric cancer was conducted using surgically resected or endoscopically biopsied samples, categorised as intestinal-type or diffuse-type, according to Lauren's classification.[25] Samples were classified as cardiac or non-cardiac in terms of location.

Statistical analysis

All statistical analyses were performed using SAS software (SAS Institute Inc., North Carolina, USA). Differences in mean age were evaluated by analysis of variance (ANOVA) with Fisher's correction. Difference in sex distribution was evaluated by the Kruskal-Wallis test with Bonferroni's correction. Incidence of gastric cancer was calculated using the Kaplan-Meier method. Independent risk factors for gastric cancer were assessed by Cox proportional hazard regression. A two sided p value of less than 0.05 was considered statistically significant.

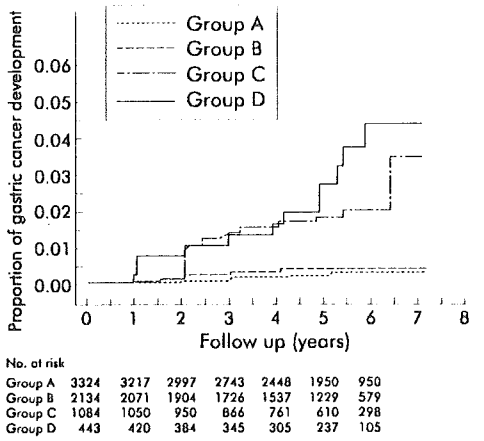


Figure 1 Kaplan-Meier analysis of the proportion of gastric cancer development classified by pepsinogen status and *Helicobacter pylori* antibody (groups A–D, see text for details). During follow up, gastric cancer developed in seven of 3324 group A patients (0.2%), six of 2134 group B patients (0.3%), 18 of 1082 group C patients (1.7%), and 12 of 443 group D patients (2.7%) ($p<0.0001$ by log rank test).

RESULTS

Baseline characteristics of study subjects

Baseline clinical characteristics of the study subjects are summarised in table 1. Of 6983 subjects, 3324 (47.6%) were categorised as group A, 2134 (30.6%) as group B, 1082 (15.5%) as group C, and 443 (6.3%) as group D. Each subject underwent 5.1 (0.05) sessions of endoscopy during a follow up period of 4.7 (0.04) years.

Gastric cancer development

Among 6983 subjects analysed, 43 (37 men and six women) developed gastric cancer during the follow up period. The annual incidence rate of gastric cancer development, as calculated by the person-year method, was 0.13% (95% confidence interval (CI) 0.10%–0.18%). Histopathological features of gastric cancer were intestinal in 34 and diffuse in nine cases. Gastric cardia was involved in two cases. All of the cancers were localised within the submucosa except for one invading the muscularis propria (group B). Twenty three cases were treated by endoscopic resection and 20 cases underwent surgical operation. All were alive in August 2004.

Table 1 Characteristics of the subgroups classified according to serum pepsinogen and *Helicobacter pylori* antibody status

	Group A	Group B	Group C	Group D	Total
Pepsinogen status	Normal	Normal	Atrophic	Atrophic	
H pylori antibody status	−	+	+	−	
No of subjects	3324	2134	1082	443	6983
Male	2260	1489	713	320	4782
Female	1064	645	369	123	2201
Age (y) (mean (SD))	47.1 (8.1)	49.2 (8.3)	52.0 (8.5)	53.3 (8.8)	48.9 (8.5)
Pepsinogen I (mean (SD))	54.3 (23.9)	73.7 (29.0)	41.9 (17.3)	35.7 (19.0)	57.1 (27.4)
Pepsinogen II (mean (SD))	10.1 (7.3)	20.6 (12.1)	20.3 (6.8)	17.9 (7.5)	15.4 (10.3)
No of endoscopies* (mean (SD))	5.1 (2.0)	5.1 (2.0)	5.0 (1.9)	5.0 (1.9)	5.1 (2.0)
Duration of follow up (y) (mean (SD))	4.8 (1.6)	4.7 (1.7)	4.7 (1.7)	4.5 (1.7)	4.7 (1.7)

*Number of endoscopic examinations.

