ことであり，そのためには，科学的根拠に基づいた有効な検査方法で，一定以上の受診率を確保することが求められている[6]。胃がん検診において間接X線検査はある程度の評価は受けているものの，これまでの取り組みから受診率の向上は期待困難な現状である。また，受診率が上がった場合の放射線被曝の問題も課題と考えられる[7]。一方，直接撮影による施設検診や内視鏡による個別検診も実施されているが，経費負担・精度管理等の課題が残されており，今後，さらに検討が必要と考えられる[3][4]。

そこで，胃がん検診のあり方について検討し，胃がん死亡率改善のために，まず，検診受診者の増加を計る対策として，簡便で理解しやすく，受診者の負担が少なく，経費的にも実施可能なPG法を採用することにした。PGは胃で特異的に産生される蛋白分解酵素ペプシンの前駆体で2種類のサブタイプ，PGI，PGIIが存在し，血清PGI値およびI／II比は，胃粘膜萎縮の程度とよく相関することが報告されている[8]。一方，胃粘膜の萎縮性変化は胃がんの発生と密接な関連があることから，PG値を指標とした胃がん高危険群の設定を行う胃がん検診の有用性が報告されている[9]。

実施に当たっては，PG法による胃がん検診の最大の問題点であるPG陰性胃がん対策として，「血清ペプシノゲン値による胃がんスクリーニングに関する研究」班（主任研究者　三木一正）により推奨されている間接X線検査の併用を採用すると共に，受診者への情報提供を十分に行った[10]。また，併用法として，PG検査と間接X線検査を同日に行う同日2段階法は機器の都合で実施困難であったため，基本検診実施時にPG測定用採血を行い，PG陰性例に対して後日，間接X線検査を行う異時2段階法で行った。このため，担当者の業務量は増加したが，対応可能な範囲であった。

平成16年度の検診において，胃がん検診受診者数は約40%増加した。市民講座，広報誌等により，PG検査は「あなたの胃がん危険度の指標」であること，および，検査の負担は，基本検診時の採血量の僅かな増加のみであるとの情報提供が十分行えた結果と考えている。今後，さらに，広報活動等により，PG検査併用胃がん検診受診者の増加に取り組む予定である。なお，胃がん検診受診者を現在の3から4倍に増加することを計る場合，その検診費用の負担についても考慮する必要がある。PG検査費用は間接X線検査の約1／4であり，また，PG陽性例については逐年の検査は不要で，1回測定後の胃がん検診としては，当分の間，必要例に対する精密検査受診勧告のみで管理可能であることも，経費的には大変な利点と考えられる。

平成16年度のPG検査結果については，全体の陽性率は47%であった。この成績は受診者の年齢構成から予想された数値に一致するものであった。当初，精密検査としての，胃内視鏡検査の受け入れ体制が地域に整っているか否か不安も指摘されたが，実際には十分対応され問題の発生は認められなかった。なお，内視鏡による精検受診者数は平成13，14年度に比べ平成15年度は約3倍，平成16年度は約5倍であった。この受検者数の増加が平成15，16年度における高いがん発見率に寄与したものと考えられる。検診全体の要精検率は約40%と，間接X線検査のみによる過去の検診に比し明らかに高頻度であった。がん検診の不利益の一つとして，過剰な検査が指摘されている。胃がん検診の精密検査の胃内視鏡検査における偶発症を考えると無視できない問題点である[11]。

一方，PGに関するこれまでの検討では，陽性度により胃がんのリスクは異なることが報告[12]されており，陽性度に従った精検制度を確立することで対応する可能性も考えられる。今回の検討では，（1＋）が13%であった。このグループの胃がん危険度は0.1%以下と報告されており，今後の検診・管理における取り扱いは現在協議中である。また，今後の経過観察において，（2＋），（3＋）陽性者の胃内視鏡検査の頻度について，逐年の内視鏡検査が必要か否か，隔年またはそれ以上の間隔をおけるか否か明確な指針は示されておらず，問題点として今後の課題である。また，PG値のみならず，環境要因，*HP*抗体，初回の内

視鏡所見等々を加味した，胃がん危険度の更なる評価方法の開発も今後の課題と考える[13)14)]。

また，PG陰性胃がん対策としての間接X線検査については，今回，機器の関係から，後日の実施となり，その受診率は27%程度であった。受診率の向上を計るためには同日の実施体制の確立が必要と考えている。また，PG検査陰性の意義に関する啓蒙活動も重要と考えている。

結語

最後に，今後のがん検診のあり方として，これまでのように同一の検査を例年全例に繰り返すことは効率的とは思われない。肝炎ウイルス検診[15)]で示されているように，危険度に従った検査体制を地域ごとに構築し，担当者による管理を十分に行っていくことが重要と考えている。石川県羽咋市では今後数年間にできるだけ多くの対象者，少なくとも対象者60%以上にPG検査を実施し，PG値からみた低リスク群には従来の間接X線検査による検診，高リスク群には医療機関の協力を得て定期的な胃内視鏡検査を実施し，このPG検査併用検診が近隣の対照地区と比較して胃がん死亡率の改善に寄与するか否かの検討を行う予定である。

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A study of stomach cancer mass screening using the pepsinogen test method in combination with the barium X-ray method.

