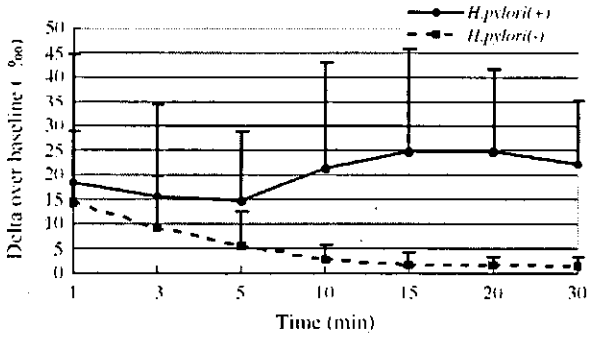

Fig. 2. The mean breath $\Delta^{13}CO_2$ values at various time points collected through the mouth in *H. pylori*-positive and -negative patients. Values are significantly different at 3 min and later ($P < 0.02$).

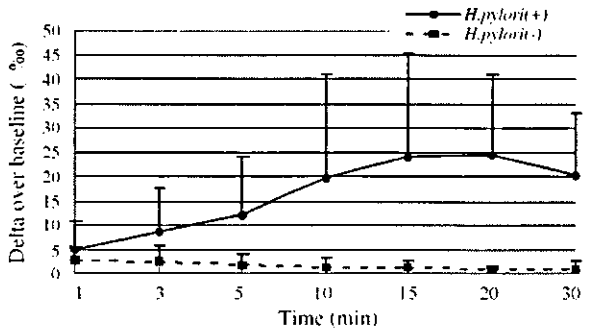

Fig. 3. The mean breath $\Delta^{13}CO_2$ values at various time points collected through the nostril in *H. pylori*-positive and -negative patients. The breath $\Delta^{13}CO_2$ values at all time points were higher in *H. pylori*-positive patients than in *H. pylori*-negative patients ($P < 0.003$).

pylori-negative patients ($P < 0.02$). When breath samples were collected through the nostril, the breath $\Delta^{13}CO_2$ value at 1 min was already higher in *H. pylori*-positive patients than in *H. pylori*-negative patients ($P < 0.003$) (Fig. 3).

Tables 1 and 2 show that the cut-off values for the modified UBT, as well as for the standard UBT, were optimal at each time point. At the 20-min sampling point, the sensitivity and specificity of the modified UBT were both 100% using 2.5‰ as the cut-off value, whereas the sensitivity and specificity of the standard UBT were 97.7 and 94.2%, respectively, using 3‰ as the best cut-off value. At the 15-min sampling point, the optimal cut-off values for the diagnosis of *H. pylori* infection were identified as 3.5‰ in the modified UBT and 5.0‰ in the standard UBT. The sensitivity and specificity of modified UBT and standard UBT at 15 min were 93.0 and 98.8%, and 90.7 and 95.4%, respectively. When shortening the duration of the test and sampling at 10 min, the modified UBT had a sensitivity of 93% and a specificity of 95.3%, using 2.5‰ as the best cut-off value (Table 1). The modified UBT was more accurate than the standard UBT for determining *H. pylori* infection with superior sensitivity and specificity ($P < 0.001$).

4. Discussion

Various modifications of UBT have been reported, including changes in dosage of urea, type of test meals used, timing of sample collection and position of patients [1,7,12–15]. A Japanese standard protocol was proposed in 1998 as having high sensitivity and specificity for UBT [1]. In this method, the patients who have fasted are given 100 mg of ^{13}C-urea in 100 ml water and then their mouth is immediately rinsed with water. After that they are placed in the left lateral decubitus position for 5 min. Breath samples are collected at the baseline and at 20 min after ingestion of ^{13}C-urea. The cut-off value of UBT for the diagnosis of *H. pylori* infection is 2.5‰. If UBT results are not affected by urease activity in the mouth, it is possible to decrease the duration of the test. The shorter the duration of the test, the more convenient it is for the patient. In addition, it becomes possible to eliminate the problem of false-positive results in late breath samples caused by urease-producing bacteria in the intestine.

To avoid interference by oral bacteria, we can change either the administration route of ^{13}C-urea or the collection route of breath samples. Some investigators have reported the endoscopic UBT in which the ^{13}C-urea was directly into

Table 1
Sensitivity, specificity and accuracy of the modified UBT in which breath samples are collected through the nostril at each cut-off value

Cut-off value (Δ‰)	Sensitivity (%) (sampling time)			Specificity (%) (sampling time)			Accuracy (%) (sampling time)		
	10 min	15 min	20 min	10 min	15 min	20 min	10 min	15 min	20 min
1.0	100	100	100	45.3	25.6	64.0	63.6	50.4	76.0
1.5	97.7	100	100	76.7	60.5	87.2	83.7	73.6	91.5
2.0	97.7	97.7	100	89.5	93.0	96.5	92.2	94.6	97.7
2.5	93.0	97.7	100	95.3	95.3	100	94.6	96.1	100
3.0	90.7	95.3	95.3	96.5	96.5	100	94.6	96.1	98.4
3.5	88.4	93.0	95.3	97.7	98.8	100	94.6	96.9	98.4
4.0	88.4	90.7	93.0	97.7	98.8	100	94.6	96.1	97.7
4.5	86.0	88.4	93.0	97.7	98.8	100	93.8	95.3	97.7
5.0	81.4	88.4	90.7	98.8	98.8	100	93.0	95.3	96.9
5.5	81.4	86.0	90.7	98.8	100	100	93.0	95.3	96.9
6.0	81.4	83.7	90.7	98.8	100	100	93.0	94.6	96.9

Table 2
Sensitivity, specificity and accuracy of the standard UBT in which breath samples are collected through the mouth at each cut-off value

Cut-off value (Δ‰)	Sensitivity (%) (sampling time)			Specificity (%) (sampling time)			Accuracy (%) (sampling time)		
	10 min	15 min	20 min	10 min	15 min	20 min	10 min	15 min	20 min
1.0	100	100	97.7	31.4	19.8	47.7	53.5	46.5	65.1
1.5	97.7	100	100	48.8	44.2	79.1	65.1	62.8	86.0
2.0	97.7	100	100	58.1	77.9	86.0	71.3	85.3	90.7
2.5	95.3	97.7	97.7	69.8	82.6	90.7	78.3	87.6	93.0
3.0	93.0	97.7	97.7	74.4	88.4	94.2	80.6	91.5	95.3
3.5	90.7	90.7	93.0	81.4	90.7	96.5	84.5	93.0	95.3
4.0	90.7	90.7	93.0	86.0	91.9	97.7	87.6	91.5	96.1
4.5	86.0	90.7	93.0	88.4	93.0	98.8	87.6	92.2	96.9
5.0	86.0	90.7	93.0	89.5	95.4	100	88.4	93.8	97.7
5.5	83.7	90.7	93.0	91.9	95.3	100	89.1	93.8	97.7
6.0	81.4	88.4	93.0	91.9	95.3	100	88.4	93.0	97.7

the stomach, bypassing the oral cavity [9–11]. These endoscopic UBT show high sensitivity and specificity. Unfortunately, the need for endoscopy makes these tests costly and inconvenient for the patient.

An alternative method in which interference by oral bacteria can be avoided is the modified UBT in which breath samples are not collected through the mouth but through the nostril. In the *H. pylori*-negative patients who have urease-producing bacteria in the mouth, $^{13}CO_2$ produced by oral bacteria should contaminate the exhaled breath and result in positive tests despite $^{13}CO_2$ is not produced in the stomach. This minor change alone was more effective for avoiding interference with oral bacteria than expected in the present study. At 3 min and all subsequent time points, the breath $\Delta^{13}CO_2$ values were significantly higher in *H. pylori*-positive patients, compared with those in *H. pylori*-negative patients (Fig. 2). The breath $\Delta^{13}CO_2$ values at 15 min and thereafter were not affected by the difference in the route of sample collection. From these results, in patients with oral urease activity, urea hydrolysis occurred in the mouth so that, by 15 min, $^{13}CO_2$ excretion had returned to near-baseline values. These suggested that when collecting breath samples through the nostril, the duration of the test might be decreased.

For the standard UBT, in which breath samples are collected through the mouth, the 20-min sample is thought to give accurate results, which are not affected by oral bacteria. In other words, it is difficult to determine the *H. pylori* infection by the standard UBT earlier than 20 min. Actually, the optimal cut-off value of the standard UBT was 5.0‰ at 20 and 15 min, and increased to 5.5‰ at 10 min (Table 2).

