	age (y.o.)	sex	PG I (ng/ml)	I:II ratio	type	Size (mm)	depth	histology	therapy
Case 1.	54	female	64.5	2.3	IIc (UI-IIs)	27	mucosa	tub2> por	ESD→gastrectomy
Case 2.	62	male	42.1	2.6	IIc	10	mucosa	tub1	ESD
Case 3.	52	male	54.3	1.5	IIc (UI-IIs)	15	mucosa	sig> por	gastrectomy
Case 4.	45	male	26.5	1.9	IIc+III	50	muscularis	tub2> por	gastrectomy
Case 5.	60	male	15.7	1.7	IIb	3	mucosa	tub1	ESD
Case 6.	60	male	15.7	1.7	IIa	21	mucosa	tub1	ESD

Table 1. Characteristics of cases of gastric cancers detected by positive pepsinogen tests.
ESD: endoscopic submucosal dissection

underwent gastroscopy. Six cancers in 5 patients, 0.13% of all participants and 0.92% of those with gastroscopy, were detected. (Table 1) Among 6 cancers, 4 were treated by ESD due to preoperative diagnoses of intramucosal intestinal-type cancers. (Figure2-5) All the cancers indicated for ESD were successfully resected with cancer free margins in a single piece. After detail histological evaluation of the specimens resected by ESD, 3 cancers fulfilling the above criteria without vessel infiltration were confirmed to be curatively resected and the other one was additionally treated by gastrectomy with lymph node dissection because diffuse-type cancer cells exist partially among the intestinal-type cancer cells. The rest of detected cancers (2 cancers) were treated by gastrectomy from the beginning because preoperative biopsies revealed diffuse-type cancers. After one year follow-up, all the patients still survived without cancer recurrence.

Conclusions

Measurement of serum PG levels was very useful to detect gastric cancers in early stages among asymptomatic individuals at a workplace. Most of detected cancers by positive PG tests, if those are intestinal-type, may be successfully resected by ESD. Combination between serum PG levels and ESD is an attractive strategy for gastric cancer patients to achieve better QOLs.

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REVIEW

Meta-analysis on the validity of pepsinogen test for gastric carcinoma, dysplasia or chronic atrophic gastritis screening

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Aim: To assess the validity of the measurement of pepsinogen I and II as a screening test for gastric cancer and pre-malignant lesions, namely low-grade dysplasia, both in the general population and in selected groups of patients.

Methods: A meta-analysis of sensitivity and specificity results from individual papers on the use of the pepsinogen test. An intrinsic cut-off effect was assumed and a random effect model was used for pooling.

Results: Forty-two data sets were included: 27 (64%) population-based screening studies (n=296,553) and 15 (36%) sets of selected individuals (n=4385). Homogenous sensitivity and diagnostic odds ratio (DOR) estimates were found in studies using both pepsinogen I levels and pepsinogen I/II ratio calculations. Pooled pairs of sensitivity and false positive rates (FPr) for pepsinogen I ≤70; pepsinogen I/II ratio ≤3, pepsinogen I ≤50; pepsinogen I/II ratio ≤3; and pepsinogen I ≤30; pepsinogen I/II ratio ≤2, were sensitivity 77%/FPr 27%, sensitivity 68%/FPr 31%, and sensitivity 52%/FPr 84%, respectively. Positive predictive values (PPV) varied between 0.77% and 1.25%, and negative predictive values (NPV) varied between 99.08% and 99.90%. In selected groups, pooling was only possible when considering pepsinogen I ≤70; pepsinogen I/II ratio ≤3: giving sensitivity 57%, specificity 80%, PPV 15% and NPV 83%. As for the diagnosis of dysplasia, studies considering pepsinogen I <50; pepsinogen I/II ratio <3 obtained sensitivity 65% and specificity ranging from 74%–85%, both with NPV >95%.

Conclusion: Pepsinogen test definition should include pepsinogen I/II ratio as consistency was obtained, both in population based studies and in selected groups for those studies that used pepsinogen I serum levels together with pepsinogen I/II ratio for screening for gastric cancer in high-incidence regions other than Japan. Further studies of this test in the management of high-risk patients seem to be worthwhile.

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Gastric cancer remains a major cause of cancer mortality worldwide.[1] It is generally accepted that serum pepsinogen concentrations are related to gastric mucosal lesions, and particularly to chronic atrophic gastritis (CAG).[2,3] At least for intestinal-type gastric carcinoma, CAG is considered to be a preceding condition in the sequential histopathological changes that lead to cancer.[4,5] Pepsinogen has therefore been used as a serological biopsy for more than 20 years in different countries and sets of patients.[6–15] In Japan, where a screening program based on radiology followed by endoscopy had already proven its efficacy,[16] pepsinogen screening is mainly used to improve population compliance and the cost-effectiveness of gastric cancer screening.

Generalized screening as it is practiced in Japan may not be easily defensible in all countries. Owing to its low positive predictive value, some authors[17,18] report their concern about pepsinogen effectiveness and applicability in countries with a lower prevalence of gastric cancer than that in Japan. Furthermore, significant differences in methodologies may prejudice consistency assessment. For instance, different cut-off values are known to be used for positivity definition; either pepsinogen I levels (based on ecological evidence)[10,19–21] or both pepsinogen I and II[22,23] were considered; and not all papers considered other factors such as gender, age, smoking and drinking habits, or *Helicobacter pylori* infection, which are said to influence pepsinogen levels. Nevertheless, as a non-invasive test, pepsinogen screening deserves further evaluation.

Therefore, we firstly aimed to evaluate the use of pepsinogen as a screen for gastric cancer as far as the best methodology is concerned (pepsinogen I alone, or pepsinogen I and II), and with regard to the best cut-off point, based on the assessment of consistency among studies in diagnostic validity. We also aimed at defining the usefulness of pepsinogen tests to identify individuals with CAG and other associated lesions, namely intestinal metaplasia and low grade dysplasia, as in most Western countries the strategies for an early diagnosis of gastric cancer have been focusing on follow-up protocols for these individuals. Although a discussion about histopathological classifications is beyond the scope of this text, it is generally agreed that following up those lesions may lead to an early diagnosis of gastric cancer.[24]

METHODS

Search strategy

After defining the search strategy (see inclusion criteria), published papers on pepsinogen test validity were found using a computer-aided search for papers in the MedLine database (PubMed®) and data reports from Japan.

Paper inclusion criteria

No restriction in language was considered. Inclusion criteria were defined for papers' quality as follows:

1. Population under study and available data on variables such as age, gender, smoking or alcohol habits, and *H. pylori* infection had to be clearly defined.
2. Only those studies in which gastric endoscopic examination (with biopsies) was performed as a reference test or gold standard were considered. Two different results were considered: diagnosis of gastric cancer; and diagnosis of lesions associated to gastric cancer, such as atrophy or dysplasia. It was assumed that as diagnosis is based on histology, definitions have not changed over the time during which the studies took place, and there are no differences between Japanese and Western pathologists. In addition, a discussion of histopathological classifications is beyond the scope of this text. Adenoma was also considered to be a synonym of low-grade dysplasia.
3. Radioimmunoassay[20,26–28] and enzyme immunoassay[29–31] were acceptable as methods for pepsinogen test definition, as long as results were expressed in nanograms per millilitre (ng/mL) or equivalent.[32] A pepsinogen test was defined as the measurement of at least pepsinogen I, but ideally of both pepsinogens, and thus the pepsinogen I/II ratio, were measured. All cut-offs for positivity were considered as long as they were clearly defined or easily assessed from paper methods or results.
4. Other details were considered as far as internal and external validity requests are concerned, such as blindness for reference and index test. In screening programs based on the positivity of the pepsinogen test, however, neither endoscopists nor pathologists were blind.

Studies that were not related to the clinical use of pepsinogen for the diagnosis of gastric cancer, or did not contain any data on pepsinogen levels and its variation to gastric lesions or other factors, were excluded.

Data extraction

A standardized data extraction form was used after a short period of pilot use by two reviewers. Agreement was obtained on data and studies to be included, and those to exclude or not to consider for statistical analysis.

Data analysis

The data from each study were plotted in a two by two table, enabling us to calculate validity measures for individual studies. Consistency will be defined using visual exploration after a plot of sensitivity and specificity, with confidence intervals for each study calculated as for proportions, and also plotted. Further assessment of heterogeneity was estimated by using a Chi-square test with Meta-DiSc for Windows (version 1.0.9; XI Cochrane Colloquium, Barcelona, Spain). A random-effects model was used for pooling sensitivity, specificity and estimated diagnostic odds ratio, by addressing both within-study sampling error and variation between studies. Based on previous concerns and results reports, we assumed an implicit cut-off effect; thus we consider diagnosis (cancer or precancerous) and the best cut-off after pooling for each outcome.