Masashi UNOURA, Hiroshi YONEJIMA, Naoki IKEDA

Department of Internal Medicine, Hakui Public Hospital

In order to cope with the trend of decrease in the participation rate of Hakui City residents in stomach cancer mass screenings and the fact that the participants tend to be the same with no new residents joining the screenings, we investigated the efficiency of stomach cancer mass screening in Hakui City using the serum pepsinogen (PG) test method in combination with the barium X-ray method. The serum PG-I and -II levels were measured by chemiluminescent immunoassay as the first step. PG-positive subjects were recommended to undergo further screening by endoscopy, and PG-negative subjects were recommended to undergo examination by the barium X-ray method as the second step. In 2004, 1868 persons were enrolled in the study; the number of enrolled persons increased by 40% compared to the previous year. The total number of cases in which stomach cancer was discovered was 6, and the rate of discovery was 0.32%, a significant increase. Four of these were diagnosed as early cancer by endoscopy. The total PG-positive rate was 47%: 13% for 1+, 25.9% for 2+ and 8.2% for 3+. The subjects who needed further thorough examinations accounted for 39.9%, and 78.4% of the positive subjects were further examined by endoscopy. The total cost for the 2004 screening was almost half of that for the previous year. In conclusion, the two-step strategy comprising the PG test and barium X-ray can be used as a mass screening method for stomach cancer, because this method not only allows a larger population to participate, but also enables efficient examination, cost effectiveness, and improvement of the participants' safety. Further studies are needed to establish a method for following up those who have been found PG-positive and who are therefore at high risk for stomach cancer.

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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*

T. KAMADA*, J. HATA†, K. SUGIU*, H. KUSUNOKI*, M. ITO‡, S. TANAKA§, K. INOUE¶, Y. KAWAMURA**, K. CHAYAMA‡ & K. HARUMA*

**Division of Gastroenterology, Department of Internal Medicine, Kawasaki Medical School, Kurashiki; †Department of Clinical Pathology and Laboratory Medicine, Kawasaki Medical School, Kurashiki; ‡Department of Medicine and Molecular Science, Graduate School of Biomedical Science, Hiroshima University, Hiroshima; §Department of Endoscopy, Hiroshima University Hospital, Hiroshima; ¶Department of Internal Medicine, Matsue Red Cross Hospital, Matsue; **Department of Internal Medicine, Kawamura Hospital, Hiroshima, 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]

Correspondence to: Dr T. Kamada, Division of Gastroenterology, Department of Internal Medicine, Kawasaki Medical School, Matsushima 577, Kurashiki 701-0192, Japan.
E-mail: tkamada@med.kawasaki-m.ac.jp

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 ($n = 5$).

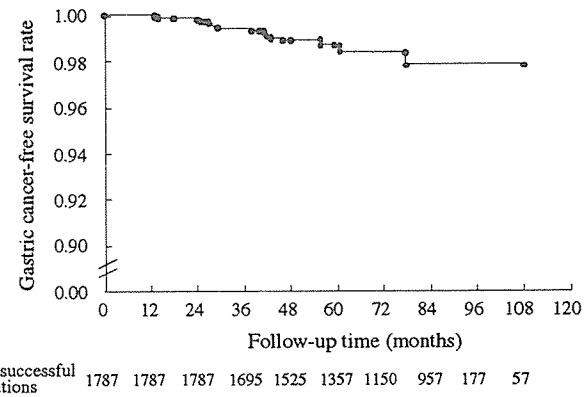

Figure 1. Kaplan–Meier analysis of gastric cancer-free survival after eradication of *Helicobacter pylori*. During follow-up, gastric cancer was discovered in 20 of 1787 (1.1%) patients who underwent successful eradication therapy.

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

H Watabe, T Mitsushima, Y Yamaji, M Okamoto, R Wada, T Kokubo, H Doi, H Yoshida, T Kawabe, M Omata

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See end of article for authors' affiliations

Correspondence to: Dr H Watabe, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan; hwatabe-gi@umin.ac.jp

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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.[1–3 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.[3] 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.[3]

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.