In contrast, the optimal cut-off values of the modified UBT were lower than those of the standard UBT at all time points. At the 20-min sampling point, the sensitivity and specificity of the modified UBT were both 100% using 2.5‰ as the cut-off value. Since the mean breath $\Delta^{13}CO_2$ values of modified UBT at 1 min was already higher in *H. pylori*-positive patients than in *H. pylori*-negative patients (Fig. 3), we attempted to calculate sensitivity and specificity at earlier time points. The optimal cut-off value of the modified UBT for the diagnosis of *H. pylori* infection were identified as 3.5‰ at 15 min with high sensitivity and specificity more than 93%. When shortening the duration of the test and sampling at 10 min, the modified UBT had a sensitivity of 93% and a specificity of 95.3%, using 2.5‰ as the best cut-off value (Table 1). Since these results were comparable to those of serological tests [16,17] and previous reports [2,5], we suggest that 10 min after ingestion of ^{13}C-urea is sufficient for the clinical use of UBT, and the shortening of the test duration is a feasible option.

Indeed, the shorter the duration of the test, the more convenient it is for the patient. The sensitivity and specificity of the modified UBT at 20 min were both 100% using 2.5‰ as the cut-off value, whereas both results at 15 min were less than 99% (Table 1). Although it is desired that the duration of the test is decreased, 20-min time point should be selected as the optimal sampling time in the modified UBT.

In the present study, we did not use the test meals according to the Japanese Standard Protocol [1], although test meals, including citric acid, have been used in most of the previous studies because of its slowing effect on gastric emptying [14,15,18].

A delay in gastric emptying can maximise the gastric residence time of ^{13}C-urea and exposure time of the organisms to ^{13}C-urea. Therefore, the accuracy of UBT may be improved by prolonging the contact of the test meal with *H. pylori* urease. If test meals were used in the modified UBT, the accuracy might increase at earlier time-point.

On the other hand, some investigators have reported high sensitivity and specificity of UBT protocols without test meals [1,6]. The disadvantage of a test meal in the UBT has been noted when breath samples from early time-points were used [7]. The aim of the present study is to determine whether the duration of the test is decreased. Then, the modified UBT did not employ a test meal. The necessity for a test meal in the UBT needs further evaluation.

Main indication for UBT is the confirmation of successful *H. pylori* eradication therapy [3]. In Japan, it is currently recommended that UBT be performed no less than 2 months after the completion of eradication therapy. Since $^{13}CO_2$

values in UBT after eradication therapy are likely to become lower, reflecting a low *H. pylori* density, high sensitivity and specificity of UBT are required for determining the results of treatment. In addition, a clear recommendation of the modified UBT for clinical practice is the diagnosis of active *H. pylori* infection in patients with atrophic gastritis because they are also likely to have a low density of *H. pylori* [19]. We will make a further study to evaluate the efficacy of the modified UBT for determining the results of treatment or *H. pylori* status in patients with severe atrophic gastritis, especially in the elderly.

In conclusion, the simple modification, in which breath samples are collected through the nostril, provides an easy way of avoiding false-positive readings without need for mouth washing, or supplying ^{13}C-urea as a rapid-release tablet. This easy procedure is well tolerated by the patient. Considering that a more rapid, non-invasive and simple test is desirable, we believe that the modified UBT is valid for diagnosing active *H. pylori* infection in clinical practice.

Conflict of interest statement

None declared.

List of abbreviations

CO_2, carbon dioxide; UBT, ^{13}C-urea breath test.

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Serum Pepsinogens as a Predicator of the Topography of Intestinal Metaplasia in Patients with Atrophic Gastritis

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The importance of atrophic gastritis with intestinal metaplasia is related to the fact that it increases the risk of gastric cancer development. The aim of this study is to evaluate the diagnostic potential of serum pepsinogens in predicting the topography of intestinal metaplasia. Both dye endoscopy and ^{13}C-urea breath test were carried out in 878 subjects. Serum pepsinogen I, pepsinogen II, and IgG antibody to *Helicobacter pylori* were measured. The overall prevalence of intestinal metaplasia was higher in subjects with lower PG I/II ratios and lower PG I values. Based on ROC curves, a cutoff value for pepsinogen I/II ratio of less than 3.0 would have identified intestinal metaplasia with a sensitivity of 71.7% and a specificity of 66.7% in *Helicobacter pylori*-positive subjects. It is possible that serum pepsinogens could be used as a screening test for high-risk subjects with intestinal metaplasia.

KEY WORDS: intestinal metaplasia; serum pepsinogens; *Helicobacter pylori*; atrophic gastritis.

The clinical importance of atrophic gastritis with intestinal metaplasia is related to the fact that it increases the risk of gastric cancer development. (1–3). In the process of carcinogenesis, at least for the intestinal type of gastric carcinoma, it was proposed that the gastric mucosa evolves through the stages of chronic active gastritis, glandular atrophy, intestinal metaplasia, and dysplasia before developing gastric adenocarcinoma (3). The risk of gastric neoplasias rises with increasing grade and extent of atrophic gastritis (4). Atrophic gastritis is usually diagnosed with endoscopy and biopsies. However, there is significant potential sampling error in identifying intestinal metaplasis by random biopsy because intestinal metaplasia of the gastric mucosa is reported to be patchy. Thus we assessed the topography of intestinal metaplasia using vital staining in this study instead of taking biopsies from the antrum and corpus. The efficacy of using vital staining with methylene blue to help identify areas of intestinal metaplasia in the distal stomach and cardia, including Barrett's esophagus, has been documented (5–8). The results of staining showed a good correlation with the histological grading of intestinal metaplasia (9).

Although an endoscopic examination has a high reliability for the diagnosis of atrophic gastritis, it is invasive and stressful for the patient. In previous clinical studies (10–13), serum pepsinogen (PG) is a known marker of gastric mucosal status, including mucosal atrophy. Very low serum PG I levels and a low PG I:II ratio are accurate predictors of severe gastric atrophy and are frequently found in gastric cancer (14–16). However, the severity and topography of gastritis vary considerably between individuals. Recently, the serum PG method has been the first screening step in Japan, instead of photofluorography (10, 11, 16, 17), because several problems have been noted, such as its cost effectiveness, the risks of X-ray exposure,

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and its low sensitivity (less than 40%) in detecting early gastric cancer (18). This has made it possible to screen large populations without the need for endoscopy. Intestinal metaplasia is usually diagnosed with dye endoscopy or biopsies. Although the PG method has many advantages, there have been no studies of relations between serum PGs and extent of intestinal metaplasia. The aim of this study is to evaluate the diagnostic potential of serum PGs in predicting the topography of intestinal metaplasia.

MATERIALS AND METHODS

Between December 1999 and October 2001, the dye-endoscopic study was carried out in 878 subjects who consecutively underwent upper gastrointestinal endoscopy. They were 322 men and 556 women, with a mean age of 58.1 years (range, 19–90 years). Exclusion criteria included prior gastric surgery, pregnancy, or a history of *Helicobacter pylori* eradication therapy. We also excluded subjects with a history of recent intake of proton pump inhibitors, H2-receptor antagonists, or antibiotics in the preceding month because we considered the possibility of modification to PG levels as a consequence of medication.

Endoscopic procedures were performed by a single endoscopist (Y.U.). Patients first underwent standard upper endoscopy with examination of the esophagus, stomach, and duodenum. Next, a spray of 20 ml of 0.5% methylene blue solution was applied sequentially to the entire gastric mucosa. Immediately after the application of methylene blue, approximately 50 to 100 ml of tap water was sprayed on the gastric mucosa to wash off excess dye. Positive staining was defined as blue-stained mucosa that persisted despite vigous water irrigation.

After methylene blue staining, the pattern of mucosal staining was classified into four groups. For grade A, the positive staining lesion is located at the antrum; for grade B, the positive staining lesion is found from the antrum to the middle part of the lesser curvature aspect; and for grade C, the positive staining lesion is in the antrum and the body of the greater curvature as well as the lesser curvature.

All patients underwent a ^{13}C-urea breath test (UBT) within 2 weeks after endoscopy. After overnight fasting, 20 ml of water containing 100 mg of ^{13}C-urea was administrated to the patient. Patients were kept in the sitting position during testing. Breath samples were collected at baseline and 20 min after ingestion of ^{13}C-urea. ^{13}C was measured as the $^{13}CO_2/^{12}CO_2$ isotope ratio and is expressed as Δ over baseline (‰). Breath samples were analyzed by mass spectrometry. A change in the $\Delta^{13}C$ value over baseline of more than 2.5‰ was considered positive (19). *H. pylori* infection was established by a positive UBT.

Blood samples for measurements of PG I, PG II, and IgG antibody to *H. pylori* were taken prior to endoscopy, centrifuged immediately at 4°C, and stored at −20°C until use. Serum PG concentrations were assayed using PG I and PG II Riabead Kits (20) (Dainabot Co Ltd, Tokyo). Serum samples were also examined for *H. pylori* antibody by an enzyme-linked immunosorbent assay (ELISA) using the EPI HM-CAP IgG (Enteric Products, Inc., New York) assays (21). All assays were performed in accordance with the manufacturer's instructions. The assays were performed and quantitative ELISA values (EV) extrapolated for each sample according to the manufacturer's instructions. Assay values thus calculated for each kit were interpreted as positive, negative, or indeterminate. The calculated ELISA is read as negative if the ELISA value of HM-CAP IgG is below 1.8, positive if it is above 2.2, and indeterminate if it is between 1.8 and 2.2.