Table 2 Association of subgroups classified according to serum pepsinogen and *Helicobacter pylori* antibody status

	Group A	Group B	Group C	Group D
No of subjects	3324	2134	1082	443
Gastric cancer	7	6	18	12
Annual incidence rate (%/y)	0.04	0.06	0.35	0.60
Histopathological features				
Site*				
Cardia	2	0	0	0
Non-cardia	5	6	18	12
Differentiation				
Intestinal	5	5	14	10
Diffuse	2	1	4	2

*p = 0.0148 by Kruskal-Wallis test with Bonferroni's correction.

Antibody-pepsinogen status and gastric cancer development

Of 43 cases with gastric cancer, seven were from group A, six from group B, 18 from group C, and 12 from group D. The annual incidence rate was 0.04% (95% CI 0.02%–0.09%), 0.06% (0.03%–0.13%), 0.36% (0.23%–0.57%), and 0.60% (0.34%–1.05%) in groups A, B, C, and D, respectively. The cumulative incidence of gastric cancer by Kaplan-Meier analysis is shown in fig 1, as stratified by group. Groups C and D had a significantly higher incidence of gastric cancer than groups A and B (fig 1). Histopathological features of gastric cancer are shown in table 2. Two cases were found in the gastric cardia and the other 41 elsewhere. Both cardiac cancers occurred in group A. In contrast, no association was found between the groups and histopathological differentiation of cancer.

Risk factors for gastric cancer and establishment of super high risk group

Age, sex, and "group" were revealed to be independent risk factors by the Cox proportional hazard model (table 3). Hazard ratios (95% CI) compared with group A were 1.1 (0.4–3.4; p = 0.81) in group B, 6.0 (2.4–14.5; p<0.0001) in group C, and 8.2 (3.2–21.5; p<0.0001) in group D.

Incidence rates of gastric cancer stratified by age, sex, and "group" are shown in fig 2. Males older than 60 years in group D showed the highest annual incidence of 1.8% (95% CI 0.81%–3.82%). The incidence rate in the same age group was much lower in groups A and B, being less than 0.5% per year.

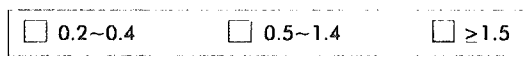
DISCUSSION

Gastric cancer is the second (in males) and fourth (in females) lethal cause of malignancy in the world.[26] It still remains the most common malignancy in many countries.[27] *H pylori* has been established as a definite carcinogen for gastric cancer.[28] However, the magnitude of the association in reports has been diverse, especially in Eastern countries suffering high prevalence rates of gastric cancer.[10 12 15] Uemura *et al* claimed from the results of their follow up study that all gastric cancers developed from patients with *H pylori* infection, and that the risk was highly associated with gastric atrophy status induced by *H pylori*.[5] The result is epoch making and revealing in terms of understanding and preventing gastric carcinogenesis. However, their results were based on hospitalised patients with gastrointestinal diseases, as well as other follow up studies.[29 30] It should be validated in other settings, in particular in the general population.

Ours is the first large scale prospective follow up study using serum pepsinogen and anti-*H pylori* antibody to estimate the incidence of gastric cancer in the general population. Subjects in our study were consecutive participants in a general health checkup programme, a very common activity in Japan.[17 22 24 31] Participants were symptom free, and those with peptic ulcers or gastric cancers were excluded from the cohort, as they were receiving treatments such as gastric acid suppression, *H pylori* eradication, or surgery. It is likely that our subjects represent the healthy Japanese population, with fewer biases than hospitalised patients. Moreover, as was shown by the average number of endoscopic examinations, gastric cancer development was closely and evenly surveyed in each group. Thus gastric cancer development could be accurately detected with