RESULTS

Table 1[2,16,18,25,33–54] describes the studies included in this analysis (n=42) related to the diagnosis of gastric cancer or associated lesions.

Several studies or reports, namely those on screening results (n=19) referred only to the number of patients from whom blood was collected for the pepsinogen test, positivity rate and true positive cases. These studies will be considered to calculate the rate of pooled positivity, and to estimate positive predictive value but not for other validity measurements. The studies (n=21) that allowed us to consider the number of cases and number of non-patients with positive and negative tests allowed us to calculate all validity measurements – sensitivity, specificity, diagnostic odds ratio and estimation of predictive values.

Screening of gastric cancer

Twenty-five studies were considered as studies on population settings for the diagnosis of gastric cancer. Ten other studies addressed pepsinogen test validity for the diagnosis of carcinoma on a selected group of patients.

In the first group of studies,[16,33–41] pepsinogen test was measured in 293,758 individuals. According to cut-off values for positivity of pepsinogen test (pepsinogen I <70; pepsinogen I/II ratio <3, pepsinogen I <50; pepsinogen I/II ratio <3, pepsinogen I <30; pepsinogen I/II ratio <2, and pepsinogen I <25) in only seven studies,[16,33–35] four studies,[16,33,35,38] three studies[16,35,39] and one study,[40,41] respectively, was it possible to assess the study validity by plotting a two by two table. In those studies on selected patient groups (n=2007), eight[25,42–45] were considered to have the data needed for validity assessment (Table 1).

Both groups of studies – those based on the general population and those in selected groups – showed homogeneous results in sensitivity estimates and DOR (Table 2) for those studies that used as criteria for positivity pepsinogen I ≤70; pepsinogen I/II ratio ≤3 (Figure 1).

In population studies, positivity rates did not vary significantly – 23%, 22% and 18% for the three above mentioned cut-off strategies. Positive predictive values or their estimates were 0.77%, 0.78% and 1.25% for population setting according to cut-off (pepsinogen I <70; pepsinogen I/II ratio <3, pepsinogen I <50; pepsinogen I/II ratio <3, and pepsinogen I <30; pepsinogen I/II ratio <2, respectively). There is an increase in prevalence, this value having increased to 15% in selected groups. An estimate of pooled negative predictive values was also calculated. They were very high, 83% in selected groups in Japan and Portugal and ranging from 99.08% to 99.62% in population studies in Japan.

Sensitivity varied between 77% for pepsinogen I <70; pepsinogen I/II ratio <3; 68% for pepsinogen I <50; pepsinogen I/II ratio <3; and 51.9% for pepsinogen I <30; pepsinogen I/II ratio <2. Pooled false positive rates were 27%, 31% and 16%, respectively. In selected groups, pepsinogen I <70; pepsinogen I/II ratio <3 presented a sensitivity of 57% and a specificity of 80%. Two of these

Table 1 Positivity rate and validity of pepsinogen (PG) serum levels ('PG test') for screening of gastric cancer, dysplasia and atrophy, both in population based studies and in selected groups according to cutoff[1]