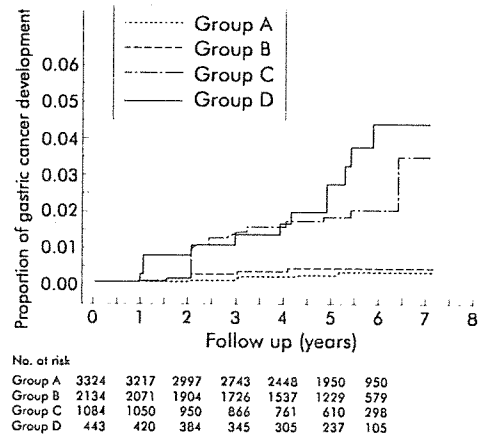


Figure 1 Kaplan-Meier analysis of the proportion of gastric cancer development classified by pepsinogen status and *Helicobacter pylori* antibody (groups A–D, see text for details). During follow up, gastric cancer developed in seven of 3324 group A patients (0.2%), six of 2134 group B patients (0.3%), 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.

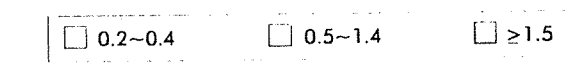
DISCUSSION

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 42] 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.

Authors' affiliations

H Watabe, Y Yamaji, Department of Gastroenterology, Graduate School of Medicine, University of Tokyo, Tokyo, Japan, and Makuhari Clinic, Chiba, Japan
T Mitsushima, Makuhari Clinic, Chiba, Japan, and Department of Gastroenterology, Kameda General Hospital, Chiba, Japan
M Okamoto, H Yoshida, T Kawabe, M Omata, Department of Gastroenterology, Graduate School of Medicine, University of Tokyo, Tokyo, Japan
R Wada, Department of Gastroenterology, Kameda General Hospital, Chiba, Japan
T Kokubo, Department of Pathology, Kameda General Hospital, Chiba, Japan
H Doi, Makuhari Clinic, Chiba, Japan

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.

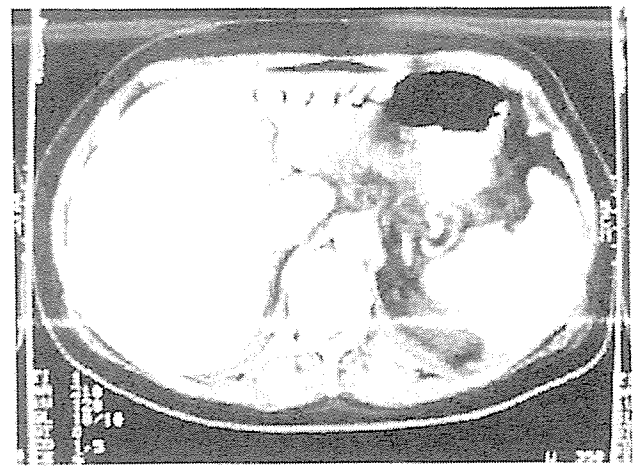

Figure 1

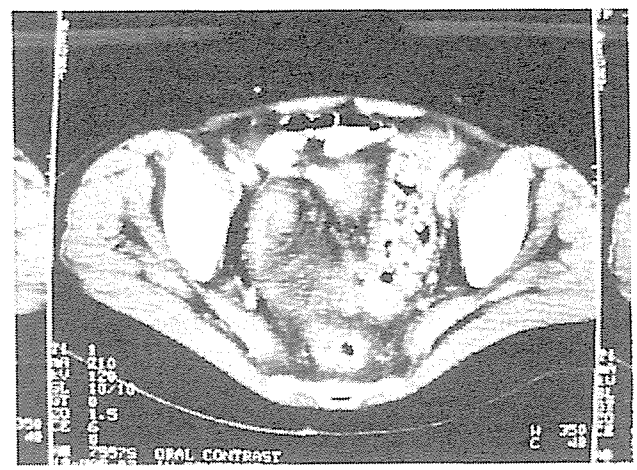

Figure 2

Question

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

See page 796 for answer

This case is submitted by:

S S Thethy
Department of Orthopaedics and Trauma, Royal Infirmary of Edinburgh, Edinburgh, UK
M A Potter
Department of Colorectal Surgery, Western General Hospital, Edinburgh, UK

Correspondence to: Dr S S Thethy, Department of Orthopaedics and Trauma, Royal Infirmary of Edinburgh, 26 Fernieside Gardens, Edinburgh EH17 7HN, UK; sthethy@hotmail.com

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Individual and joint impact of family history and *Helicobacter pylori* infection on the risk of stomach cancer: a nested case–control study

H Yatsuya*[,1], H Toyoshima[1], A Tamakoshi[2], S Kikuchi[3], K Tamakoshi[1], T Kondo[4], T Mizoue[5], N Tokui[6], Y Hoshiyama[7], K Sakata[8], N Hayakawa[9] and T Yoshimura[6], for the Japan Collaborative Cohort Study Group[10]