Data on serum PG levels and age are presented as mean ± SD (standard deviation). Comparisons of groups were made using the paired t test. A P value <0.05 was accepted as indicating statistical significance.

RESULTS

A total of 878 patients were included in the study and underwent dye endoscopy and UBT. Of the 878 patients, 47 (5.4%) had an indeterminate result. The remaining 831 patients were classified into four groups according to positivity and negativity for *H. pylori* antibody and UBT: group A (UBT[+] and *H. pylori* antibody[+], group B (UBT[+] and *H. pylori* antibody[−], group C (UBT[−] and *H. pylori* antibody [+]), and group D (UBT[−] and *H. pylori* antibody[−]). Of the 831 subjects, 454 (54.6%) were allocated to group A, 68 (8.2%) to group B, 93 (11.2%) to group C, and 216 (26.0%) to group D.

As shown in Table 1, group B showed a significantly older mean age than the other groups. There was no statistically significant difference in sex distribution among the four groups. Serum PG I level was highest in group A, followed by group B, group D, and group C. Serum PG II levels in groups A to D tended to decrease. Serum PG I/II ratio was lowest in group A.

Overall, intestinal metaplasia was present in 358 (65.4%) of 547 patients with positive serology and in 339 (64.9%) of 522 UBT-positive patients, whereas only 36 (16.7%) of 216 patients who tested negative on both tests had intestinal metaplasia. These differences were statistically significant ($P < 0.001$ by χ^2 analysis). The prevalence of intestinal metaplasia was higher in group A than in the other groups. Despite the fact that the overall rates of intestinal metaplasia were significantly higher in group A than in group C (67.0 vs 58.1%; $P = 0.0055$, $\chi^2 = 7.72$), the proportion of grade C was significantly higher in group C (21/54; 38.9%) than in group A (69/304; 22.7%; $P < 0.01$, $\chi^2 = 6.98$). The difference between group C and group B (10/35; 28.6%; $P = 0.32$, $\chi^2 = 0.99$) was not statistically significant (Table 2).

The overall prevalence of intestinal metaplasia was 52% (455/878) and higher in subjects with lower PG I/II ratios and lower PG I values. Intestinal metaplasia was found in 252 (82%) of 299 subjects with a PG I/II ratio of less than 2.5 and in 58 (88%) of 66 subjects with a PG I value of less than 25 ng/ml (Tables 3 and 4).

Receiver operating characteristic (ROC) analysis was used to determine an optimum cutoff for serum PG I and PG I/II ratio in distinguishing atrophic gastritis with versus without intestinal metaplasia (Figures 1–4). As for PG I,

TABLE 1. CHARACTERISTICS OF THE FOUR GROUPS CLASSIFIED BY POSITIVITY OR NEGATIVITY FOR UBT AND SEROLOGY

	UBT(+)		UBT(−)	
H. pylori *antibody*	H. pylori *antibody*(+)	H. pylori *antibody*(−)	H. pylori *antibody*(+)	H. pylori *antibody*(−)
Group	A	B	C	D
No. of subjects	454	68	93	216
Age (mean ± SD)	57.8 ± 12.8	52.7 ± 13.4	63.1 ± 12.9*	57.8 ± 14.2
Male/female	185/269	27/41	31/62	68/148
PG I (ng/ml)	61.7 ± 28.3	55.0 ± 28.0	42.8 ± 33.8	48.7 ± 22.8
(95% CI)	(59.1–64.2)	(48.2–61.8)	(35.9–49.7)	(45.7–51.8)
PG II (ng/ml)	23.0 ± 10.1	17.0 ± 10.6	13.1 ± 9.15	9.07 ± 5.36
(95% CI)	(22.1–24.0)	14.5–19.6)	(11.2–15.0)	(8.36–9.89)
PG I/PG II	2.83 ± 1.22	3.85 ± 2.10	3.73 ± 2.33	5.57 ± 1.64
(95% CI)	(2.72–2.94)	(3.26–4.36)	(3.25–4.21)	(5.35–5.79)

*$P < 0.001$.

the cutoff value that gave the most favorable sensitivities and specificities was 60 ng/ml in group A, 50 ng/ml in group B, 40 ng/ml in group C, and 35 ng/ml in group D. A cutoff value of 35 ng/ml in group D was the most favorable among the four groups and would have identified intestinal metaplasia with a sensitivity of 75% and a specificity of 80% (Figure 4). As for PG I/II ratio, the most favorable cutoff values in groups A to D were 3, 3, 4, and 5, respectively. A cutoff value for PG I/II ratio of less than 3 would have identified intestinal metaplasia with a sensitivity of 71.7 and 67.6% and a specificity of 66.7 and 73.5% in group A and group B, respectively.

Although cutoff values varied in each group, PG I/II ratio had achieved a higher sensitivity than PG I in all groups. Therefore, PG I/II ratio was considered to be a more useful index for distinguishing atrophic gastritis with intestinal metaplasia than that without intestinal metaplasia.

DISCUSSION

It is now clear that intestinal metaplasia is a part of the spectrum of atrophic gastritis with *H. pylori* infection. Xia et al. (22) showed that the prevalence of intestinal metaplasia was significantly higher at the gastric antrum in patients with *H. pylori* infection compared with uninfected subjects. However, only a portion of infected patients go on to develop intestinal metaplasia, suggesting that factors other than *H. pylori*, such as environmental and host genetic factors, may contribute to the progression from atrophic gastritis to intestinal metaplasia. Previous studies demonstrated the low prevalence of intestinal metaplasia in some ethnic populations, despite a much higher prevalence of *H. pylori* infection (23, 24). This suggests that *H. pylori* alone may be insufficient for the development of intestinal metaplasia.

On the other hand, several authors (25, 26) have demonstrated a reduction in sensitivity of serological tests for *H. pylori* infection in patients with intestinal metaplasia. The use of the serological test may result in a systemic underestimate of *H. pylori* infection effect in any case. As reported by Hala et al. (27), the detection rate of intestinal metaplasia increased from 48 to 75% when the biopsy sites were changed from the anterior and posterior wall of the corpus and antrum to the greater and lesser curvatures and by adding one biopsy from the angular incisura. Thus, sampling errors may affect the prevalence of intestinal metaplasia. For these reasons, in the present study, we assessed the topography of intestinal metaplasia using vital staining and evaluated *H. pylori* infection using a combined method with serology and UBT.

TABLE 2. PREVALENCE OF INTESTINAL METAPLASIA (IM) IN EACH GROUP

	UBT(+)		UBT(−)	
Serology	*Serology*(+)	*Serology*(−)	*Serology*(+)	*Serology*(−)
No. of subjects	454	68	93	216
Grade of IM				
None	150 (33.0%)	33 (48.5%)	39 (41.9%)	180 (83.3%)
Grade A	21 (4.6%)	2 (2.9%)	3 (3.2%)	6 (2.8%)
Grade B	214 (47.1%)	23 (33.8%)	30 (32.3%)	17 (7.9%)
Grade C	69 (15.2%)	10 (14.7%)	21 (22.6%)	13 (6.0%)
Grades A+B+C	304 (67%)	35 (51.5%)	54 (58.1%)	36 (16.7%)

TABLE 3. ASSOCIATION BETWEEN THE PREVALENCE OF INTESTINAL METAPLASIA (IM) AND SERUM PG I/II RATIOS

	IM(+)	*IM*(−)	*No. of patients*	*Incidence of IM(%)*
<1.0	34	3	37	91.9
1.0–1.5	60	8	68	88.2
1.5–2.0	64	14	78	82.1
2.0–2.5	94	22	116	81.0
2.5–3.0	61	28	89	68.5
3.0–3.5	50	28	78	64.1
3.5–4.0	36	32	68	52.9
4.0–4.5	16	50	66	24.2
4.5–5.0	11	44	55	20.0
>5.0	29	194	223	13.0

Sensitivity and specificity of available ELISA tests are sufficient, generally ranging from 94 to 100% and from 87 to 100%, respectively (21, 28–31), and there is a very high concordance between serology and UBT (29). However, high serum IgG levels were found in some patients with no sign of *H. pylori* infection (32). These false positives might result from the fact that patients had a past infection, since IgG titers are known to decline very slowly after eradication of *H. pylori* (30). It has been thought that IgG depends mainly on the complex interaction between bacterial infection and immunological host response (32). A great advantage of serology is the fact that it reflects the evidence of contact with the bacteria without the problem of sampling errors. False-negative results may occur in the early stages of infection, when it is impossible to detect appreciable IgG levels.