	N	PG Method & cutoff	Pos rate (%)	S (95%CI)	Sp (95%CI)	FPR (95% CI)	PPV (95%CI)	NPV (95%CI)	DOR (95%CI)
Gastric cancer screening in population based studies									
[33] Japan, 1993	4876	RIA, PGI≤70 & PGI/II ≤3	18.7	83.3 (82.2–84.3)	74.4 (73.1–75.6)	25.6 (24.4–26.9)	1.2 (0.8–1.5)	99.9 (99.8–99.9)	14.5 (13.4–15.5)
[34] Japan, 1996	5113	RIA, PGI≤70 & PGI/II ≤3	26.7	84.6 (83.5–85.6)	73.5 (72.2–74.7)	26.5 (25.3–27.8)	0.8 (0.5–1.0)	99.9 (99.8–99.9)	15.2 (14.2–16.2)
[35] Japan, 1994–1999	5264	RIA, PGI≤70 & PGI/II ≤3	22.1	72.7 (70.0–75.3)	78 (75.5–80.4)	22 (19.6–24.5)	0.7 (0.2–1.1)	99.9 (99.7–100)	9.4 (7.7–11.1)
[35] Japan, 1997–1999	5583	RIA, PGI≤70 & PGI/II ≤3	23.3	71.4 (68.8–73.9)	76.7 (74.3–79)	23.3 (21–25.7)	0.4 (0.0–0.0)	100 (100–100)	8.2 (6.6–9.7)
[35] Japan, 1995	4576	RIA, PGI≤70 & PGI/II ≤3	26.1	81.5 (79.2–83.7)	74.2 (71.6–76.7	25.8 (23.3–28.4)	1.8 (1.0–2.5)	99.9 (99.7–100	12.7 (10.7–14.5)
[16] Japan, 1995–1999	4151	RIA, PGI≤70 & PGI/II ≤3	43	74.5 (72.4–76.5)	57.4 (55–59.7)	42.6 (40.3–45)	2.3 (1.5–3.0)	99.4 (99–99.7)	3.9 (3.0–4.8)
[35] Japan, 1994–1998	17770	RIA and EIA, PGI≤70 & PGI/II ≤3	26.4	73.7 (72.4–74.9)	73.7 (72.4–74.9)	26.3 (25.1–27.6)	0.3 (0.1–0.4)	100 (100–100)	7.9 (7.0–8.6)
[35] Japan, 1996–1999	23914	RIA, PGI≤70 & PGI/II ≤3	27.4				0.9 (0.5–1.2)		
[35] Japan, 2000	3707	RIA, PGI≤70 & PGI/II ≤3	16.9				1.3 (0.1–2.4)		
[35] Japan, 1993–1999	8497	RIA, PGI≤70 & PGI/II ≤3	21.9				0.8 (0.3–1.2)		
[35] Japan, 1992–1999	6628	RIA, PGI≤70 & PGI/II ≤3	24.2				1.0 (0.4–1.5)		
[35] Japan, 1996–1999	35788	RIA, PGI≤70 & PGI/II ≤3	25.1				0.9 (0.6–1.1)		
[35] Japan, 1997–1999	3298	RIA, PGI≤70 & PGI/II ≤3	13.2				0.5 (0.0–1.1)		
[35] Japan, 1996	2013	RIA, PGI≤70 & PGI/II ≤3	20.2				1.4 (0.0–2.8)		
[35] Japan, 1998–1999	12585	RIA, PGI≤70 & PGI/II ≤3	23.7				0.9 (0.6–1.0)		
[36,37] Japan, 1992–1995	20768	RIA, PGI≤70 & PGI/II ≤3	17.7				1.0 (0.3–1.6)		
[35] Japan, 1995–2000	69600	PGI≤70 & PGI/II ≤3	13.6				0.7 (0.4–0.9)		
[35] Japan, 1999	5567	RIA, PGI≤70 & PGI/II ≤3	23.6					0.8 (0.2–1.2)	
[35] Japan, 1997–1999	982	RIA and EIA, PGI≤70 & PGI/II ≤3	14.5					6.8 (0.2–13.3)	
[33] Japan, 1993	4876	RIA, PGI≤50 & PGI/II ≤3	16.5	66.7 (65.3–68)	81.5 (80.3–82.6)	18.5 (17.4–19.7)	1.3 (0.9–1.6)	99.8 (99.6–99.9)	8.8 (8–9.6)
[38] Japan, 1993	10996	RIA, PGI≤50 & PGI/II ≤3	27.9	65 (62.8–67.1)	84.0 (82.3–85.6)	16 (14.4–17.7)	1.0 (0.5–1.4)	99.9 (99.7–100)	9.7 (8.4–11.0)
[35] Japan, 1995	11151	RIA, PGI≤50 & PGI/II ≤3	16.4	62.5 (60.0–64.9)	47.4 (44.8–49.9)	52.6 (50.1–55.2)	1.2 (0.6–1.7)	99.2 (98.7–99.6)	1.5 (0.8–2.1)
[36,37] Japan, 1991	4657	RIA, PGI≤50 & PGI/II ≤3	18.7				0.6 (0.0–1.1)		
[16] Japan, 1995–1999	4151	RIA, PGI≤50 & PGI/II ≤3	31	63.6 (60.9–66.2)	69.4 (66.8–71.9)	30.6 (28.1–33.2)	2.7 (1.7–3.6)	99.3 (98.8–99.7)	4.0 (2.8–5.0)
[33] Japan, 1993	4876	RIA, PGI≤30 & PGI/II ≤2	14.5	77.8 (76.6–78.9)	83.2 (82.1–84.2)	16.8 (15.8–17.9)	1.7 (1.3–2.0)	99.9 (99.8–99.9)	17.4 (16.2–18.4)
[16] Japan, 1995–1999	4151	RIA, PGI≤30 & PGI/II ≤2	15	40 (36–43.9)	85.3 (82.4–88.1)	14.7 (11.9–17.6)	3.5 (2–4.9)	99.1 (98.3–99.8)	3.9 (2.3–5.4)
[35] Japan, 1997–1999	5583	RIA, PGI≤70 & PGI/II ≤2	23.3	100 (99.9–100)	85.1 (81.4–88.7)	14.9 (11.3–18.6)	1 (0–2)	100 (100–100)	51.4 (2.8–957.7)
[39] Japan, 1993	2709	RIA, PGI≤30 & PGI/II ≤2	23.4				10.5 (7.1–13.8)		
[35] Japan, 1993 & 1997	1129	RIA, PGI≤30 & PGI/II ≤2	21.3				1.1 (0–3.2)		
[40,41] Finland, 2000	22436	RIA, PGI ≤25	6	99 (93–99.9)	9.3 (7.8–10.7)	90.7 (89.3–92.2)	1.0 (0.5–1.4)	100 (99.9–100)	10.3 (6.5–11.8)
Gastric cancer screening in selected groups									
[25] Japan, 1989	117	RIA, PGI≤70 & PGI/II ≤3	31.6	58.2 (49.1–67.4)	75.3 (67.3–83.2)	24.7 (16.8–32.7)	37.8 (28.8–46.7)	87.5 (81.3–93.6)	4.3 (0.5–7.9)
[42] Japan, 1989	322	RIA, PGI≤70 & PGI/II ≤3	24.2	54.7 (49.1–60.2)	89.3 (85.8–92.7)	10.7 (7.3–14.2)	74.4 (69.5–79.2)	77.7 (73–82.3)	10.1 (6.7–13.4)
[43] Portugal, 2001	136	EIA, PGI≤70 & PGI/II ≤3	36.8	65.2 (57–73.3)	69 (61–76.9)	31 (23.1–39)	30 (22.1–37.8)	90.7 (85.7–95.6)	4.2 (0.7–7.5)
[44] China, 1991	262	RIA, PGI≤70	51.9	29.2 (23.5–34.8)	84.3 (79.8–88.7)	15.7 (11.3–20.2)	83.6 (79–88.1)	30.3 (24.6–35.9)	2.2 (0.3–4.0)
[45] Japan, 1989	425	RIA, PGI≤35	52.1	81 (76.6–85.3)	61.1 (55.6–66.5)	38.9 (33.5–44.4)	49.8 (44.2–55.3)	87.1 (83.3–90.8)	6.7 (3.9–9.4)
[45] Japan, 1989	425	RIA, PGI≤30	43.3	69.3 (64.1–74.4)	70.1 (64.9–75.2)	29.9 (24.8–35.1)	52.5 (46.9–58)	82.8 (78.5–87)	5.3 (2.7–7.7)
[45] Japan, 1989	425	RIA, PGI≤25	20	61.3 (55.8–66.7)	79.9 (75.4–84.3)	20.1 (15.7–24.6)	59.2 (53.7–64.6)	81.3 (76.9–85.6)	6.3 (3.5–9)
[45] Japan, 1989	425	RIA, PGI≤20	19	43.1 (37.5–48.6)	91 (87.8–94.1)	9 (5.9–12.2)	69.4 (64.2–74.5)	77.1 (72.4–81.7)	7.7 (4.6–10.6)
[46] Japan, 1986	320	RIA, PGI/II≤2.5		84.2 (80.1–88.2)	64 (58.6–69.3)	36 (30.7–41.4)			9.5 (6.1–12.7)
[2] Japan, 1989	425	RIA, PGI/II ≤2		87.5 (84.2–90.7)	82.5 (78.8–86.1)	17.5 (13.9–21.2)			33 (28.4–37.5)
Displasia screening in population based studies									
[37,38] Japan, 1992–1995	20768	RIA, PGI≤70 & PGI/II ≤3	17.7				2.1 (0.9–4.6)		
[38] Japan, 1993	10996	RIA, PGI≤50 & PGI/II ≤3	27.9	65.3 (63.1–67.4)	85.7 (84.1–87.2)	14.3 (12.8–15.9)	1.8 (1.2–2.8)	99.8 (99.6–99.9)	11.3 (9.8–12.6)
[36,37] Japan, 1991	4657	RIA, PGI≤50 & PGI/II ≤3	18.7				1.2 (0.3–2.0)		
[40,41] Finland, 2000	22436	RIA, PGI ≤25	6	98.4 (97.7–99)	100 (99.9–100	0 (0–0.1)	4.5 (3.4–5.5)	99.3 (98.8–99.7)	8.6 (7.5–9.3)
Displasia screening in selected groups									
[43] Portugal, 2001	136	EIA, PGI≤70 & PGI/II ≤3	36.8	72.7 (65–80.3)	66.4 (58.2–74.5)	33.6 (25.5–41.8)	16 (9.7–22.2)	96.5 (93.3–99.6)	5.3 (1.4–9)
[43] Portugal, 2001	136	EIA, PGI≤50 & PGI/II ≤3	23.8	65.2 (58.6–76.3)	74.3 (68.4–83.8)	25.7 (16.2–31.6)	34.1 (26.7–38.2)	91.3 (893.3–97.6)	6.4 (1.2–9.8)
Chronic atrophic gastritis screening in population based studies									
[47] China, 2000	2646	EIA, PGI/II < 5	23.5	19 (17.4–20.5)	72.1 (70.3–73.8)	27.9 (26.2–29.7)	0.6 (0.3–0.9)		
[41,42] Finland, 2000	22436	RIA, PGI ≤25	6.0	98.6 (98–99.1)	100 (99.9–100)	0 (0–0.1)	90.9 (89.4–92.3)	87.5 (85.8–89.1)	0.3 (0.1–0.9)
[18] Mexico, 2001	149	RIA, PGI ≤25	9.0	13.6 (7.9–19.2)	95.6 (92.2–98.9)	4.4 (1.1–7.8)	87.5 (82–92.9)	32.6 (24.9–40 2)	0.9 (0–2.5)
[18] Mexico, 2001	149	RIA, PGI/II < 2.5	2.9	5.8 (1.9–9.6)	100 (99.9–100)	0 (0–0.1)	100 (100–100)	32.2 (24.5–39.8)	0.9 (0–2.5)
Chronic atrophic gastritis screening in population based studies									
[48] UK, 1999	59	RIA, PG < 25	23.4	44.4 (31.4–57.3)	97.6 (93.6–100)	2.4 (0–6.4)			32.5 (20.4–44.6)
[46] Japan, 1986	320	RIA, PG < 30	31.3	59 (53.5–64.4)	96.3 (94.1–98.4)	3.7 (1.6–5.9)			37.3 (32–42.8)
[46] Japan, 1986	320	RIA, PGI/II < 2.5	60.1	84.2 (80.1–88.2)	64 (58.6–69.3)	36 (30.7–41.4)	72.3 (67.2–77.3)	93.2 (90.3–96)	36.0 (30.6–41.4)
[49] Japan, 1998	200	RIA, PGI <70 & PGI/II < 3	36.5	65 (58.2–71.7)	92 (88.1–95.8)	8 (4.2–11.9)			21.4 (15.6–27.1)
[49] Japan, 1998	200	RIA, PGI <40 & PGI/II < 2.5	53.7	82.1 (76.6–87.5)	74.7 (68.5–80.8)	25.3 (19.2–31.5)			13.5 (8.7–18.3)
[49] Japan, 1998	200	RIA, PGI <30 & PGI/II < 2	9.5	18.8 (13.2–24.3)	100 (99.9–100)	0 (0–0.1)			
[50] UK, 1998	87	RIA, PGI/II < 1.5	18.8	26.7 (17.2–36.1)	89.1 (82.4–95.7)	10.9 (4.3–17.6)			3.0 (0–6.6)
[51] Sweden, 2000	199	EIA, PGI < 30	14.6	87.9 (83.2–92.5)	80.7 (75.1–86.2)	19.3 (13.8–24.9)	81.8 (76.3–87 2)	87.1 (82.3–91.8)	30.4 (23.8–36.8)
[52] Finland, 1996	144	EIA, PGI < 30	10.4	16.7 (10.4–22.9)	100 (99.9–100)	0 (0–0.1)	100 (99.9–100)	41.9 (33.6–50.1)	176.0 (150–183.5)
[54] Finland, 1991	773	EIA, PGI < 30	15.3	89.5 (87.2–91.7)	91.6 (89.6–93.5)	8.4 (6.5–10.4)	21.3 (18.3–24.2)	98.7 (99.3–100)	2.9 (2.1–5.6)

95% CI=95% confidence interval; CAG=Chronic atrophic gastritis; DOR=Diagnostic odds ratio; Dys +=Diagnosis of lesions as severe as low-grade dysplasia; FPR=False positives rate; GC=Gastric Cancer; IM=Intestinal metaplasia; NPV=Negative predictive value estimate; PPV=Positive predictive value estimate; Pos rate (%)=Positivity rate according to cutoff defined; S=Sensitivity; Sp=Specificity.