Table 3 Hazard ratio assessment adjusted by Cox proportional hazard model

	Hazard ratio	95% CI	p Value
Group			
A	1		
B	1.1	0.4–3.4	0.81
C	6.0	2.4–14.5	<0.0001
D	8.2	3.2–21.5	<0.0001
Age (y)			
<60	1		
≥60	5.3	2.9–9.9	<0.0001
Sex			
Female	1		
Male	3.2	1.3–8.2	0.01



		Group A	Group B	Group C	Group D
Pepsinogen index		Normal	Normal	Atrophic	Atrophic
Hp-Ab		Negative	Positive	Positive	Negative
Age <60 y	Female	0/971 0%/y	1/571 0.04%/y	0/319 0%/y	0/92 0%/y
	Male	5/2103 0.1%/y	1/1307 0.02%/y	11/563 0.4%/y	4/237 0.4%/y
Age ≥60 y	Female	0/93 0%/y	1/74 0.3%/y	1/50 0.5%/y	2/31 1.5%/y
	Male	2/157 0.3%/y	3/182 0.4%/y	6/150 1.0%/y	6/83 1.8%/y

Incidence/subjects (% year)

Figure 2 Incidence rates of gastric cancer stratified by age, sex, and serological status. Subjects older than 60 years in group D showed the highest annual incidence of 1.8% in males and 1.5% in females. The incidence rate in the same age group was much lower in groups A and B, being less than 0.5% per year. Hp-Ab, *Helicobacter pylori* antibody.

minimum delay or aberration. The present study would no doubt estimate precise incidence rates of gastric cancer in the general population.

Serological markers were used in this study for gastric atrophy status induced by *H pylori*. Subjects were stratified according to *H pylori* antibody and pepsinogen status into groups A, B, C, and D. Group A (negative for *H pylori* and normal pepsinogen normal) was assumed to have no *H pylori* infection whereas the other groups were infected with *H pylori*. As was discussed in our previous study, group D was assumed to have the most advanced gastric atrophy due to *H pylori* infection in spite of being negative for *H pylori* antibody.[17] Pepsinogen levels indicated the most severe gastric atrophy in group D.[4 20 32] It is generally known that the *H pylori* burden decreases dramatically in such situations,[33] and *H pylori* antibody spontaneously disappears.[34] In fact, our preliminary data from the same cohort of the present study showed a small but significant progression of gastric atrophy and reduction of serum pepsinogen at eight year intervals in groups B and C, leading to group advancement in some patients.[35]

In the present study, among 6983 subjects analysed, 43 developed gastric cancer during the follow up period. The annual incidence rates of groups A–D steadily increased in this order. Our results are in agreement with those of Uemura *et al*, irrespective of the difference in study population and diagnostic method for *H pylori*.[5] In addition, we are able to define a super high risk group for the development of gastric cancer (group D). Group D comprised 25.7% of subjects older than 60 years, and gastric cancer developed at the highest rates of 1.8%/year in males and 1.5%/year in females from this group. In contrast, group B (*H pylori* positive and pepsinogen normal) showed the same low risk as group A without *H pylori* infection. Approximately 58% of those with *H pylori* infection could be regarded as having a negligible risk for at least five years.

In terms of histopathological features, cardiac cancers, which have been suspected to have little association with *H pylori*,[2 16] all developed in group A. Both intestinal- and diffuse-type gastric cancers were highly associated with *H pylori* infection, as has been reported in previous studies.[12 16]

In the present study, all of the gastric cancers detected by endoscopic follow up were resectable and most are expected to be curative. Although it is still to be confirmed by longer observation, close endoscopic follow up could be valuable for subjects in the high risk group. Furthermore, eradication of *H pylori* may be recommended in the population, even in low risks group who are infected with *H pylori*, if steady progression of gastric atrophy is assumed.