Discrepancies between serology and UBT have been reported by several investigators (33,34). They could be due to recent acquisition of infection and, consequently, a delay in development of antibodies. The positive testing for antibodies to *H. pylori* but negative testing for UBT may

TABLE 4. ASSOCIATION BETWEEN THE PREVALENCE OF INTESTINAL METAPLASIA (IM) AND SERUM PG I VALUES

	IM(+)	*IM*(−)	*No. of patients*	*Incidence of IM(%)*
<5	4	0	4	100
5–10	12	2	14	85.7
10–15	23	3	26	88.5
15–20	19	3	22	86.4
20–25	27	9	36	75.0
25–30	29	16	45	64.4
30–35	36	32	68	52.9
35–40	31	43	74	41.9
40–45	29	33	62	46.8
45–50	34	41	75	45.3
50–60	58	72	130	44.6
60–70	41	61	102	40.2
>70	112	108	220	50.9

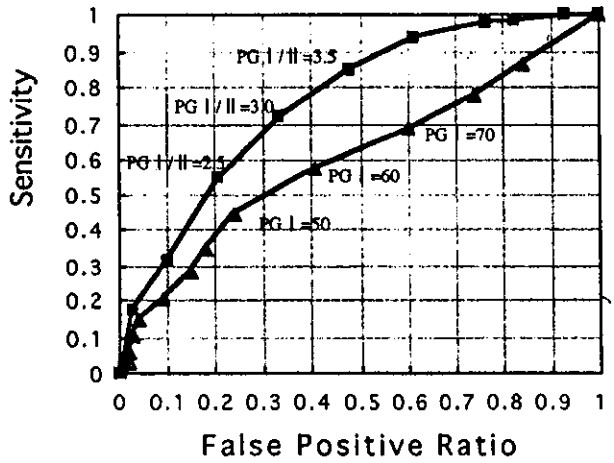

Fig 1. Receiver operating characteristic curves (ROC) of serum pepsinogen (PG) I (▲) and PG I/II ratio (■) in distinguishing subjects with and without intestinal metaplasia in group A.

be due to the use of antimicrobials for other common infections or spontaneous elimination of the infection (35). Malaty et al. (33) showed that the prevalence of *H. pylori* infection varied from 32%, when diagnosis of the infection was based on UBT, to 18%, when the diagnosis was based on serology. Thus, since both UBT and serology have important limitations, the subjects were classified into four groups according to positivity and negativity for *H. pylori* antibody and UBT. In the present study, 68 (23.9%) of 284 subjects with negative serology had positive UBT results and 93 (17.0%) of 547 subjects with positive serology did not have *H. pylori* antibody.

Serology depends on the interaction between bacterial infection and immunological response, whereas the serum PG method is linked mainly to local mucosal damage

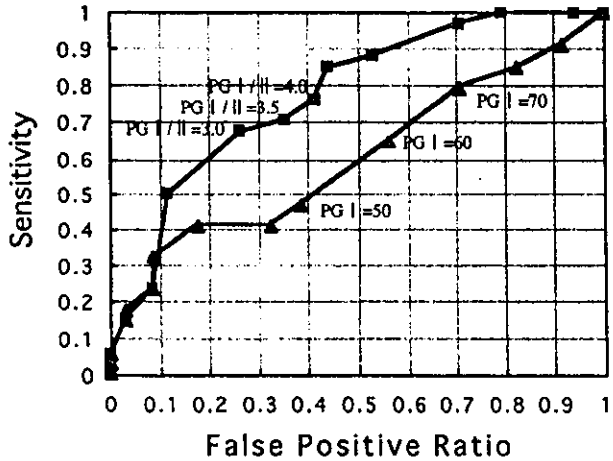

Fig 2. ROC of serum PG I (▲) and PG I/II ratio (■) in distinguishing subjects with and without intestinal metaplasia in group B.

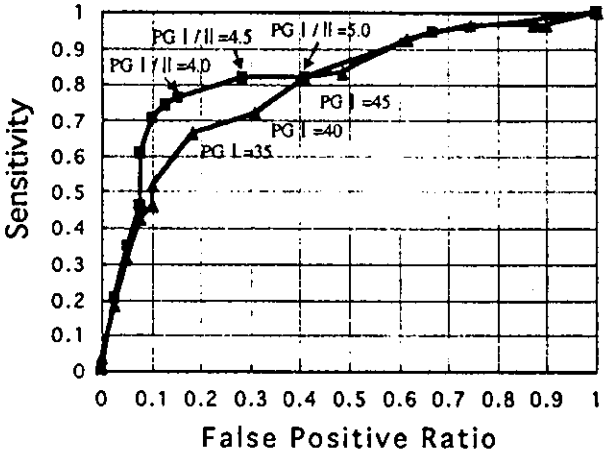

Fig 3. ROC of serum PG I (▲) and PG I/II ratio (■) in distinguishing subjects with and without intestinal metaplasia in group C.

(32). Yamaji et al. (36) demonstrated that 0.14% of patients with gastric cancer had a nagative serology result and concluded that a weak *H. pylori* antibody response meant a high risk for gastric cancer. Although it has been shown that *H. pylori* infection is associated with an increased risk for the development of gastric cancer (37), a reduction in sensitivity of serological tests for *H. pylori* infection in patients with intestinal metaplasia has been demonstrated by several authors (25,26). Thus, it is possible that patients with severe atrophic gastritis and intestinal metaplasia which was considered to be a precancerous lesion could not be detected by serology alone. Actually, in the present study, intestinal metaplasia was present in 358 (65.4%) of 547 patients with positive UBT, whereas only 36 (16.7%) of 216 patients who tested negative on both two tests had intestinal metaplasia.

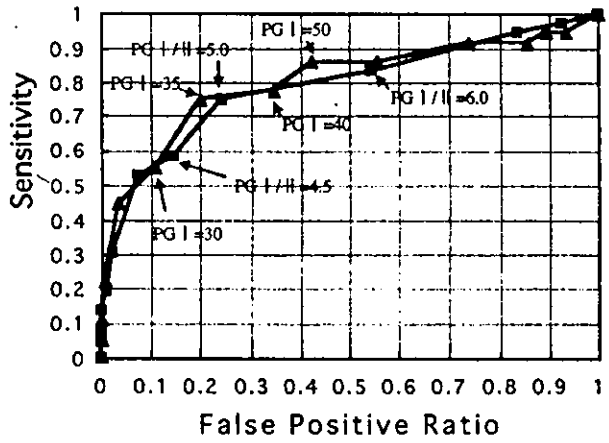

Fig 4. ROC of serum PG I (▲) and PG I/II ratio (■) in distinguishing subjects with and without intestinal metaplasia in group D.

Serum pepsinogen parameters; especially PG I/II and PG I/II ratio, have been proven to be markers for atrophic gastritis (10–13). Therefore, the measurement of serum PGs has recently drawn attention as a candidate for a new screening test for gastric cancer in Japan (11, 16–18). It has been reported that subjects with *H. pylori* infection had significantly higher PG I and PG II concentrations and a significantly lower PG I/II ratio than those without *H. pylori* infection (38) and that these levels are changed by eradication of *H. pylori* (39). In Japan, several studies (38,40) have shown that the prevalence of infection is strongly associated with age and this age-related increase in infection occurs in the elderly. Thus, the absence of serum antibodies in patients with active or previous infection seems to increase in the elderly (40,41). It is possible that patients who had a previous infection and do not have serum antibodies are not detected as a high-risk group for gastric cancer, despite the presence of severe atrophic gastritis. The measurement of serum PGs is able to detect patients with extensive atrophic gastritis, regardless of *H. pylori* status.

In our study, intestinal metaplasia was detected in 358 (65.4%) of 547 patients with serum antibody and in 339 (64.9%) of 522 patients with positive UBT. Thus, because the measurement of serum antibodies alone cannot assess the presence of intestinal metaplasia, we used additional serum markers, PG I and PG I/II ratio, for detecting patients with intestinal metaplasia in this study.

Although several determinations of a suitable cutoff point for gastric cancer screening have previously been reported based on the findings of X-ray methods, using a serum PG I concentration of less than 70 ng/ml and a PG I/II ratio of less than 3.0 as the cutoff point has been widely accepted in Japan (11,17). When the measurement of serum PGs is used for detecting individuals with intestinal metaplasia, we have to determine the suitable cutoff point. Based on ROC curves in this study, the cutoff points of serum PG I and PG I/II ratio for intestinal metaplasia varied among the four groups from 35 to 60 ng/ml and from 3 to 5, respectively.