Table 2 Pooled sensitivity, specificity and diagnostic odds ratio considering gastric cancer diagnosis according to the studies' setting and different cutoffs using a random effects-model and Chi-square test to assess for heterogeneity

PG Method & cutoff	Pos rate (%)	S (95%CI)	p*	Sp (95%CI)	p*	DOR (95%CI)	p*	AUC sROC (95%CI))
Gastric cancer screening in population based studies								
PGI ≤70 & PGI/II ≤3 (n=7)[16,33-35]	23%	**77.3 (69.8-83.8)**	**0.942**	73.2 (72.8-73.6)	<0.001	**7.9 (5.0-12.4)**	**0.285**	**82.0 (77.2-86.8)**
PGI ≤50 & PGI/II ≤3 (n=4)[16,33,35,38]	22%	**68.4 (59.1-76.8)**	**0.259**	69.3 (68.6-70.0)	<0.001	**4.7 (2.2-9.8)**	**0.083**	**74.4 (60.6-89.2)**
PGI ≤30 & PGI/II ≤2 (n=3)[16,35,39]	18%	51.9 (40.3-63.5)	0.001	84.4 (83.7-85.0)	0.016	10.3 (2,5-42.8)	0.018	69.3 (63.1-75.5)
Gastric cancer screening in selected groups								
PGI ≤70 & PGI/II ≤3 (n=3)[25,42,43]	26%	**56.9 (48.6-64.8)**	**0.642**	80.2 (75.9-84.0)	<0.001	**6.2 (3.3-11.7)**	0.163	**91.1 (89.1-93.1)**

p for heterogeneity Chi-square test among each group of studies (p<0.05 indicating loss of homogeneity); AUC sROC (SE) – area under the curve for studies' Receiver Operating Curves; n=number of studies included.

studies, the Portuguese one and the one in Japan, showed very similar results, despite having been carried out 12 years apart.

Screening for CAG and dysplasia

Six studies addressed adenoma or dysplasia diagnosis,[36-38,40-41,43] but only three studies[38,40,41,43] (two population based and one in a selected cohort) possessed the data for the measurement of sensitivity and specificity. Data pooling was determined not to be possible as different cut-offs were considered. Low positive predictive values are present but so are very high negative predictive values, even in selected groups (96.5%) where the prevalence is expected to be high. As far as the diagnosis of dysplasia is concerned, studies considering cut off points pepsinogen I <50; pepsinogen I/II ratio <3 obtained sensitivity of 65% and specificity ranging from 74% to 85%, both with negative predictive values >95%. Those studies that used both pepsinogen I and pepsinogen II for their ratio calculation obtained similar results but the cut-off was pepsinogen I/II ratio <2.5.

Twelve studies were also aimed at diagnosing CAG. Four were based on population settings[18,41,42,47] – that is, patients without previously known lesions – and nine on patients with known lesions.[46,48-52,54] Only in eight studies was it possible to address sensitivity and specificity. Beyond the shown heterogeneity, most of them considered different cut-offs, which did not allow pooling.

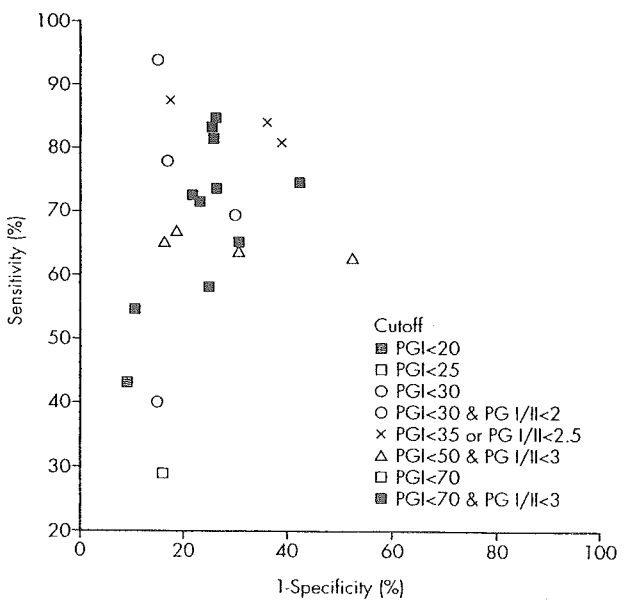

Figure 1 Sensitivity (%) and false positive rates (%) pairs according to cutoff showing a high variability of results according to cutoff. Homogeneity was only obtained considering intrinsic cutoff effect, allowing further pooling, and improving of AUC [82.0% (95%CI=77.2-86.8%) and 91.1% (89.1-93.1) for pepsinogen test defined as PGI<70ng/mL and PGI/II<3 for screening of gastric cancer, both in population based studies, and in selected groups.].

Other factors considered

It was not possible to assess the validity of the diagnosis of gastric cancer or other lesions, based on factors such as age, gender, smoking and drinking habits, or *H. pylori* infection, mainly because most studies did not address this issue adequately. That is, no data is given for these factors to be considered for eventual cut-offs changes. Nevertheless, ageing seems to increase pepsinogen II levels consistently and decrease the pepsinogen I/II ratio.[2,34-35,57] There is no agreement on the results concerning pepsinogen I levels (no differences,[34,44,56] decrease in both sexes,[33] and increase in men[56]).

Although, pepsinogen I levels seem to increase in men,[34,56,57] no differences are found in pepsinogen II, and pepsinogen I/II ratio either decreases in women[36,37,57] or no differences are found.[34,56]

Two studies noted that adjustment according to age or gender groups was tried,[44,46] with either no changes or with significant decreases in sensitivity.

No definite results could be reported concerning smoking and drinking habits. Studies relating to alcohol found no differences[57-59] or there was a decrease in both pepsinogen I and pepsinogen II, with no differences in pepsinogen I/II ratio .[60] In addition, smoking did not consistently affect pepsinogen I/II ratio. Although an increase in logarithm transformation of pepsinogen I was referred in another study, no modified cut-off was reported.

As for *H. pylori*, pooled data was performed, but only as far as an infection is concerned.[57,61-67] *H. pylori* seems to consistently increase pepsinogen I (mean 58.0 ng/mL in *H. pylori* positive individuals [n=3887] *versus* 45.4 ng/mL in *H. pylori* negative individuals [n=3366]) and pepsinogen II (16.8 ng/mL in *H. pylori* positive individuals *versus* 9.0 ng/mL in *H. pylori* negative individuals), and decrease pepsinogen I/II ratio (3.9 *versus* 5.7). Furthermore, no differences were found when considering the diagnosis of Hp infection diagnosis with the use of histology or serology. But it was not possible to note or access a modified cut-off.

Best cut-off assessment

After the assessment of pooled results (Table 2) and by plotting pairs of sensitivity values and positivity rates according to cut-off used in different studies (Figure 2), we were able to conclude that the best cut-off (with the best

sensitivity/specificity balance) is the pepsinogen test defined as pepsinogen I <70; pepsinogen I/II ratio <3, with a pooled sensitivity of 77.3%, a false positivity rate of 26.8%, and with a gain of information of 32% in population settings. This same cutoff used in selected groups seems quite specific for gastric cancer diagnosis, with an area under the curve of 91.1%.

DISCUSSION

A diagnostic test should be reproducible and valid; those with a screening purpose in particular should be free of discomfort or risk, and they should be economical. For the gastrointestinal tract, direct visualization through endoscopic examination is probably the best method for the diagnosis of most protruded and depressed cancer lesions. It easily allows the collection of mucosal specimens for histopathological evaluation, although a very high inter-observer variability exists for flat lesions or changes, including gastric atrophy, intestinal metaplasia, and even dysplasia. But endoscopic examination is invasive, not patient friendly, nor always easily accessible. Therefore, the selection of individuals for endoscopic examination seems to be attractive for most screening programs, for instance the use of FOBT for colon and rectum neoplasias.

Mass screening has been conducted in Japan for about 40 years to detect gastric cancers, and 6,000,000 people are screened annually, mainly by X-ray examination. In 1999, 5,718,191 individuals were evaluated with a radiological study. A tenth (11.4%) were sent for endoscopic examination, and in 0.105% a cancer was detected. There is, however, a decreasing trend in the total number of individuals inspected. To improve compliance with gastric mass screening,[33,36] a non-invasive test was introduced to identify subjects at high risk of developing gastric cancer.