[1]Department of Public Health/Health Information Dynamics, Field of Social Life Science, Program in Health and Community Medicine, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya, Aichi 466-8550, Japan; [2]Department of Preventive Medicine/Biostatistics and Medical Decision Making, Field of Social Life Science, Program in Health and Community Medicine, Nagoya University Graduate School of Medicine, Nagoya, Japan; [3]Department of Public Health, Aichi Medical University, Aichi, Japan; [4]Department of Medical Technology, Nagoya University School of Health Sciences, Nagoya, Japan; [5]Department of Preventive Medicine, Kyushu University Graduate School of Medical Sciences, Fukuoka, Japan; [6]Department of Clinical Epidemiology, Institute of Industrial Ecological Sciences, University of Occupational and Environmental Health, Kirakyushu, Japan; [7]Department of Public Health, Showa University School of Medicine, Tokyo, Japan; [8]Department of Public Health, Wakayama Medical University, Wakayama, Japan; [9]Department of Epidemiology, Hiroshima University Research Institute for Radiation Biology and Medicine, Hiroshima, Japan

We used 202 cases of stomach cancer and 394 controls nested within the Japan Collaborative Cohort Study For Evaluation of Cancer Risk (JACC study) to investigate whether family history has an independent effect on the risk of stomach cancer after controlling for the *Helicobacter pylori* infection. A positive history of stomach cancer in one or more first-degree relatives was associated with an increased risk of the disease in women, but not in men after controlling for *H. pylori* infection and other confounding variables. Women with both a family history and *H. pylori* infection were associated with more than five-fold increased risk of the disease (OR 5.10, 95% CI 1.58–16.5) compared to those without these factors. These results suggest the existence of inherited susceptibility to the disease in women, and that measurements of *H. pylori* infection together with the family history allow meaningful evaluation of risk beyond that provided by either factor alone.
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Keywords: family history; *Helicobacter pylori*; stomach cancer; sex difference; nested case–control study; JACC study

Familial aggregation of stomach cancer has long been noted (Macklin, 1960; Toyoshima *et al*, 1997; Yatsuya *et al*, 2002; Kondo *et al*, 2003). Certain evidence, however, suggests that both genetic and environmental factors are responsible for familial clustering (Palli *et al*, 2001). One environmental risk factor is infection with *Helicobacter pylori* (*H. pylori*) (Talley *et al*, 1991), and previous studies have revealed that this also aggregates within families (Dominici *et al*, 1999).

A case–control study found that a family history of stomach cancer significantly increased the risk of the disease independent of *H. pylori* infection (Brenner *et al*, 2000). In addition, positive family history in individuals with *H. pylori* infection appeared to be a stronger risk factor for the disease compared to those without such an infection. There are, however, no prospective studies of this subject. We, therefore, conducted a nested case–control investigation within a cohort study to examine the independent effect of family history on the risk of stomach cancer after controlling first for the *H. pylori* infection, and, second, to evaluate any joint contribution of these two factors to the disease risk.

*Correspondence: Dr H Yatsuya; E-mail: h828@med.nagoya-u.ac.jp
[10] See Appendix A for the investigators (name and affiliation) involved in the JACC Study
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MATERIALS AND METHODS

JACC study

The study was part of the Japan Collaborative Cohort Study For Evaluation of Cancer Risk Sponsored by the Ministry of Education, Science, Sports and Culture of Japan (JACC Study), a nation-wide multicenter collaborative study to evaluate prospectively various risks or protective factors on cancer mortality and incidence. Details of the study design were reported previously (Ohno and Tamakoshi, 2001; Hoshiyama *et al*, 2002). Briefly, the cohort included 110 792 men and women (46 465 and 64 327, respectively), 40–79 years old at recruitment, enrolled in 1988–1990. Enrollment was based on the participants of a general health checkup that is periodically provided by the 45 municipalities involved. Informed consent procedures were approved by the Ethics Committee of Medical Care and Research, University of Occupational and Environmental Health, Kitakyushu, where the chief investigator of stomach cancer group is affiliated, and the Ethical Board of the

Nagoya University School of Medicine, Japan, where the present chairman of the JACC study is affiliated.

At the time of recruitment, baseline characteristics were gathered by self-administered questionnaires, which covered the medical history and included lifestyle-related items such as drinking and smoking, level of education, and family history of several medical conditions including cancer. About one-third of the cohort members ($n = 39\,293$) also donated a residual serum sample (about 2 ml) used for the general health checkup. It was partitioned into 0.3–0.5 ml aliquots and stored at −80°C until laboratory analyses.

Follow-up and identification of stomach cancer cases, and selection of control subjects

Vital statuses of the participants were checked annually by each regional research centre, with permission to review their population-register sheets from the Ministry of Public Management, Home Affairs, Post and Telecommunications. Incidence of cancer was ascertained in 24 study areas ($n = 65\,184$) and coded according to the tenth revision of International Classification of Diseases and the second edition of International Classification of Diseases for Oncology. These data were collected at the central office of the Research Committee.