Although the cutoff values varied in each group, the PG I/II ratio achieved a higher sensitivity than PG I in all groups. Therefore, the PG I/II ratio was considered to be more useful for detecting atrophic gastritis with intestinal metaplasia. Patients with positive UBT results, regardless of the presence of serum antibody, had the lowest cutoff point among the four groups. Consistent with previous reports (11, 17), in which a PG I/II ratio of less than 3.0 was determined as the cutoff point for detecting atrophic gastritis, the suitable cutoff point for PG I/II ratio was 3.0 for detecting intestinal metaplasia. However, patients with negative UBT results had higher cutoff points.

Unexpectedly, intestinal metaplasia was present in 36 (16.7%) of 216 patients who tested negative on both two tests. When using serum antibodies alone for detecting intestinal metaplasia, these patients should be excluded. Using a serum PG I/II ratio of less than 5.0 as the cutoff point, patients who had severe atrophic gastritis with intestinal metaplasia but negative testing for UBT and serology can be detected with a sensitivity of 75.0% and a specificity of 75.6%. As reported previously, if a serum PG I/II ratio of less than 3.0 is used as the cutoff point for gastric cancer, this value provides a sensitivity of only 19.4% and a number of patients with intestinal metaplasia should be overlooked. Thus, it seems that determinations of a suitable cutoff point in the respective groups are essential to intestinal metaplasia screening.

The proportion of grade C intestinal metaplasia was significantly higher in group C (21/54; 38.9%) than group A and was 6.0% (13/216) in group D. The 13 group Δ patients with extensive intestinal metaplasia could not be detected by either UBT or serology. Using a serum PG I/II ratio of less than 5.0 as the cutoff point, 10 (77%) of 13 patients were detected.

Despite the world decline in incidence and mortality, gastric cancer is a leading cause of cancer death in many countries (42). Although the prevalence of *H. pylori* infection in Japan has fallen in recent years (38), those who are infected remain at risk of gastric cancer. *H. pylori* infection was detected in up to 70% of the population by the age of 40 years in Japan (38). Since early life acquisition of *H. pylori* has been considered to increase the risk of developing gastric cancer (43), infected individuals aged 40–50 years, belonging to the age group with the largest number of people in Japan, will be at higher risk of gastric cancer in the near-future. The high prevalence of intestinal metaplasia among *H. pylori*-infected patients suggests that the risk of development of gastric cancer will remain high. Since gastric cancers are potentially curable if they are diagnosed at early stages, screening for intestinal metaplasia is necessary for early detection of gastric cancer.

In conclusion, it is possible for serum PGs to be used as a screening test for high-risk subjects with atrophic gastritis with intestinal metaplasia, rather than as a test for gastric cancer itself. The measurement of serum PGs provides much information on the presence of intestinal metaplasia as well as atrophic gastritis.

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血清ペプシノゲン

三木一正*

キーワード◉胃癌　胃癌検診　ペプシノゲン法　萎縮性胃炎

はじめに

血清ペプシノゲン(pepsinogen；PG)は萎縮性胃炎のマーカーであり，純粋な意味での腫瘍マーカーとはいえない．しかし，萎縮性胃炎が胃癌の前癌病変であることから，PG法陽性者を胃癌ハイリスク群としてスクリーニングする手法が胃癌検診として実用化されている．

わが国において，間接X線による胃癌検診は40年の歴史をもち，その有効性も疫学的に証明されているが，近年受診者数の減少や固定化といった問題を抱えている．一方，血清PG値による胃癌検診，PG法は簡便な検体検査であることから，徐々に広がりつつある．

I. 血清ペプシノゲンとは

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あるPGは，99%が胃内腔に放出される．しかし，1%が血中に流入し，これが血清PGとして測定される．

PGには2種類のサブタイプ，PG I，PG IIが存在し，PG Iは胃底腺領域で産生され，PG IIは胃粘膜全域で産生される．PG Iは胃酸分泌能と相関し，胃壁細胞量をよく反映し，PG I値の上昇は胃の攻撃因子の増大を示唆する．PG II値の変動はPG I値に比べてわずかである．PG I，IIとも日内変動や季節変動はなく，食事による影響も受けず，個人において安定した値を示す．しかし，プロトンポンプ阻害薬やH_2受容体拮抗薬投与の影響を受けるので，測定時には投薬歴の確認が必要である．

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II. ペプシノゲン法による胃癌検診

血清PG値は，幽門腺側から口側に進展する胃粘膜の萎縮性変化を反映して低下する．コンゴーレッドを用いた色素内視鏡検査によって診断した胃粘膜萎縮の進展に伴う腺境界の上昇と，血清PG I値およびPG I/II比の低下には，高い相関が認められる（**図1**）[1]．

また近年，慢性萎縮性胃炎は分化型胃癌や胃腺腫の発生と密接な関連があることが，多数の疫学的調査や動物実験などの基礎研究によって明らかにされてきている[2,3]．慢性萎縮性胃炎と胃癌との関連，PG値と慢性萎縮性胃炎との相関を利用し，PG I値およびPG I/II比を指標として胃癌ハイリスク群である進展した萎縮性胃炎を同定し，胃癌検診に応用したのがPG法である．

胃癌患者群と健常対照群の血清PG値を比較検討したところ，

PG I：70μg/*l* かつ PG I/II比：3.0以下

の組み合わせで両群の分離が良好であり，胃癌スクリーニングでは，この値をカットオフ値の

基準値に採用している[4].

1998（平成10）年，厚生省（当時，現厚生労働省）三木班では，11,707人のボランティアに対して，内視鏡検査とこの基準値によるPG法を同時施行した．内視鏡検査をゴールドスタンダード（至適基準）とすると，基準値を用いたPG法の精度は，胃癌発見率0.44%（発見胃癌51例），偽陰性率20%（陰性胃癌13例），陽性反応的中度1.5%であった（表1）[5].

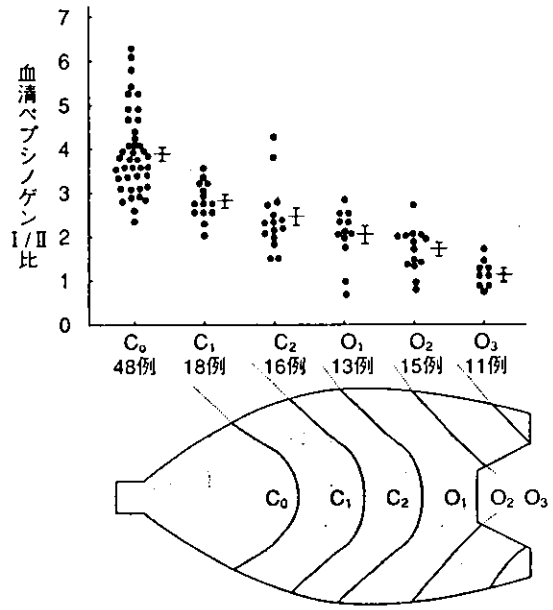


図1　血清ペプシノゲンI/II比と内視鏡的コンゴーレッド法による腺境界分類
（Miki K, *et al* : *Gastroenterol Jpn* 1987 ; 22 : 133—141より引用）

富山県下事業所において7検診機関による検診（カバー率82.2%）で同意が得られ，3人の胃切除者を除いた従業員5,567人（男性3,791人，女性1,776人，男女ともに平均年齢48歳）を対象として，X線（間接または直接）法とPG法を同時に行い（同時併用法），胃癌10例（早期胃癌9例，進行胃癌1例）を発見した．X線法とPG法の要精検率はそれぞれ12%と24%，精検受診率は55%と52%，胃癌発見率は0.05%と0.18%，陽性反応的中度は0.8%と1.4%であった[6].

三木班協力施設における605例の胃癌症例の術前PG値を検討したところ，PG法陽性率は65%であった．このうち，人間ドックで発見された胃癌症例184例に限ってみるとPG法陽性率は85%であり，無症状者に対する胃癌スクリーニングにおいてPG法は有用であることが示唆された[7]．しかしながら，PG法が背景胃粘膜の萎縮を診断するマーカーであり，カットオフ値による診断であるため，陰性胃癌症例があることは免れない．陰性胃癌を落とさないために，厚生労働省三木班では，図2[8]に示すように，PG法とX線検査を組み合わせて実施することを提唱している．

III. 内視鏡検診の一次スクリーニングとしてのペプシノゲン法の位置づけ

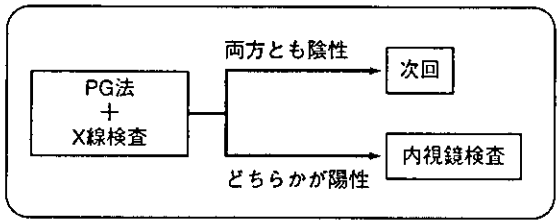
人間ドックの胃癌検診は，内視鏡検査が一般的になってきている．住民検診や職域検診でも，