Pepsinogen levels in blood seem to be related to functional changes in the stomach, and its use as a serological biopsy has been reported for over 20 years.[2,39,46,57,69] Authors focused mainly on the diagnosis of atrophy, as its relation with gastric cancer has been reported. If in most Western countries the focus was on the identification of individuals for intervention studies, in Japan, its use was meant to identify those for endoscopic examination, and for the diagnosis of gastric cancer. It is not surprising that studies with different purposes tend to use different methodologies.

Some questions remain unanswered, namely the consistency of the pepsinogen test in several countries and population sets and the definition of the best cut-off.

It is always ambitious to consider a meta-analysis because even if all papers are tracked, publication bias is always troublesome. Furthermore, with the previous stated heterogeneity of methods it is almost an impossible task, and probably for that reason no meta-analysis has been performed on the validity of the pepsinogen test both for gastric cancer or pre-malignant lesions before now.

We decided to evaluate the results of several studies and reports, focusing our search mainly on reports from different countries and with different purposes (screening or follow-up). We considered addressing the reproducibility of pepsinogen test by using sensitivity and specificity, as these measures show little variation with the prevalence of the disease. Assuming cut-off points have an intrinsic effect on test validity, we first aimed at assessing consistency according to different cut-off used, and then at pooling and defining the best discriminatory value for cancer or other lesions diagnosis if possible.

Globally, low positive predictive values were found on population studies. To improve this problem some authors tried to adjust cut-off or modify strategies[51,69,70] by measuring confounding factors known to influence pepsinogen levels in blood. From our analysis we were only able to find out that pepsinogen I/II ratio tends to decrease with age and with the presence of *H. pylori*, but it was not possible to define any modification on cut-off. There were no conclusions on other factors, such as gender or smoking and drinking habits. Age seems to be related to an increase in acid secretion in humans,[71] and the decrease of pepsinogen I and pepsinogen I/II ratio found in most studies may be related not to age but to atrophic changes diagnosed that way. The presence of *H. pylori*, either addressed by serological evaluation or by immunohistochemistry in bioptic specimens, seems to increase pepsinogen I and II levels and decrease pepsinogen I/II ratio in conjunction with inflammation.[72–74] As suggested, no modifications in cut-off of pepsinogen test, or the inclusion of *H. pylori* serology, were reported or showed any improvements. Some authors[43,74] showed that the decrease of pepsinogen I/II ratio is independent of the presence of *H. pylori*. Furthermore, as IgG may persist for several years after the disappearance of *H. pylori* infection, its measurement in high-incidence countries may not be effective, as no information is gained. Some authors consider that the value for its negativity is more important. That is, in high-prevalence countries it may be more important to diagnose an individual with gastric atrophy or other changes negative for *H. pylori*; that could mean that a long time has passed since infection and mucosal changes occurred, thus representing a great risk of cancer.

According to our review, around 600 individuals should be screened using the pepsinogen test to diagnose one cancer in Japan. Considering that the main drawback is positivity rate (around 20%), this strategy has to be available at a low price, as in Japan (US$10). It could be an attractive strategy, as 75% of all gastric cancers discovered in these studies were EGC[16,25,34,36–40,75] curable forms, with almost 100% survival for five years. It was possible to evaluate the best strategy for screening as the use of pepsinogen I <70; pepsinogen I/II ratio <3. Pooled sensitivity was 77.3% and specificity 73.2%. Studies using only pepsinogen I obtained heterogeneous results, even considering obvious differences after cut-off, probably related to other factors, as discussed above. Only pepsinogen I <30; pepsinogen I/II ratio <2 criteria, and not pepsinogen I <50; pepsinogen I/II ratio <3, showed a significant increment in specificity (84%).

We also noted very high negative predictive value in all studies, which was unchanged in population or selected groups, and was 99.9% and 81%, respectively, even considering expected differences in prevalence. This could be the rationale to use the pepsinogen test under follow-up scenarios. As stated before, endoscopy shows a low inter-observer agreement as far as neoplastic or non-neoplastic flat lesions are concerned. The use of a non-invasive test that simultaneously measures all gastric mucosal status may be able to be allocate several patients who would otherwise undergo several and eventually inefficacious examinations to a less intensive follow-up scheme. Screening in Japan already uses this strategy, as another assay is proposed only five years after a negative result in any individual.[11] Although no study has specifically analyzed the relationship between the decline of pepsinogen I/II ratio and the risk of gastric cancer,[66] it was noted that the variation in pepsinogen I/II ratio is thought to reflect mainly the advance of atrophy. Other authors (Dinis-Ribeiro M *et al.*[43] and Kato *et al.*[57]) showed a mean pepsinogen I/II ratio lower than that for CAG for dysplasia (mean=2.79; n=6) and for intestinal

metaplasia (mean=3.03; n=26). In western countries, where gastric cancer has been declining, these results may be more attractive for early diagnosis strategies focusing on the follow-up of patients with precancerous lesions. Unfortunately we were not able to assess and define the best cut-off for this purpose, which may be related to low inter-observer agreement in the endoscopic assessment of atrophy, to biopsy protocols and sample error, and even to pathologists differences. We can speculate that it should be the same as the one used for the diagnosis of gastric cancer, as in fact the intention is to measure functional changes after atrophy. The highest specificity and negative predictive value were noted when the cut-off pepsinogen I <30; pepsinogen I/II ratio <2 was used. As most follow up programs may be endoscopy-based, the most important fact is to accurately diagnose the absence of disease or severe lesions.

To conclude, the use of the same cut-off for positivity of pepsinogen test obtained similar and comparable results in different sets of individuals and in different countries, both for the diagnosis of gastric neoplastic lesions, dysplasia or carcinoma, which attests for its consistency. Thus, if a reasonable cost is obtainable in a screening scenario in high-incidence regions other than in Japan, and for the management of high-risk patients, studies to assess the efficacy and validity of the pepsinogen test seem to be worthwhile as no other non-invasive test has revealed better results until now.

Pepsinogen test definition should include pepsinogen I/II ratio, as homogeneity was obtained both in population based studies and in selected groups for those studies that used pepsinogen I serum levels together with pepsinogen I/II ratio. For screening gastric cancer in high-incidence regions other than in Japan, and for high-risk patient management, further studies using this test seem to be worthwhile.

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〔会長講演〕

胃がんスクリーニングのハイリスクストラテジーに関する研究

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Study for the high-risk strategy for gastric cancer screening.

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要　旨

ペプシノゲン（PG）法に加えて，*Helicobacter*（*H*）*pylori*（*p*）に対するImmunoglobulin（Ig）G抗体，Cytotoxin- associatedantigen（Cag）A抗体等を用いた胃がんのハイリスク集団（高危険群）の最適なスクリーニング方法を明らかにし，最終的には胃X線検査や胃内視鏡検査と組み合わせた経済的でかつ胃がん死亡減少をもたらすマネージメント方法を提案することを目的とし，胃がん高危険群のスクリーニング方法に関する研究とPG法単独やPG法と胃X線検査併用胃がん検診の胃がん死亡率減少効果の評価を行い，①血清PG値と*Hp*抗体とCagA抗体の3者の測定は，胃がん高危険群スクリーニングだけでなく，胃がんの病理組織型（分化・未分化型の鑑別）診断にも有用である。②*Hp*感染のない群（A群）を低リスク（危険）群として胃がん検診対象から外し，高危険群；萎縮性胃炎合併群（B，C，及びD群）のみを選択的にスクリーニングする胃がん検診方法は合理的である。③未分化型胃がん（PG法陰性群の多数）に対応するため，X線検査と血清PG検査を組み合わせる検診方式（二段階同日判定法）は合理的である。④PG法受診による胃がん死亡率の減少効果を症例対照研究で認めた，などの結果を得た。

キーワード　胃がんハイリスクスクリーニング，ペプシノゲン法，*H.pylori*に対するIgG抗体，CagA抗体

○はじめに

疫学的に死亡率減少効果が明らかにされたわが国の間接胃X線検査[1)~5)]による胃がん検診が全国で実施されてきたが，21世紀に入ってもなお胃がん死亡者数は毎年約5万人を数え，わが国のがん死亡の中でなお第2位を占めている。21世紀におけるわが国の国民健康づくり運動である健康日本21においても，胃がんを含む各がん検診の受診者の5割以上の増加が目標としてあげられている。しかし，地方分権の推進を背景とした国の予算編成において今後地方交付税の大幅な削減が予想され，単純な受診者数の増加ではなく，より効率的な胃がんスクリーニング体制の整備が急務である。

地域における疾病対策の基本は，地域住民全体の疾病への罹患や死亡のリスクを減少させるポピュレーションストラテジーと，元々疾病への罹患や死亡のリスクの高いハイリスク集団への介入を行うハイリスクストラテジーの2つの方法があり，これまでの老人保健事業による胃がん検診は，40歳以上の地域住民を対象としたいわばポピュレーションストラテジーとして位置付けられる。

