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.[1–3 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.[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.

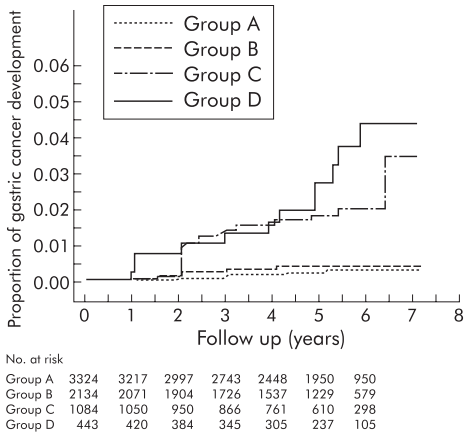

Figure 1 Kaplan-Meier analysis of the proportion of gastric cancer development classified by pepsinogen status and *Helicobacter pylori* antibody (groups A–D, see text for details). During follow up, gastric cancer developed in seven of 3324 group A patients (0.2%), six of 2134 group B patients (0.3%),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

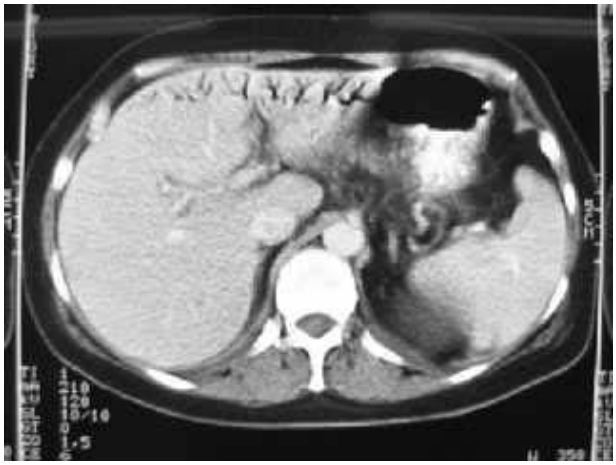

Figure 1

Figure 2

Question

What abnormalities do the CT images (figs 1, 2) show?
See page 796 for answer
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