表1　内視鏡をゴールドスタンダード（至適基準）としたペプシノゲン法の胃癌発見精度

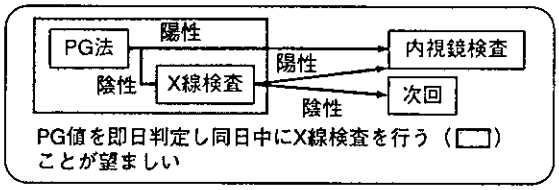
報告者（年）	人　数	発見数	発見率	感　度	特異度	陽性反応的中度
北原（1995～96）	5,113	11	0.22%	85%	74%	0.9%
小松（1996～97）	1,000	5	0.50%	83%	77%	1.7%
井上（1995～96）	2,870	12	0.42%	86%	72%	1.5%
西沢（1995～97）	2,724	23	0.84%	74%	71%	2.1%
合　計	11,707	51	0.44%	80%	70%	1.5%

［三木一正：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．厚生省がん研究助成金平成10年度報告集（9-8），1999；39—41より引用］

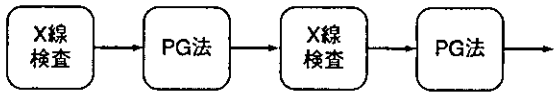
1. 同時併用法　　は同一年度であることを示す



2. 二段階法



3. 異時併用法



交互でなくとも，XXPXXPXXPやXXXXPXXXXPなどの組み合わせも可能である．X：X線検査，P：PG法

4. 単独法

図2　ペプシノゲン法の具体的施行法
（吉原正治他：ペプシノゲン法の具体的実施法．三木一正編，ペプシノゲン法ハンドブック―21世紀の胃がん検診のために，メジカルビュー社，東京，2001；16―28より引用）

X線検査よりも内視鏡検査を希望する受診者に対して，内視鏡の選択を可能にする自治体や職域も増えてきている．また，一般診療の場でスクリーニング的に行われている内視鏡検査は，かなりの件数に上ると思われる．そこで，PG法を用いて胃癌ハイリスク群を集約し，リスクに応じた内視鏡検査を実施するという方法が考えられる．

厚生労働省三木班が，PG法による胃癌検診を実施している5,000人規模の職域集団を1～5年間にわたり追跡を行ったところ，全対象者におけるPG陽性者（995例）の陰性者（4,173例）に対する胃癌発生の相対危険度は6.05[95%信頼区間（CI）1.80～20.30]，男性のPG陽性者（865例）の陰性者（3,494例）に対する胃癌発生の相対危険度は8.34（95%CI 2.18～31.87）であった[9]．

表2　検診受診翌年度以降（1～5年）発見された胃癌の頻度

		血清Hp抗体価	
		(－)	(＋)
PG法	(－)	0% (0/823)	0.17% (3/1,755)
	(＋)	1.45%* (14/967)	

Hp判定保留群：0%　*$p < 0.01$
（井上和彦：厚生労働省厚生科学研究費補助金による「血清学的スクリーニングによる胃癌検診の効果と効率に関する研究」班（主任研究者：三木一正）平成14年度研究報告書より引用）

IV. ヘリコバクター検査との併用による胃癌スクリーニングの可能性

血清PG値に血清ヘリコバクター・ピロリ（Hp）IgG抗体価検査を併用し，同時に胃内視鏡検査を行った人間ドック受診者の検診実施翌年以降の胃癌発見頻度を比較したところ，PG法陽性者からの胃癌発見率は有意に高く，反対にPG法陰性かつHp抗体陰性の者からは胃癌発見がなく，胃癌ローリスク群といえることが分かった（表2）[10]．

血清PG値と血清Hp抗体価の組み合わせによって胃癌のハイリスク群を集約し，またローリスク群を設定することで効果的に内視鏡検診を実施する方法を検討できる可能性があり，調査を続けている．

V. ペプシノゲン法の有効性評価

2001年3月に公表されたわが国における癌検診の有効性に関する評価報告書[11]において，PG法は胃癌死亡率減少効果に関する研究がなされていないため，評価を保留されている．

厚生労働省三木班ではPG法の胃癌死亡率減少効果を証明すべく研究を進めている．PG法による胃癌検診を節目検診の際に受診した約5,500人を受診日から5年間追跡し，基準人口

を日本全体として胃癌死亡の標準化死亡比(SMR)を算出した．胃癌のSMRは0.3を若干超える値であり，SMRの95%信頼区間は，1を含まないで1未満に分布しており，全国の胃癌死亡状況と比較して統計学的に有意に胃癌死亡率が低下していた．自己選択バイアス（self-selection bias）の影響は否定できないが，PG法による胃癌検診の胃癌死亡率減少効果を示唆する結果であった[12]．

しかしながら，この検討のみでPG法の有効性を判断することはできない．厚生労働省三木班においては，症例対照研究の手法で調査を続けている．

おわりに

萎縮性胃炎のマーカーである血清PGは，胃癌のマーカーとしてスクリーニングに応用され，従来の間接X線検診を補う方法として実施する施設が増えてきている．

陰性胃癌の問題や，要精検率が高すぎるなど，単独の胃癌スクリーニングマーカーとしては問題点が多く，また有効性評価も確立していない．しかしながら，間接X線検査だけではなく，Hp検査との組み合わせや，内視鏡検査を前提としたハイリスク群の絞り込みなど，他の検査との併用を工夫していくことで，胃癌検診システム全体を向上させることが期待される．

なお，PG法についての情報は，厚生労働省三木班提供『ペプシノゲン・ホームページ(http://www.pepsinogen.org)』をご参照ください．

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【原 著】

足立区におけるペプシノゲン法による胃検診の5年間の追跡調査による有効性の検討

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Five years follow up study of gastric cancer screening using the pepsinogen test method in Adachi city

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要 旨

足立区では特定年齢(40・50・60歳)を対象とした区民健診としてペプシノゲン法(PG法)による胃がんのマススクリーニングを1996年4月から開始した。今回1996年度に行ったPG法による胃がん検診受診者5449人(40歳1464人、50歳1829人、60歳2156人)を対象に、胃がん検診受診から5年間の生存、死亡、転出につき追跡調査を行った。調査にあたっては足立区個人情報保護条例に基づき必要な情報を収集した。血中ペプシノゲンⅠ値が70ng/mL以下かつペプシノゲンⅠ/Ⅱ比が3.0以下をカットオフ値として、陽性者に対しては内視鏡による二次精密検査の受診勧奨を行った結果、精検受診者1009人(61.2%)中、検診受診後2年間で早期胃がん5人、進行がん3人が発見された。5年間の観察期間中、胃がんによる死亡者3人、胃がん以外の死亡者47人、観察中止者654人であった。対象者の5年後の標準化死亡比(95%信頼区間)は、対象年齢における全国での胃がん死亡率を基準として0.34(0.07-0.98)であった。観察期間中に胃がんで死亡した3名中2名がPG法陰性がんであった。今回の検討ではX線などの他検査やPG法複数回受診の影響を極力排除した上で、PG法を受診した集団における胃がんによる実死亡者数が受診から5年後に約1/3に抑制されていたが、これはPG法単独単回施行後の胃がん死亡抑制の最大評価と考えられた。

キーワード:ペプシノゲン法、スクリーニング、胃がん

Purpose: We started a new screening method for gastric cancer in 1996 by measuring the serum concentration of pepsinogen (PG) I and II. This PG test method can identify individuals with atrophic gastritis. We have conducted a follow up study to reveal the reduction of gastric cancer mortality among participants in the PG test method in the five years observation period after the screening.

Methods: A total of 5,449 residents in Adachi city aged 40, 50 and 60 years old in 1996 were measured serum PGI and PGII levels. Individuals with PGI level ≦ 70 ng/ml and PGI/PGII ≦ 3.0 were advised to have an upper gastro-intestinal (GI) endoscopy to detect the gastric cancer. The participants who moved out of the city, had second screening by the PG test

method, or died from other causes than gastric cancer were defined as censored cases during the 5 years follow up period. Standardized mortality ratios (SMR) of gastric cancer among participants were calculated based on the sex, age and year specific gastric cancer mortality using Japan as a standard population.

Results: Five early gastric cancer cases and 1 advanced gastric cancer case were diagnosed within a year after screening. Two advanced gastric cancer cases were found by further examinations during the follow up period of 2 - 5 years. There were 701 censored cases and 3 gastric cancer death cases including 2 cases with negative result at the screening. SMR (95% confidence interval) of gastric cancer in the 5 year observation period were 0.34 (0.07 ? 0.98) .

Conclusions: Participants for screening by the PG test method showed a reduction in gastric cancer mortality in comparison with the general population in Japan.