我々は，これまで厚生省がん研究助成金[6]や厚生労働科学研究費補助金[7]による研究において胃がんのハイリスクである萎縮性胃炎の有無を血清学的にスクリーニングし，萎縮性胃炎保有者に胃内視鏡検査を実施するPG法を地域における胃がんに対する新たなポピュレーションストラテジーとして位置付け，その精度や胃がん死亡率減少効果について研究[8][9]を行ってきた。その結果，PG法の精度は胃X線検査による胃がんスクリーニングとほぼ同等[10]であり，PG法が胃がん死亡率を減少させることを示唆する結果はいくつか得られたものの，効果評価についてはまだ十分とは言えなかった[11]。

PG法はそもそも萎縮性胃炎という胃がんのハイリスク集団のスクリーニング方法であり，PG法に加えて*Hp*に対するIgG抗体やCagA抗体等をも含めた胃がんのハイリスクストラテジーとしての位置づけを明らかにし，単なるがん検診としてだけではなく，X線検査等の他のスクリーニング方法や精密検査，更には治療も含めて，対象集団において胃がん死亡率減少効果をもたらすマネージメント方法を開発することを最終目的とした点で，単なる胃がん検診の評価を超えた胃がん対策に関する研究である点に本研究の最大の特徴がある。すなわち，PG法だけによる胃がん対策を模索しているのではなく，PG法の弱点でもあった未分化胃がん対策としてCagA抗体等も含めたり，精密検査も含めた経済的効率性にもアプローチする点で，これまでになかった独創的な取り組みである。

○血清ペプシノゲン(PG)

萎縮性胃炎の血清マーカーであり，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がんの前がん病変であることから，PG法陽性者を胃がんハイリスク群としてスクリーニングする手法が，胃がん検診として実用化されている。

また，これまでに報告された胃がんおよび前がん病変に対するPG法の精度に関する国内外42編の主要文献（対象集団延べ約30万人）のメタアナリシスによる検討[11]で，PG法基準値（PGⅠ70ng/mlかつPGⅠ/Ⅱ比3.0以下）の感度は77%，偽陽性率（FPR）は27%，陽性反応的中率（PPV）は0.77%～1.25%，陰性反応的中率（NPV）は99.03%～99.9%であり，胃がん症例4,385例のPG法基準値の精度は感度57%，特異度80%，PPV 15%，NPV83%であった。PG法は一貫性があり，日本人以外のハイリスク群の抽出にも有用と考えられた。近年，コスタリカなどの中米諸国，ポルトガル，中国[12][13]（東北部）などの胃がん多発地域において試用され始めており，今後の成績報告が注目されている。

わが国において，間接X線による胃がん検診は40年以上の歴史を持ち，その有効性も疫学的に証明されている[1]~[5]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値による胃がん検診，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。

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，PGⅠ，PGⅡが存在し，PGⅠは胃底腺領域で産生され，PGⅡは胃粘膜全域で産生される。PGⅠは胃酸分泌能と相関し，胃壁細胞量をよく反映し，PGⅠ値の上昇は胃の攻撃因子の増大を示唆する。PGⅡ値の変動はPGⅠ値に比べてわずかである。PGⅠ，Ⅱとも，日内変動，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，プロトンポンプイン阻害薬やH_2受容体拮抗薬投与の影響を受けるので，測定時には投与歴の確認が必要である。

○ペプシノゲン(PG)法による胃がん検診

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PGⅠ値およびPGⅠ/Ⅱ比の低下には，高い相関が認め

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がん発見精度

報告者(実施年度)	人数	陽性率	感度	特異度	陽性反応的中度	発見率(数)
北原(1995-96)	5,113	25%	85%	75%	0.9%	0.22(11)
小松(1996-97)	1,000	30%	83%	70%	1,7%	0.50(5)
井上(1995-96)	2,870	29%	86%	72%	1.5%	0.42(12)
西澤(1995-97)	2,724	40%	74%	60%	2.1%	0.84(23)
	[中等度陽性値]	28%	61%	72%	2.5%	0.70(19)
	[強陽性値]	14%	42%	86%	3.4%	0.48(13)
(陽性値小計)	11,707	30%	80%	70%	1.5%	0.44(51)

(厚生省がん研究助成金　三木班、1998)

られる[14]。また近年，慢性萎縮性胃炎は分化型胃がん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[15][16]。

慢性萎縮性胃炎と胃がんとの関連，PG値と慢性萎縮性胃炎との相関を利用し，PGⅠ値およびPGⅠ/Ⅱ比を指標として胃がんハイリスク群である進展した萎縮性胃炎を同定し，胃がん検診に応用したのがPG法である。胃がん患者群と健常対照群の血清PG値を比較検討したところ，PGⅠ70 ng/mlかつ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，胃がん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[17][18]。

1998（平成10）年，厚生省（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，胃がん発見率0.44%（発見胃がん51例），偽陰性率20%（偽陰性胃がん13例），陽性反応的中度1.5%であった[19]（表1）。

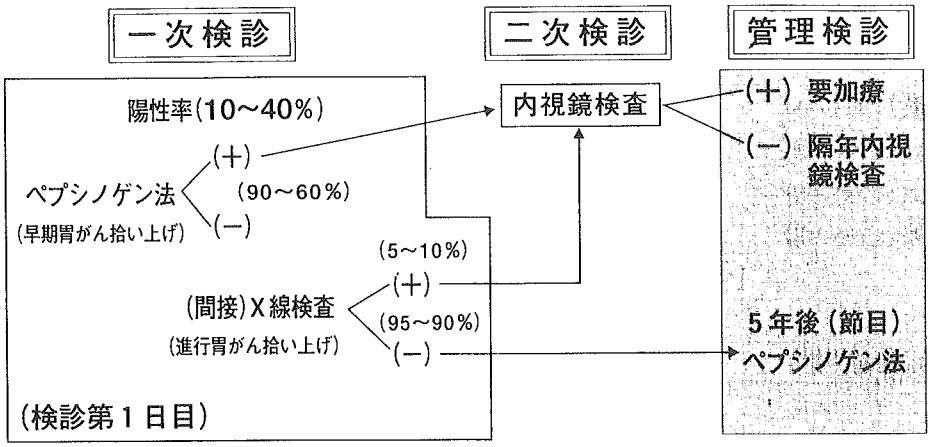
富山県下事業所において7検診機関による検診（カバー率82.2%）で同意が得られ，3人の胃切除者を除いた従業員5,567名（男性3,791名，女性1,776名，男女ともに平均年齢48歳）を対象として，X線（間接または直接）法とPG法を同時に行い（同時併用法），胃がん10例（早期胃がん9例，進行胃がん1例）を発見した。X線法とPG法の要精検率はそれぞれ12%と24%，精検受診率は55%と52%，胃がん発見率は0.05%と0.18%，陽性反応的中度は0.8%，1.4%であった[20]。

三木班協力施設における605例の胃がん症例の術前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がん症例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がん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[21]。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，陰性胃がん症例があることは免れない。陰性胃がんを落とさないために，厚生労働省三木班では，PG法とX線法を組み合わせて実施することを提唱している（二段階同日判定法[22][23]：図1）。

○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

人間ドックの胃がん検診では，内視鏡検査が一

図1：胃がん検診二段階(同日判定)法



(厚生省がん研究助成金　三木班，2000)

般的になってきている。住民検診や職域検診でも，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な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法を用いて胃がん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法による胃がん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）に対する胃がん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）に対する胃がん発生の相対危険度は8.34（95%CI 2.18～31.87）であった[24]。

○ヘリコバクター検査との併用による胃がんスクリーニングの可能性

血清PG値に血清*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がん発見頻度を比較したところ，PG法陽性者からの胃がん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がん発見が1例もなく，胃がんローリスク群といえることがわかった[25]。

血清PG値と血清*Hp*抗体価の組合せによって胃がん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る[26][27]。

○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がん検診の有効性に関する評価報告書[28]において，PG法は，胃がん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法の胃がん死亡率減少効果を証明すべく研究を進めている。

PG法による胃がん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がん死亡の標準化死亡比（SMR）を算出した。胃がんの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，全国の胃がん死亡状況と比較して統計学的に有意に胃がん死亡率

表2：血清抗*H.pylori* IgG抗体価・CagA蛋白抗体価・ペプシノゲン値3者組合わせた胃がんオッズ比の検討

―対象・方法―

①胃がん(診断時)血清・対照(登録住民)血清(ハワイ大;Nomúra AMY)
（ハワイ州・オワフ島在住、期間;1993～1999年手術;主要8病院）
②血清ペプシノゲンⅠ・Ⅱ値測定(東邦大;三木一正)
③血清抗*H.pylori* IgG抗体価測定(ニューヨーク大;Blaser MJ)
④血清抗*H.pylori* CagA蛋白抗体価測定(ニューヨーク大;Blaser MJ)
⑤病理組織診断・分類;Lauren分類(ハワイ大;Stemmermann GN)
⑥統計学的解析;Uncond.Log回帰分析でオッズ比(ハワイ大;Wilkens LR)

