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

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.
Serum \textit{H pylori} antibody

Serum anti-\textit{H pylori} antibody was measured using a commercial ELISA kit (GAP-IgG kit; Biomerica Inc., California, USA). Seropositivity for \textit{H pylori} antibody was defined by optical density values according to the manufacturer’s protocol. Sensitivity for \textit{H pylori} infection in Japanese were reported to be 95% and 83%, respectively, with the results of specific culture.\textsuperscript{21}

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 <70 ng/ml and a pepsinogen I/II ratio (serum pepsinogen I (ng/ml)/serum pepsinogen II (ng/ml)) ≤ 3.0 were simultaneously fulfilled, as proposed by Miki and colleagues.\textsuperscript{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.\textsuperscript{23} These criteria have been widely applied to mass screening for gastric cancer in Japan.\textsuperscript{17 \textsuperscript{22 \textsuperscript{24}}}

Classification by anti-\textit{H pylori} antibody and serum pepsinogen status

Subjects were classified into four groups according to serum pepsinogen status and \textit{H pylori} status antibody at enrolment. Group A had “normal” pepsinogen and were negative for \textit{H pylori} antibody. Group B had “normal” pepsinogen and were positive for \textit{H pylori} antibody. Group C had “atrophic” pepsinogen and were positive for \textit{H pylori} antibody. Group D had “atrophic” pepsinogen and were negative for \textit{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.\textsuperscript{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. Differences 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.

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>
<thead>
<tr>
<th>Table 1</th>
<th>Characteristics of the subgroups classified according to serum pepsinogen and \textit{Helicobacter pylori} antibody status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>Group B</td>
</tr>
<tr>
<td>Pepsinogen status</td>
<td>Normal</td>
</tr>
<tr>
<td>\textit{H pylori} antibody status</td>
<td>-</td>
</tr>
<tr>
<td>No of subjects</td>
<td>3324</td>
</tr>
<tr>
<td>Male</td>
<td>2260</td>
</tr>
<tr>
<td>Female</td>
<td>1064</td>
</tr>
<tr>
<td>Age (y) (mean (SD))</td>
<td>47.1 (8.1)</td>
</tr>
<tr>
<td>Pepsinogen I (mean (SD))</td>
<td>54.3 (23.9)</td>
</tr>
<tr>
<td>Pepsinogen II (mean (SD))</td>
<td>10.1 (7.2)</td>
</tr>
<tr>
<td>No of endoscopies* (mean (SD))</td>
<td>4.8 (3.6)</td>
</tr>
</tbody>
</table>

*Number of endoscopic examinations.
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% Cl 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% Cl) 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% Cl 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.27 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

### Table 3: Hazard ratio assessment adjusted by Cox proportional hazard model

<table>
<thead>
<tr>
<th>Group</th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>1.1</td>
<td>0.4–3.4</td>
<td>0.81</td>
</tr>
<tr>
<td>C</td>
<td>6.0</td>
<td>2.4–14.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>D</td>
<td>8.2</td>
<td>3.2–21.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age (y)</td>
<td>&lt;60</td>
<td>5.3</td>
<td>2.9–9.9</td>
</tr>
<tr>
<td></td>
<td>&gt;60</td>
<td>3.2</td>
<td>1.3–8.2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age (&lt;60 y)</th>
<th>Female</th>
<th>0/971</th>
<th>0% /y</th>
<th>1/571</th>
<th>0.04% /y</th>
<th>0/319</th>
<th>0% /y</th>
<th>0/92</th>
<th>0% /y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>5/2103</td>
<td>0.1% /y</td>
<td>1/1307</td>
<td>0.02% /y</td>
<td>11/563</td>
<td>0.4% /y</td>
<td>4/237</td>
<td>0.4% /y</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age (&gt;60 y)</th>
<th>Female</th>
<th>0/93</th>
<th>0% /y</th>
<th>1/74</th>
<th>0.3% /y</th>
<th>1/50</th>
<th>0.5% /y</th>
<th>2/31</th>
<th>1.5% /y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>2/157</td>
<td>0.3% /y</td>
<td>3/182</td>
<td>0.4% /y</td>
<td>6/150</td>
<td>1.0% /y</td>
<td>6/83</td>
<td>1.8% /y</td>
<td></td>
</tr>
</tbody>
</table>

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 *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.\(^{21, 22}\) It is generally known that the *H. pylori* burden decreases dramatically in such situations,\(^{13}\) and *H. pylori* antibody spontaneously disappears.\(^{14}\) 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.\(^{15}\)

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*.\(^{23}\) 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*,\(^{24}\) 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.\(^{13, 14}\)

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 gastrocancerogenesis 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 Omo, Department of Gastroenterology, Graduate School of Medicine, University of Tokyo, Tokyo, Japan

R Wada, Department of Gastroenterology, Kameda General Hospital, Chiba, Japan

\*Correspondence to: T Kokubo, Department of Pathology, Kameda General Hospital, Chiba, Japan

H Doi, Makuhari Clinic, Chiba, Japan

Conflict of interest: None declared.

Part of this study was presented in the research forum at the Annual meeting of the American Gastroenterology Association, Orlando, Florida, 20 May 2003.

**REFERENCES**


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.

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 EH11 7HN, UK; sthethy@hotmail.com
doi: 10.1136/gut.2004.057729

Figure 1

Figure 2
An unusual complication of Crohn's colitis

S S Thethy and M A Potter

Gut 2005 54: 768
doi: 10.1136/gut.2004.057729

Updated information and services can be found at:
http://gut.bmj.com/content/54/6/768

These include:

Email alerting service

Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/