Key words: pepsinogen test method, screening, stomach neoplasms

【はじめに】

足立区では集団胃検診としてペプシノゲン法(PG法)導入以前の平成4年から7年度まで4年間、バリウムを用いた間接X線法による検診を行っていたが、検診受診率の低減化とX線検診受診者の再検診固定化により硬直化していた胃検診から更に一般区民への普及をはかるために、平成8年4月から特定年齢(40・50・60歳)を対象とした区民健診(節目健康診査)に本法による集団胃検診を開始した。PG法による胃がん検診についてはこれまでの報告で有用性につき一定の評価が得られている[1]。足立区におけるPG法導入後のこれまでの4年間の検討では、採血検査のため簡便に実施可能であり、受診者における身体的負担が少なく一次検診受診率の改善が認められたこと、要精検者あたりの胃がん発見率は、PG法導入前の間接X線法と比較して共に0.40％と同等で、費用対効果が改善したことがあげられた。更にPG法検査では早期胃がんの発見率が高いことも特徴とされているが、PG法導入前の4年間のX線検診では発見胃がんにおける早期胃がんの割合は56％であったのに対してPG法導入後は68.7％に増加していた[2,3]。今回の検討では、胃がん検診の有用性評価として同法を受診することによる胃がん死亡率の改善効果につき、足立区でのPG法導入初年度である平成8年度に施行したPG法の受診から5年間の経過を観察した。

【対　象】

1996年(平成8年)度に足立区の節目健診時に行ったPG法による胃がん検診受診者を対象とした。PG法による胃がん検診を行うに当たっては、事前に問診を行い、上部消化器症状がある人、胃手術後の人、

表1 対象群の観察期間中の経過

年齢	経過		開始時	1年後	2年後	3年後	4年後	5年後
40	生存	男性	620	593	584	574	558	540
		女性	844	824	806	788	747	710
	死亡（胃がん以外）	男性		1	2	0	0	0
		女性		0	1	1	1	1
	胃がん死亡	男性		1	0	0	0	0
		女性		0	0	0	0	0
	転出	男性		25	7	10	16	18
		女性		20	17	17	40	36
50	生存	男性	627	620	616	602	581	558
		女性	1202	1192	1176	1158	1104	1048
	死亡（胃がん以外）	男性		1	2	0	2	2
		女性		0	0	0	1	2
	胃がん死亡	男性		0	0	0	0	0
		女性		0	0	0	0	0
	転出	男性		6	2	14	19	21
		女性		10	16	18	53	54
60	生存	男性	793	781	773	759	737	709
		女性	1363	1352	1340	1317	1243	1180
	死亡（胃がん以外）	男性		4	4	3	3	4
		女性		2	1	2	4	3
	胃がん死亡	男性		0	1	0	0	0
		女性		0	0	0	0	1
	転出	男性		8	3	11	19	24
		女性		9	11	21	70	59

プロトンポンプ阻害剤内服中の人、腎不全のある人については同検査に不適当として除いた。またPG法による検査は胃がんの有無を測定するのではなく、胃がんの高危険群である萎縮性胃炎の検出を行なう方法であることにつき同意を得てから行なった。表1に対象者における年齢・性別に観察期間中の経過を示す。対象者は5449人で、40歳1464人(男性 620人、女性 844人)、50歳1829人(男性 627人、女性 1202人)、60歳2156人(男性 793人、女性 1363人)であった。同年度中に検診対象となった年齢層全体のうち、PG法を受診した区民の割合は、22.0%(男性 15.9%、女性 28.4%)であった。

表2に対象者の年齢・性別のPG法の結果を示す。PG法による陽性者(要精検者)は、1650人(30.3%)で、そのうち二次精検を受診した人は1009人(61.2%)であった。

表2 対象群におけるPG法の結果

年齢	性別	対象者数	要精検者数 (PG法陽性者数)	要精検率 (PG法陽性率)	二次精検 受診者数	二次精検 受診率	発見胃がん者数	発見胃がん率
40	男性	620	96	15.5%	47	49.0%	0	0%
	女性	844	117	13.9%	78	66.7%	0	0%
50	男性	627	180	28.7%	82	45.6%	0	0%
	女性	1202	318	26.5%	204	64.2%	0	0%
60	男性	793	349	44.0%	201	57.6%	5	2.49%
	女性	1363	590	43.3%	397	67.3%	3	0.76%

【方 法】

上記対象者の検診受診日を確認し、受診日から6年目に足立保健所の保健衛生情報システム(区民の検診受診歴データベース)をもとに住民基本台帳の登録の有無と検診受診歴を確認した。登録者は「生存」(観察期間5年)に区分した。登録抹消者は「死亡または転居」に分類し、登録抹消時点で観察を打ち切った。「死亡または転居」に分類されたものは要精検者台帳から検診発見胃がん者を、死亡小票から胃がん死亡者の匿名化リストを作成し、それ以外のものは「区外転出」とした。以上の情報については各々足立区個人情報保護条例第57条に基づき足立保健所が閲覧し、必要な情報を収集した。また、足立区では節目健診の他に35歳以上を対象とした自由申し込みによる「PG法消化器がん検診」を平成11年度から施行している。対象者のうち観察期間中に節目検査外のPG法を受診した者については、2回目の検査受診時に観察打ち切りとした。

その他考察資料として、胃がん検診要精検者台帳を参照し、対象者のうち胃がん検診で胃がんを発見された者及び対象者の内で観察期間中に間接X線による胃がん検診を受診し、かつ胃がんを発見された者についても、各々匿名化されたリストを作成した。これらのリストは、連結不可能な匿名リストとし、個人情報保護の観点から最大限の配慮を行った。

以上のリストを参照し、追跡開始から1年ごとに5年間の観察を、性別・各年齢階層別に行った。平成8年から各年度5年間、全国・東京都・足立区それぞれの対象年齢層の人口及び実胃がん死亡者数を用いて、対象群での、性・年齢構成の影響を除去した期待胃がん死亡数(対象群の胃がん死亡予測数)を算出し、統計処理による期待胃がん死亡者数誤差範囲を確認した。また同期間に観察された対象者中の胃がん死亡数から各々の標準化死亡比(SMR)と95%信頼区間(95% CI)を求めた。血清ペプシノゲン値の測定はPG I値が70ng/mL以下かつPG I/II比が3.0以下をカットオフとし、該当者は要精検者として医療機関への受診勧奨を行った。さらに一次検診直後の二次精検受診率の改善をはかる目的で、PG法の初回受診時陽性者のうち、2年間精検受診を行っていない人に対して個別に勧奨通知を発送し、精検結果の把握につとめた。

【結 果】

対象者中の胃がん死亡者を表3に示す。5年間の観察期間中、胃がんによる死亡者は3人(40歳1人、60歳2人)、胃がん以外の死亡者数は47人(40歳7人、50歳10人、60歳30人)、転出者は299人(40歳136人、50歳88人、60歳75人)、節目健診外でPG法検査を受診したことによる観察途中打ち切り者355人(40歳70人、50歳125人、60歳160人)。観察期間中の総観察人年は25914.9人年で、5年間の追跡率は87.1%であった。

PG法受診後の二次精検で発見された胃がん者につき表4に示す。今回の対象者のうち、検診直後の初回精検による胃がん発見者は6人で、早期胃がん5人、進行がん1人。2年後の受診勧奨で、更に進行がんが2人追加発見された。検診で発見された胃がん者の観察期間中における死亡者は認めなかった。基準人口別に5年間観察後の期待死亡者数、

SMR、95％CIを表5に示す。観察期間を通じての胃がんによる期待死亡者数は、全国を基準人口とした場合、8.91人。東京都を基準人口とした場合、8.98人。足立区全体を基準人口とした場合、9.57人であった。PG法による胃がん検診受診者の5年後のSMR(95％CI)は、各々0.34(0.07-0.98)、0.33(0.07-0.98)、0.31(0.06-0.92)であった。全国を基準人口とした場合の観察期間中のSMRの推移を図1に示す。1年ごとのSMRの推移では、受診後より次第にSMRは低下しており、検査後4年で最小となっていた。

また足立区においては、節目健診時に行う胃がん検診のほかに間接X線検査による「消化器がん検診」も引き続き行っている。表6に間接X線法受診により発見された胃がん者の内訳を示す。1996年度に節目健診を受診した対象者のうち、1997年以降に間接X線検査を受けた人は324人で、その内4人にがんが発見され、全例早期がんであった。

表3 対象者中の胃がん死亡者

年齢	性別	死亡日	PG法受診日	PG法結果	二次精検受診日	精検結果
40	男性	1997.2	1996.6	陰性		受診勧奨無
60	男性	1998.2	1996.10	陰性		受診勧奨無
60	女性	2001.12	1997.2	陽性	1997.11	ポリープ

表4 PG法受診後の二次精検による胃がん発見者

年齢	性別	PG法受診日	精検結果(直後)	精検受診日(2年後受診勧奨後)	精検結果(2年後受診勧奨後)
60	男性	1996.4	早期がん		
60	女性	1996.4	未受診	1999.4	進行がん
60	男性	1996.4	胃炎	2000.1	進行がん
60	男性	1996.7	早期がん		
60	女性	1996.8	進行がん		
60	男性	1996.10	早期がん		
60	女性	1996.10	早期がん		
60	男性	1997.1	早期がん		