(Nomura AMY, Miki K. et al : J Infect Dis, 2005, 191:2075-81)

表3：血清抗*H.pylori* IgG抗体価・CagA蛋白抗体価・ペプシノゲン値3者組合わせた胃がんオッズ比の検討

―症例―

①胃がん;	299(例)	男/女:183/116(人)	平均年齢:70.7±11.8(歳)
②対　照;	366	228/108	70.6±12.7
③胃がん発生部位;	噴門部 35(12%)		体・幽門部 264(88%)
④胃がん組織型;	分化型 212(71%)		未分化型 65(22%)
	混合型 22(7%)		

(Nomura AMY, Miki K. et al : J Infect Dis, 2005, 191:2075-81)

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法による胃がん検診の胃がん死亡率減少効果を示唆する結果であった[29]。

○平成16年度厚生労働省三木班研究成果

1）胃がん患者と性・年齢・人種をマッチさせた同一地域住民対照で①血清PGⅠ，Ⅱ値②血清抗*Hp*IgG抗体価（*Hp*Ab）③血清抗*Hp* CagA蛋白抗体価（CagA）を測定し，胃がん罹患オッズ比を検討したところ，血清*Hp*AbとCagA陽性で，かつPGⅠ低値の組み合わせは，*Hp*AbとCagAの両者が陰性で，かつPGⅠが正常の場合よりも41倍未分化型胃がんのリスクを高めていた[30]（表2～4）。

2）健常男性4,655人のコホートを10年間追跡した結果，胃がん発生が全て*Hp*感染陽性者から生じており，慢性胃炎進展に伴う胃がん発生のリスクの上昇があり，特に化生性胃炎で年率1.25%であった[31)32)]（図2）。

3）人間ドックで直接胃X線検査とPG法を同時に受診した9,993人を地域がん登録により1年間追跡した。直接胃X線検査の胃がん診断の感度は55.6%，特異度は93.8%，陽性反応適中度は1.6%，要精検率は6.3%であった。同様に，基準値（カットオフ値：PGⅠ70ng／ml以下かつPGⅠ／Ⅱ3.0以下）を要精検の判定基準とした場合のPG法の胃がん診断の感度は61.1%，特異度は85.3%，

表4：血清抗*H.pylori* IgG抗体価・CagA蛋白抗体価・ペプシノゲン値3者組合わせた胃がんオッズ比の検討

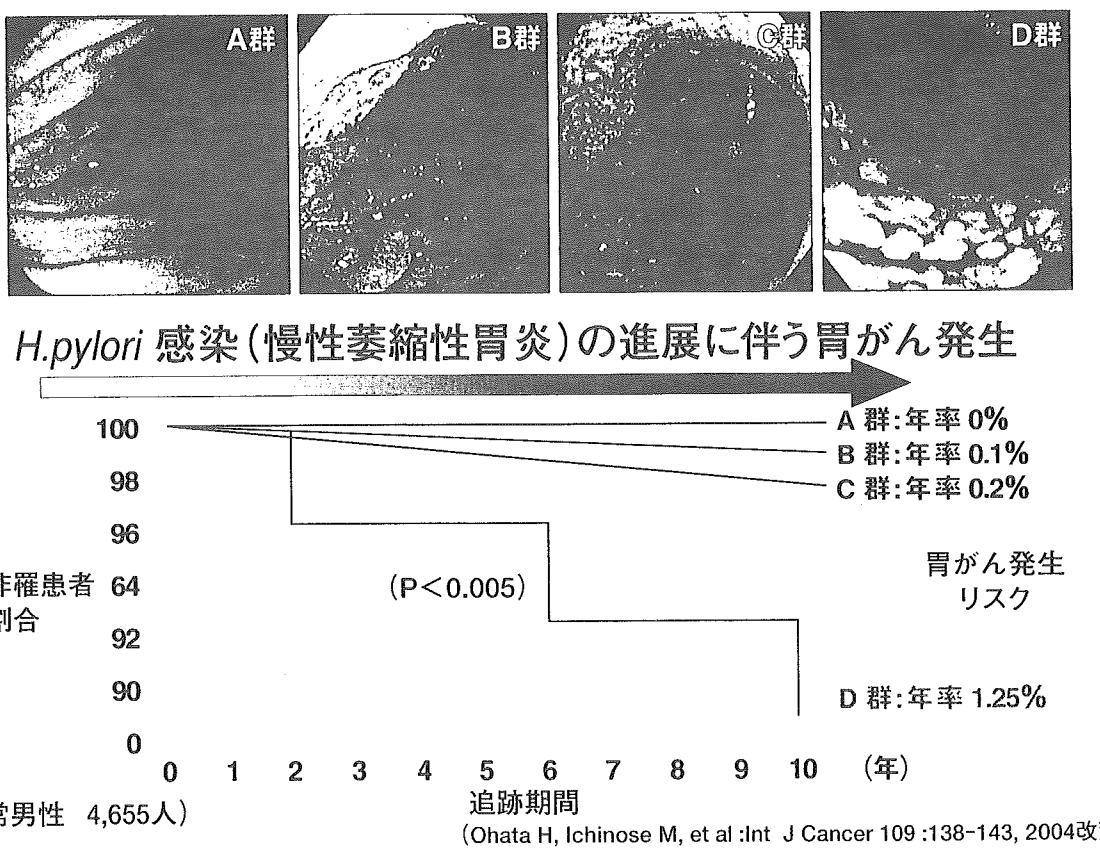
—*H.pylori* IgG抗体価・CagA蛋白抗体価・ペプシノゲン(PG)値の3者—

	全胃がん	分化型	未分化型
H.p.(−) ・ CagA(−)・PGI 正常	1	1	1
H.p.(−) ・ CagA(−)・PGI 低値	5.40※	5.06※	8.92
H.p.(+) か CagA(+)・PGI 正常	4.86※	3.64※	14.84※
H.p.(+) か CagA(+)・PGI 低値	9.21※	6.91※	40.74※
H.p.(−) ・ CagA(−)・PGI/Ⅱ 正常	1	1	1
H.p.(−) ・ CagA(−)・PGI/Ⅱ 低値	4.22※	3.54※	8.25
H.p.(+)か CagA(+)・PGI/Ⅱ 正常	3.77※	2.57※	15.05※
H.p.(+)か CagA(+)・PGI/Ⅱ 低値	6.88※	5.78※	12.58※

PGI 正常：≧30ng/ml，PGI/Ⅱ正常：≧2.0，※：$p<0.01$

(Nomura AMY, Miki K. et al : J Infect Dis, 2005, 191:2075-81)

図2：*H.pylori*感染(慢性萎縮性胃炎)の進展に伴う胃がん発生



(Ohata H, Ichinose M, et al :Int J Cancer 109 :138-143, 2004改変)

表5：直接胃X線法胃がんスクリーニングの妥当性

—精度—

	X線法(+)(人)	X線法(−)(人)	合　計(人)
胃がん(+)	10	8	18
胃がん(−)	615	9,360	9,975
合　計(人)	625	9,368	9,993

感度　　：　55.6%（10/18）
特異度　　：　93.8%（9,360/9,975）
陽性反応適中度：　1.6%（10/625）
（要精検率:6.3%）（胃がん有病率: 0.18%）

（厚生労働科学研究費補助金　三木班，2005）

表6：ペプシノゲン(PG)法胃がんスクリーニングの妥当性

—基準値の精度—

	PG法(+)(人)	PG法(−)(人)	合　計(人)
胃がん(+)	11	7	18
胃がん(−)	1,467	8,508	9,975
合　計(人)	1,478	8,515	9,993

感度　　：　61.1%（11/18）
特異度　　：　85.3%（8,508/9,975）
陽性反応適中度：　0.7%（11/1,478）
（要精検率:14.8%）（胃がん有病率: 0.18%）

（厚生労働科学研究費補助金　三木班，2005）

陽性反応適中度は0.7%，要精検率は14.8%であった[33]（表5，6）。

4）症例対照研究の手法によりPG法実施自治体におけるPG法受診の胃がん死亡減少効果を評価した。胃がん死亡症例41名のそれぞれに対して，同性で年齢±3歳の同じ地域在住者3名を対照とした。過去1年未満のPG法受診歴は，症例41名中0名で，対照では123名中23名（18.7%）の受診率であった（p＝0.0012）。過去2年未満のPG法受診歴は，症例41名中2名（4.9%），対照123名中37名（30.1%）で，過去2年未満の受診オッズ比（95%信頼区間）は0.119（0.027-0.520）と有意に胃がん死亡の減少効果を認めた[34]（表7，8）。