We first restricted the subjects to those who lived in the study areas where cancer incidence was ascertained. We then excluded 857 participants with a self-reported history of cancer at any site. Among the remaining 64 327 subjects, diagnosis of stomach cancer 12 or more months after cohort recruitment was documented in 804 cases until the end of 1997. Serum had been obtained from 218 out of the initial 804 cases. However, seven cases without enough serum for laboratory analysis, and one case without an eligible control subject were excluded. In addition, one of the 24 study areas where family history was not assessed was excluded from the analysis. Thus, the study reported here included 202 cases (105 men and 97 women) in total. Lag time between blood sampling and stomach cancer diagnosis varied between 12 and 113 months (median 50 months). Each of these subjects was matched with two control subjects for gender, age at recruitment (as near as possible), and study area, who had also provided an adequate baseline blood sample and who were alive and remained free of confirmed cancer as of the end of 1997. Owing to a lack of eligible subjects, a few sets ($n = 10$) contained only one control; a total of 394 controls was available for the present analysis. As information on the location of cancer within the stomach or the histological type was not available in all cases, we did not use it to classify cases.

Laboratory assays

Serum samples from each case and matched controls were retrieved from storage and shipped on dry ice to a single laboratory for the assay. None of the samples had been previously defrosted. *H. pylori* infection was investigated serologically using HM-CAPTM (Enteric Products, Westbury, NY, USA) with antigen from Japanese (J-HM-CAP), and the serum titer of immunoglobulin G antibodies 2.3 or greater was defined as positive infection.

Definition of family history and covariates

Family history of stomach cancer was defined as when the subject had at least one first-degree relative with a history of stomach cancer. Risk factors that could potentially confound the relation between family history and stomach cancer other than *H. pylori* infection were collected at the baseline, using a self-administered questionnaire. A drinking habit was first categorised into three statuses (none, past, present). If present, it was further categorised into two levels by weekly consumption (light, heavy), that is, daily alcohol consumption times days of drinking per week. Smoking status was classified into three levels (never, past, current). Consumption frequency of vegetables, citrus fruits, and green tea was initially assessed in five levels (everyday, 3–4 times a week, 1–2 times a week, 1–2 times a month and seldom). For the present analysis, the former two and the latter three categories were combined. Salty-food preference was categorised into three levels (dislike, neutral, like). Information on educational level was measured as the age of formal schooling completed and was classified into two categories: $\leqslant 15$ years old (corresponds to $\leqslant 9$ years of schooling) and $\geqslant 16$ years old (corresponds to $\geqslant 10$ years of schooling). Missing values in each variable were treated as an additional category in the variable, and were included in the analyses.

Statistical analysis

We compared the baseline characteristics of case subjects and control subjects by one-way analysis of variance for continuous variables and χ^2 tests for categorical variables. We then performed logistic regression analysis, conditioned on the matching variables of gender, age, and study area, and presented the odds ratios (ORs) that represent the risk associated with a positive family history of stomach cancer. Adjusted estimates of risk were obtained with multivariate models that controlled for *H. pylori* infection, and other covariates listed above. To assess the joint effect of family history and *H. pylori* infection on the risk of stomach cancer, four categories were created by the combination of these two factors. Another logistic regression analysis was performed taking a category with no family history and no *H. pylori* infection as a reference. The 95% confidence intervals (95% CIs) are presented for all ORs. All reported *P*-values are two-sided. All analyses were performed separately for men and women with SPSS statistical package for windows version 11.5.

RESULTS

Table 1 shows the baseline characteristics of the 202 cases and the 394 matched controls. In this sample, the women diagnosed with stomach cancer were more likely to have a family history of stomach cancer, whereas men were not. The proportion of case subjects who reported a history of stomach cancer in a first-degree relative was 15.2 and 24.7% in men and women, respectively, against 16.3% in men and 15.1% in women in control subjects (*P*-values for the χ^2 test were 0.87 in men, 0.054 in women; case *vs* control). The proportion of individuals infected with *H. pylori* was high even in control subjects (79.7 and 78.6% for men and women, respectively). However, it was higher in cases with stomach cancer in men and especially in women. Cases and controls did not differ significantly in terms of smoking status, alcohol intake, or other diet-related items for both sexes. The proportion of women with a higher educational level seemed to be higher in controls compared to that in cases.

Table 2 shows the relation of family history of stomach cancer to the risk of the disease incidence. Family history of stomach cancer was significantly related to the risk of the disease incidence only in women. This association became attenuated after adjustment for *H. pylori* infection or other potentially confounding variables. A family history of stomach cancer did not seem to be related to the risk of the disease incidence in men in the present dataset.