In conclusion, we prospectively observed the natural course of gastric cancer development in the Japanese general population. We found *H pylori* antibody and serum pepsinogen to be good predictive markers for the development of gastric cancer. There is an increasing tendency for gastrocarcinogenesis with progression of *H pylori* infection. We believe this study provides definitive baseline data for future prevention studies in gastric cancer.

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Conflict of interest: None declared.

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EDITOR'S QUIZ: GI SNAPSHOT

Robin Spiller, *Editor*

An unusual complication of Crohn's colitis

Clinical presentation

A 58 year old woman with Crohn's disease was admitted to our hospital with malaise, rigors, bloody diarrhoea, and a vague perianal pain. Her Crohn's disease was previously well controlled on mesalazine, with few exacerbations and no admissions to hospital. Routine colonoscopy three months previously had shown no active disease.

At admission, her temperature was 39.9°C, blood pressure 90/60 mm Hg, and pulse rate 110/minute. Physical examination was unremarkable with no evidence of perianal sepsis.

Laboratory blood analysis revealed a normal full blood count, urea, and electrolytes. Liver function tests showed bilirubin 92 µmol/l, alanine aminotransferase 204 IU/l, alkaline phosphatase 2320 IU/l, and gamma glutamyl transferase 14401 IU/l. Amylase was 122 U/l and C reactive protein was 312 mg/l. Blood gas analysis revealed a moderate metabolic acidosis.

Plain abdominal and chest *x* rays were unremarkable. An abdomino-pelvic ultrasound scan showed no abnormalities, and therefore an urgent computed tomography (CT) scan was performed.

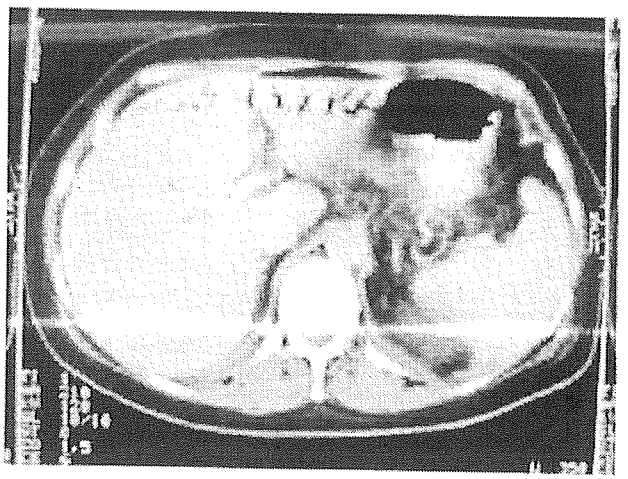

Figure 1

Question

What abnormalities do the CT images (figs 1, 2) show?

See page 796 for answer

This case is submitted by:

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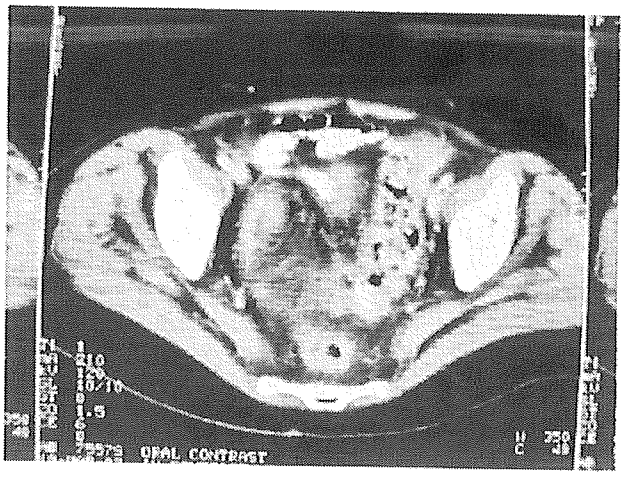

Figure 2