○倫理面への配慮

1）個人情報を取り扱う研究であるので，それぞれの研究課題について，主任研究者の所属する東邦大学医学部の倫理審査委員会や分担研究者の所属施設における倫理審査委員会において審査を受けた。

2）死亡情報は，総務省の許可[35]を得て使用し，住民情報は当該自治体等の協力を得て使用した。

3）平成16年12月28日官報に掲載された文部科

表7：ペプシノゲン(PG)法胃がん検診の有効性評価

―症例・対照―

胃がん死亡:49例(対象地域人口動態統計)

把　握　例:46例(男/女＝28/18)(把握率93.9%)

(死亡小票，腫瘍登録資料，自治体担当課の保管する個人情報を含まない資料等)

[診断日がPG法施行前の5例(男/女=3/2)を除く]

症例	胃がん死亡:41例 [男/女=25/16，平均年齢70.3歳(45-92歳)]
対照	症例1例に対して3人 性は同一，年齢は±3歳で選定

(厚生労働科学研究費補助金　三木班，2005)

表8：ペプシノゲン(PG)法胃がん検診の有効性評価

―受診状況別オッズ比―

	1年未満のPG法			
	受診あり		受診なし	
胃がん死亡症例: 41(人)	0(人)	0(%)	41(人)	100(%)
生存対照者:123	23	18.7	100	81.3

	2年未満のPG法			
	受診あり		受診なし	
胃がん死亡症例: 41(人)	2(人)	4.9(%)	39(人)	95.1(%)
生存対照者:123	37	30.1	86	69.9

2年未満受診のオッズ比(95%信頼区間)
＝ 0.119(0.027－0.520)

χ^2 p値（Yates補正）＝0.0064，Fisherの直接法 p値＝0.0012

(厚生労働科学研究費補助金　三木班，2005)

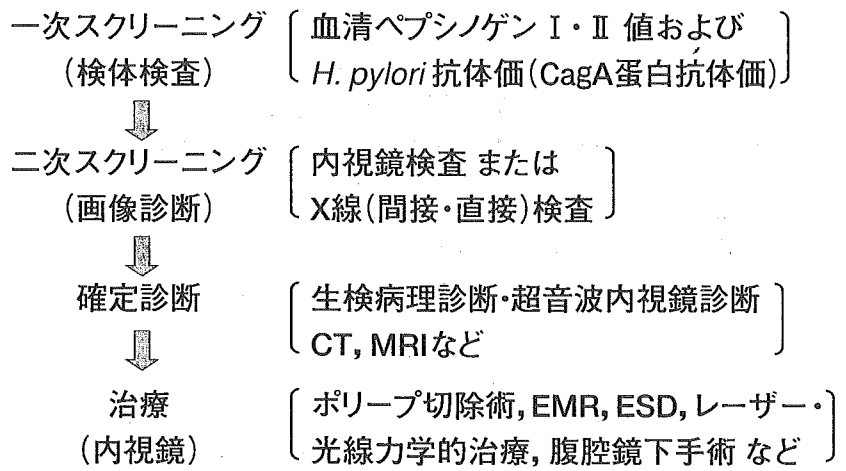
学省と厚生労働省の合同の改訂版疫学研究ガイドラインにしたがって研究を行った。加えて，主任研究者が管理するPG法による胃がん検診についてのホームページ等で研究の概要を掲載し市民へ周知を図って行うと同時に実際の解析に際しては個人識別情報を添付しないで用いた。

4）自治体職員が自治体内部で研究を行う場合は，その個人情報保護条令に従い，外部へは個人情報を提供せず，班員は個人情報の付与されない資料を用いてサポートした。

○平成17年度研究報告およびDDW－Japan2005神戸PD－12「胃がん高危険群に対する効率的な検診法をめぐって」特別発言から

渡部らは，PG法と*Hp*抗体による検診受診者9,293人を平均4.7年間追跡し，この間に平均5.1回

図3：胃がん検(健)診の近未来



の胃内視鏡検査を施行した。A群（PG正常，*Hp*陰性）を基準とした胃がん罹患のハザード比は，B群（PG正常，*Hp*陽性）1.1，C群（PG陽性，*Hp*陽性）6.0，D群（PG陽性，*Hp*陰性）8.2であり，PG法*Hp*抗体による検診受診者の集約の可能性を示した[27]。また，PG法による層別が，その後どの程度変動するかを内視鏡所見とあわせて検討を行い，内視鏡による胃がん検診受診者のうち再度内視鏡検診を受診した106人を平均7.7年間追跡し，内視鏡検診当日に血清PG値を測定し，それぞれPG値を比較検討し，初回検査時PG陰性例ではPGⅠはほとんど変動を認めず，PG陽性例ではPGⅠは低下した。初回PG陰性例の陽転化等は年率2.2%であった。胃炎スコアでも，初回PG陽性例は有意な胃炎の進行を認め，PG法による高危険群設定は，長時間にわたり有用であることを示した[36]。

井上ら[37]は背景胃粘膜からみた胃がん高危険群および低危険群の設定と胃がん検診の将来像を検討し，*Hp*抗体価測定，PG法，内視鏡検査を同日に行った人間ドック受診者5,473人を対象にした検討で，*Hp*抗体（－），PG（－）の群（A群）から発見された胃がんは1人も無く，*Hp*抗体価とPG値の組み合わせで胃がん高危険群だけでなく低危険群（A群）を設定することが可能であった。また，高危険群に対しては精度の高い内視鏡検査による1～2年毎の管理精検を，低危険群（A群）はその後の胃がん検診の対象から除外することで，効率的な胃がん検診になることを示した。

加藤ら[38]は住民検診における尿中*Hp*感染検査とPG法による胃がん高危険群設定の問題点を検討し，*Hp*感染検査とPG法を併用することで胃がん拾い上げ効果を相乗的に向上させることができるが，高齢者では尿中*Hp*抗体が偽陰性となる可能性が高く，高感度の*Hp*検査法の導入やPGⅠ値に重点をおいた判定法などの工夫が必要であると示した。

○まとめ―胃がん検(健)診の近未来と胃がん検診精度管理委員会答申意見から―

会長講演のまとめとして著者の考えている胃がん検（健）診の近未来像（図3）を提示した。胃がん検診の一次スクリーニングは検体検査になり，二次スクリーニングが画像診断となる。この画像診断には内視鏡検査だけでなくX線（間接・直接）検査もあり，受診者のニーズおよび二次精

検者のマンパワーに合わせて使い分けるという方策である。

しかし，現在，直ちに胃がん検診現場で実行しうる方策としての胃がん検診方式としては，DDW2005神戸の学会期間中（2005．9．22）に開催された，第2回学会胃がん検診精度管理委員会（委員長 今村清子理事）に著者が答申した意見書（表9，10）の通りである。なお主文（表9）は厚労省研究班（三木班）2000年度報告書として既に報告したもの[23)39)40)]である。今年度から新たに学会に設置された胃がん検診方式検討委員会で速やかに採択され，本学会推奨の方式（基準）となることを切望する。

○おわりに

第43回日本消化器集団検診学会大会会長をご下命下さり，また，本会長講演のご司会の労をお取り戴きました荒川泰行理事長に深謝申し上げます。

表9：胃がん検診精度管理委員会　答申意見

(主文) 胃がん検診方式は、ペプシノゲン(PG)法とX線(P)法併用法の一次検診とすることが望ましい。二次検診は内視鏡検査とする。

(付) 1. PG(＋)のカットオフ値は基準値(PGI 70ng/ml)以下かつI/II比3.0以下)とする。
2. PG(－)(受診者の約70%)だけにXP(直接・間接いずれでも可)を検診第1日目に施行する。(二段階同日判定法)
3. XP撮影法は新・胃X線撮影法(直接・間接)ガイドラインに準拠する。

(2005年9月22日)

表10：胃がん検診精度管理委員会　答申意見

(副文) 1. ヘリコバクターピロリ(Hp)法を一次検診に用いる場合はPG(－)，Hp(－)のA群(約30%)を二次検診から除くために使用する相応の根拠がある。
(将来、PG法・Hp法併用法一次検診が推奨される可能性はあるが、現時点では、Hp測定方法(UBTで統一するなど)や陽性者の二次検診方法など検証を要する問題点が多く今後の継続検討課題である。
2. サイトカイン遺伝子多型(IL-10やTNF-α等)，CagA蛋白等の遺伝子マーカーの応用は現在，研究課題である。今後の研究伸展を注視する。
3. 内視鏡単独検診は胃内視鏡検診標準化委員会の検討結果を参考にして推奨検診方式を呈示する。

(2005年9月22日)

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