The prevalence of *H. pylori* infection in men with a family history was 81.6%, against 82.2% in men without such a history (Table 3). In women, the prevalence was 88.7 and 81.4% in those with and without a family history, respectively. The difference in the proportion was not significant, showing that a positive family history of stomach cancer and *H. pylori* infection were not related

Table 1 Baseline characteristics of the study participants

Characteristic	Men ($n=307$)			Women ($n=289$)		
	Cases ($n=105$)	Controls ($n=202$)	*P*-value	Cases ($n=97$)	Controls ($n=192$)	*P*-value
Age category: no. (%)						
40–49	6 (5.7)	12 (5.9)	Matching factor	9 (9.3)	18 (9.4)	Matching factor
50–59	22 (21.0)	42 (20.8)		32 (33.0)	64 (33.3)	
60–69	52 (49.5)	104 (51.5)		39 (40.2)	77 (40.1)	
70–79	25 (23.8)	44 (21.8)		17 (17.5)	33 (17.2)	
Age (years): mean ± s.d.	63.6 ± 7.9	63.3 ± 7.8		61.6 ± 8.3	61.4 ± 8.3	
H. pylori infection: no. (%)						
Present	91 (86.7)	161 (79.7)	0.16	88 (90.7)	151 (78.6)	0.013
Absent	14 (13.3)	41 (20.3)		9 (9.3)	41 (21.4)	
Family history of stomach cancer: no. (%)						
Present	16 (15.2)	33 (16.3)	0.87	24 (24.7)	29 (15.1)	0.054
Absent	89 (84.8)	169 (83.7)		73 (75.3)	163 (84.9)	
Number of siblings						
0–2	11 (10.5)	28 (13.9)	0.73	13 (13.4)	25 (13.0)	0.97
3–5	46 (43.8)	79 (39.1)		42 (43.3)	88 (45.8)	
6–	31 (29.5)	57 (28.2)		28 (28.9)	51 (26.6)	
Missing	17 (16.2)	38 (18.8)		14 (14.4)	28 (14.6)	
Smoking status: no. (%)						
Never	17 (16.2)	35 (17.3)	0.35	86 (88.7)	168 (87.5)	0.52
Past	31 (29.5)	57 (28.2)		1 (1.0)	1 (0.5)	
Current	55 (52.4)	97 (48.0)		4 (4.1)	4 (2.1)	
Missing	2 (1.9)	13 (6.4)		6 (6.2)	19 (9.9)	
Alcohol intake: no. (%)						
None	21 (20.0)	42 (20.8)	0.41	69 (71.1)	146(76.0)	0.82
Past	7 (6.7)	6 (3.0)		3 (3.1)	4 (2.1)	
Light drinker	37 (35.2)	83 (41.1)		13 (13.4)	21 (10.9)	
Heavy drinker	23 (21.9)	34 (16.8)		0 (0.0)	1 (0.5)	
Missing	17 (16.2)	37 (18.3)		12 (12.4)	20 (10.4)	
Educational level: no. (%)						
⩽9 years of schooling	27 (25.7)	65 (32.2)	0.49	32 (33.0)	45 (23.4)	0.19
⩾10 years of schooling	56 (53.3)	100 (49.5)		46 (47.4)		
Missing	22 (21.0)	37 (18.3)		19 (19.6)	37 (19.3)	
Salty-food preference: no. (%)						
Dislike	10 (9.5)	31 (15.3)	0.57	24 (24.7)	29 (15.1)	0.11
Neutral	39 (37.1)	71 (35.1)		36 (37.1)	97 (50.5)	
Like	39 (37.1)	69 (34.2)		19 (19.6)	36 (18.8)	
Missing	17 (16.2)	31 (15.3)		18 (18.6)	30 (15.6)	
Tomatoes: no. (%)						
⩽1–2 times/week	52 (49.5)	105 (52.0)	0.89	47 (48.5)	94 (49.0)	0.61
⩾3–4 times/week	42 (40.0)	75 (37.1)		44 (45.4)	80 (41.7)	
Missing	11 (10.5)	22 (10.9)		6 (6.2)	18 (9.4)	
Citrus fruits: no. (%)						
⩽1–2 times/week	48 (45.7)	79 (39.1)	0.49	29 (29.9)	65 (33.9)	0.78
⩾3–4 times/week	44 (41.9)	91 (45.0)		56 (57.7)	106 (55.2)	
Missing	13 (12.4)	32 (15.8)		12 (12.4)	21 (10.9)	
Spinach and green vegetables: no. (%)						
⩽1–2 times/week	29 (27.6)	64 (31.7)	0.55	30 (30.9)	60 (31.3)	0.95
⩾3–4 times/week	65 (61.9)	112 (55.4)		58 (59.8)	112 (58.3)	
Missing	11 (10.5)	26 (12.9)		9 (9.3)	20 (10.4)	
Carrots and pumpkins: no. (%)						
⩽1–2 times/week	44 (41.9)	86 (42.6)	0.85	35 (36.1)	78 (40.6)	0.70
⩾3–4 times/week	52 (49.5)	95 (47.0)		52 (53.6)	98 (51.0)	
Missing	9 (8.6)	21 (10.4)		10 (10.3)	16 (8.3)	
Green tea: no. (%)						
⩽1–2 times/week	11 (10.5)	13 (6.4)	0.32	11 (11.3)	21 (10.9)	1.00
⩾3–4 times/week	93 (88.6)	184 (91.1)		83 (85.6)	165 (85.9)	
Missing	1 (1.0)	5 (2.5)		3 (3.1)	6 (3.1)	