表5 基準人口別のPG法受診5年後のSMR

基準人口	全国	東京都	足立区
期待死亡者数	8.91	8.98	9.57
SMR	0.34*	0.33*	0.31**
95%CI	0.07-0.98	0.07-0.98	0.06-0.92

※:p=0.07 ※※:p=0.05

表6 PG法受診後、間接X線法受診により発見された胃がん者

年齢	性別	PG法受診日	PG法結果	PG法後精検結果	間接X線法受診日	間接X線法後精検結果
60	女性	1996.6	陰性	受診勧奨無	1998.7	早期がん
60	男性	1997.1	陰性	受診勧奨無	1999.11	早期がん
60	女性	1996.12	陰性	受診勧奨無	1999.1	早期がん
60	女性	1996.6	陽性	異常なし	1998.3	早期がん

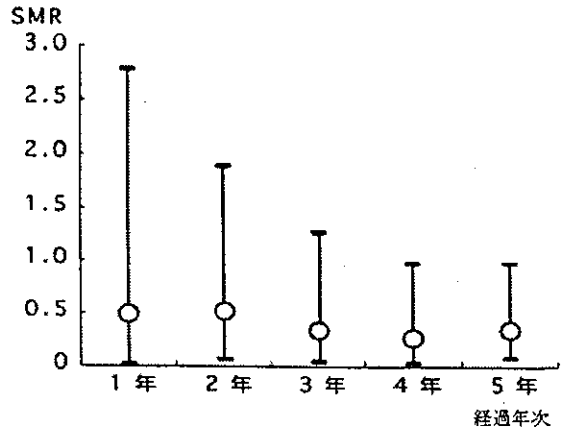

図1 全国を基準人口とした時のSMRと95%CIの年次推移

【考 察】

対象者群全体における要精検率（PG法陽性率）は年齢と共に上昇することが知られているが、年齢階級別の陽性率および胃がんの発見率は諸家の報告と類似していた[4,5]。これまでの報告では、間接X線法による胃がん検診の死亡率減少効果について過去に一度でも検診を受診した場合のオッズ比は0.3～0.6程度に見積もられている[6,7]。しかし単独単回施行されたPG法検査が胃がん死亡率の減少に対してどの程度寄与しているかについては一定の見解は得られていない。

今回の観察期間中のSMRは、単独でPG法による検査を施行した場合の胃がん死亡抑制効果の最大評価と考えられた。また間接X線法により発見された4人の胃がん者をPG法による見のがし例とみなし、全例胃がんにより観察期間中に死亡したと仮定した場合、全国を基準人口としたSMR(95％CI)は0.79(0.32-1.62)となり、これはPG法施行による胃がん死亡抑制の最小評価と考えられた。したがって今回の観察ではPG法単独単回による胃がん死亡率の抑制効果はSMRで0.34から0.79の間にあると推定される。しかし間接X線法による胃がん発見者は全例早期がんで進行がんが存在しなかったことと、早期がんの5年生存率は90％以上[8]であることを考慮すると、今回の検討における5年間の観察期間中の妥当なSMRは、胃がん死亡率抑制の最大評価に近いものと考えられた。

【まとめ】

PG法検査単独単回施行において検診5年後のSMR(95％CI)は、0.34(0.07-0.98)～0.79(0.32-1.62)と推定され、胃がん死亡率減少効果のある可能性が示唆された。

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PROGRESSION OF CHRONIC ATROPHIC GASTRITIS ASSOCIATED WITH *HELICOBACTER PYLORI* INFECTION INCREASES RISK OF GASTRIC CANCER

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We conducted a longitudinal cohort study to determine the association of *Helicobacter pylori* infection and the progression of chronic atrophic gastritis (CAG) with gastric cancer. A cohort of 4,655 healthy asymptomatic subjects was followed for a mean period of 7.7 years. *H. pylori* infection was established by serum specific antibodies and the presence of CAG was confirmed by serum pepsinogen. During the follow-up period, 45 gastric cancer cases were detected (incidence rate, 126/100,000 person-years). A univariate analysis after adjustment for age showed that both *H. pylori* and CAG were significantly associated with gastric cancer. To clarify the interaction between *H. pylori* and CAG, an analysis stratified by *H. pylori*- and CAG-status was performed. No cancer developed in the *H. pylori*(−)/CAG(−) group during the study period. This supports the theory that it is quite rare for any type of gastric cancer to develop in an *H. pylori*-free healthy stomach. With the progression of *H. pylori*-induced gastritis, the risk of gastric cancer increased in a stepwise fashion from CAG-free gastritis [*H. pylori*(+)/CAG(−) group] (HR=7.13, 95%CI=0.95-53.33) to CAG [*H. pylori*(+)/CAG(+) group] (HR=14.85, 95%CI=1.96–107.7) and finally to severe CAG with extensive intestinal metaplasia [*H. pylori*(−)/CAG(+) group] (HR=61.85, 95%CI=5.6–682.64) in which loss of *H. pylori* from the stomach is observed. Therefore, it is probable that *H. pylori* alone is not directly associated with stomach carcinogenesis. Instead, *H. pylori* appears to influence stomach carcinogenesis through the development of CAG. The observed positive correlation between the extent of *H. pylori*-induced gastritis and the development of cancer was strong, especially for the intestinal type. These results are compelling evidence that severe gastritis with extensive intestinal metaplasia is a major risk factor for gastric cancer, and they confirm the previously described model of stomach carcinogenesis: the gastritis-metaplasia-carcinoma sequence.

Key words: *atrophic gastritis; gastric cancer;* Helicobacter pylori; *cohort study; pepsinogen*

Despite a worldwide decline in incidence, gastric cancer remains one of the leading causes of cancer-related death in Japan.[1–4] There is a marked geographic variability in the gastric cancer incidence rate; the cancer is most common in China and Japan, and one of the lowest rates is in the United States.[1–4] Many epidemiologic studies have shown that the risk of gastric cancer is strongly associated with environmental factors, such as salt, nitrates and low intake of fresh fruits and vegetables.[1,4–8] Recent studies have indicated that *Helicobacter pylori* infection is also a major risk factor for the development of gastric cancer.[9–18] The prevalence of *H. pylori* infection is markedly higher in Japan than in other industrialized countries, although the reasons are not fully understood.[19–21] The observed geographic variability in gastric cancer appears to be explained by a synergistic interaction between *H. pylori* infection and other environmental factors.

The *H. pylori* bacterium colonizes the stomach mucosa and triggers a series of inflammatory reactions. It is considered an important cause of chronic atrophic gastritis (CAG),[19–23] as shown in rodent models.[24–26] CAG is considered the first step of a sequence of mucosal changes in the stomach leading to cancer. The current model for stomach carcinogenesis begins with gastritis, proceeds to CAG, then to intestinal metaplasia, dysplasia and, finally, carcinoma.[1,27] This hypothesis is supported by a considerable number of clinicopathological and epidemiological studies in countries with a high incidence of gastric cancer. However, longitudinal cohort studies that report an association of CAG with gastric cancer and a relation between the progression of CAG and the development of gastric cancer are limited.[28–30] In addition, the role of *H. pylori* infection in the above-mentioned process of stomach carcinogenesis remains unclear. To investigate these problems relating to gastric cancer development, we established a cohort of male factory workers that we followed prospectively for 8 years.

CAG in a high-risk population, such as Japanese subjects, usually begins at the gastric antrum and extends proximally towards the cardia.[31–33] As a result, gastric secretory function diminishes as the area of functional fundic gland mucosa gets smaller.[34] CAG is a histopathological diagnosis. It is difficult, however, to accurately quantify the extent of CAG based on a few endoscopic biopsy samples because CAG is usually a multifocal process.[35] Our previous study showed that the reduction in the area of the fundic gland mucosa with the progression of CAG was well correlated with the stepwise reduction in the serum pepsinogen (PG) level.[34] Thus, the serum PG level is considered a reliable marker for the extent of CAG. Since the measurement of serum PG is simple to obtain and the study subjects experience no discomfort, we used the serum test to evaluate the extent of CAG in our cohort. Along with serum PG levels, we analyzed anti-*H. pylori* IgG antibodies for the evaluation of *H. pylori* infection. Using the 2 serologic markers, we determined the incidence of gastric cancer in the cohort and evaluated the risk for gastric cancer associated with *H. pylori* infection and subsequent CAG progression.

SUBJECTS AND METHODS

Study population

Subjects were 5,706 male employees, 40 to 59 years old, who underwent an annual multiphasic health checkup in a workplace in Wakayama City, Japan. Between April 1994 and March 1995, fasting blood samples were collected as routine laboratory tests for

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