Table 2 Multivariate conditional logistic regression models examining the relation between family history and the risk of stomach cancer

	Men (105 cases/202 controls)			Women (97 cases/192 controls)		
Variables adjusted for	**RR**	**95% CI**	***P*-value**	**RR**	**95% CI**	***P*-value**
Univariate	0.96	0.48–1.91	0.907	1.92	1.02–3.64	0.044
Model 1	0.99	0.49–2.03	0.985	1.78	0.92–3.46	0.065
Model 2	0.89	0.40–1.97	0.768	1.73	0.82–3.65	0.153

CI = onfidence interval. Model 1: Adjusted for *H. pylori* infection and the number of siblings (0–2, 3–5, 6+). Model 2: Adjusted for *H. pylori* infection, the number of siblings (0–2, 3–5, 6+), smoking status (never, past, current), drinking habit self-rated preference of salty foods (dislike, neutral, like), consumption of green–yellow vegetables, citrus fruits and green tea (≥3–4 times a week, ≤1–2 times a week), and educational level (≤9 years of schooling, ≥10 years of schooling). Missing values in each variable were treated as an additional category.

Table 3 Association between family history of stomach cancer and *H. pylori* infection, and joint contribution of family history and *H. pylori* infection on the risk of stomach cancer

		No. of subjects	*P* for 2 × 2 χ^2 test	No. of cases	OR[a]	95% CI	OR[b]	95% CI
Men								
FH negative	*Hp negative*	46 (17.8%)	1.00	12	1	(reference)	1	(reference)
	Hp positive	212 (82.2%)		77	1.63	0.80–3.33	1.81	0.79–4.15
FH positive	*Hp negative*	9 (18.4%)		2	0.76	0.13–4.44	0.72	0.11–4.86
	Hp positive	40 (81.6%)		14	1.64	0.62–4.32	1.66	0.54–5.12
Women								
FH negative	*Hp negative*	44 (18.6%)	0.234	7	1	(reference)	1	(reference)
	Hp positive	192 (81.4%)		66	2.92	1.22–6.99	2.98	1.10–8.02
FH positive	*Hp negative*	6 (11.3%)		2	2.02	0.30–13.6	1.84	0.17–19.9
	Hp positive	47 (88.7%)		22	5.30	1.87–15.0	5.10	1.58–16.5

CI = confidence interval; FH = family history; Hp = *H. pylori*. OR[a]: Crude odds ratio. OR[b]: Odds ratio adjusted for the number of siblings (0–2, 3–5, 6+), smoking status (never, past, current), drinking habit self-rated preference of salty foods (dislike, neutral, like), consumption of green–yellow vegetables, citrus fruits and green tea (≥3–4 times a week, ≤1–2 times a week), and educational level (≤9 years of schooling, ≥10 years of schooling). Missing values in each variable were treated as an additional category.

in this study sample, especially in men and to a lesser degree in women (*P*-value for χ^2 test 1.00 and 0.23 for men and women, respectively).

In another logistic regression analysis comparing the risk of the disease among the four subgroups created by the combination of presence or absence of a family history and *H. pylori* infection, significantly increased risk (multivariate adjusted OR 5.10, 95% CI 1.58–16.5) was observed in women with a family history of stomach cancer and *H. pylori* infection compared with those without these risk factors. In men, however, no significant associations were observed.

DISCUSSION

In this case–control study nested within a large-scale cohort of Japanese, we found that women with a family history of stomach cancer were associated with an increased risk of the disease independent of *H. pylori* infection. Women with both a family history and *H. pylori* infection had a greater than five-fold increased risk of the disease compared to those without these factors. The combined effect of these factors on the final risk of stomach cancer is approximately equivalent to the multiplicative product of the risks from the separate factors. Some biologic interaction between these two factors has been reported previously (Sepulveda *et al*, 2002). In a study of familial gastric cancer kindred, Rocco *et al* (2003) observed genetic abnormalities in the stomach of the first-degree relatives only in the presence of *H. pylori* infection, suggesting an interplay between the infection and the genetic profile of the host.

We did not find a significant association in men. This did not seem to be caused by a confounding of *H. pylori* infection. Some previous studies found stronger impact of family history on the disease risk in women than in men, which may partly be consistent with the present finding (Nagase *et al*, 1996; Yatsuya *et al*, 2002). Family history of stomach cancer was associated with a significantly increased risk of the disease (OR 4.5, 95% CI 1.3–15.2) in women, whereas it was related to a nonsignificant increased risk in men (OR 1.2, 95% CI 0.6–2.5) in a hospital-based case–control study in Japan (Nagase *et al*, 1996). The relative risk associated with a positive family history adjusted for age and the size of the family was 1.28 (95% CI 0.95–1.72) in men and 1.92 (95% CI 1.33–2.77) in women in a prospective study of Japanese (Yatsuya *et al*). However, other studies did not necessarily find the effect restricted to women (Palli *et al*, 1994; Inoue *et al*, 1998), which would suggest that the gender difference observed in the present study may be related to the study limitations.

First, the present study is based on about one-third of the cohort members who donated residual serum sample used for the general health checkup. Due to the fact that our previous study found an increased risk associated with a family history in men, though the increase was of borderline strength (Yatsuya *et al*, 2002), it might be possible that the male sample for this nested case–control study may potentially be biased. Future study with more cases with blood sample or with another indicator of *H. pylori* infection is needed to elucidate this issue.

Second, we did not classify cases by the location of cancer within the stomach or the histological type because the relevant information was not available in all cases. Stomach cancer in

cardia was not associated with a family history of the disease in a case-control study conducted in Japan (Inoue *et al*, 1998). In addition, cancer in gastric cardia is reported to be associated more to environmental exposures, such as smoking or alcohol drinking (Inoue *et al*, 1994; Sasazuki *et al*, 2002), and environmental exposures in men were more diverse than in women, which may contribute to mask or exceed the effect of family history.

Third, recall of family cancer history is reported to differ between men and women, that is, women provided the history more accurately than men in a validation study (Kerber and Slattery, 1997); several studies have indicated the possibility of gender bias in recall as an explanation for the gender-specific association found in women (Wu *et al*, 1996). The lack of association in men in this study sample may be caused by a misclassification of subjects due to inaccurate reporting of family history, which would have attenuated the association.

Unexpectedly, family history of stomach cancer and serological prevalence of *H. pylori* infection assessed at the time of enrollment were not related in the combined sample of cases and controls in the present study. This may be due to a higher prevalence of *H. pylori* infection in the present sample than in the previous studies that found positive associations (45–70%) (Kikuchi *et al*, 1998; Brenner *et al*, 2000). Clearance of the infection in the course of development of stomach cancer via chronic atrophic gastritis may possibly explain the lack of association because such clearance is of likely relevance for some proportion of cases even when blood samples have been taken several years before diagnosis.

In conclusion, a family history of stomach cancer was associated with an increased risk of the disease in women. In addition, we observed that women with both a family history and *H. pylori* infection were associated with a greater than five-fold increased risk of the disease compared to those without these risk factors. Measurements of *H. pylori* infection together with the family history allow meaningful refinement of risk stratification beyond that provided by either factor alone. The study thereby partly confirms and extends the still quite limited empirical evidence on an issue that might well be relevant for potential screening strategies at least in women.

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Appendix A

Japan Collaborative Cohort Study Group

The present members of the JACC Study and their affiliations are as follows: A Tamakoshi (present chairman of the study group, Nagoya University Graduate School of Medicine); M Mori (Sapporo Medical University School of Medicine); Y Motohashi (Akita University School of Medicine); I Tsuji (Tohoku University Graduate School of Medicine); Y Nakamura (Jichi Medical School); H Iso (Institute of Community Medicine, University of Tsukuba); H Mikami (Chiba Cancer Center); Y Inaba (Juntendo University School of Medicine); Y Hoshiyama (Showa University School of Medicine); H Suzuki (Niigata University Graduate School of Medical and Dental Sciences); H Shimizu (Gifu University School of Medicine); H Toyoshima (Nagoya University Graduate School of Medicine); S Tokudome (Nagoya City University Graduate School of Medicine); Y Ito (Fujita Health University School of Health Sciences); S Hashimoto (Fujita Health University School of Medicine); S Kikuchi (Aichi Medical University School of Medicine); A Koizumi (Graduate School of Medicine and Faculty of Medicine, Kyoto University); T Kawamura (Kyoto University Center for Student Health); Y Watanabe and T Miki (Kyoto Prefectural University of Medicine Graduate School of Medical Science); C Date (Faculty of Human Environmental Sciences, Mukogawa Women's University); K Sakata (Wakayama Medical University); T Nose (Tottori University Faculty of Medicine); N Hayakawa (Research Institute for Radiation Biology and Medicine, Hiroshima University); T Yoshimura (Institute of Industrial Ecological Sciences, University of Occupational and Environmental Health, Japan); K Fukuda (Kurume University School of Medicine); N Okamoto (Kanagawa Cancer Center); H Shio (Moriyama Municipal Hospital); Y Ohno (former chairman of the study group, Asahi Rosai Hospital); T Kitagawa (Cancer Institute of the Japanese Foundation for Cancer Research); T Kuroki (Gifu University); and K Tajima (Aichi Cancer Center Research Institute).