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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)
[40] 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.

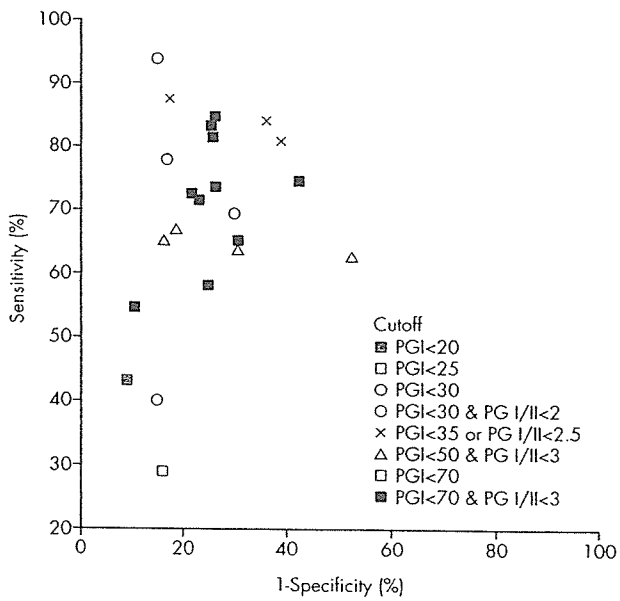

Figure 1 Sensitivity (%) and false positive rates (%) pairs according to cutoff showing a high variability of results according to cutoff. Homogeneity was only obtained considering intrinsic cutoff effect, allowing further pooling, and improving of AUC [82.0% (95%CI=77.2–86.8%) and 91.1% (89.1–93.1) 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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Seroconversion and Seroreversion of *Helicobacter pylori* Antibodies Over a 9-Year Period and Related Factors in Japanese Adults

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ABSTRACT

Background. There are still insufficient data on the frequency of seroconversion and seroreversion of *Helicobacter pylori* antibodies. The frequency of serochange and related factors were investigated in this study over 9 years.

Subjects and methods. Using sera from 3104 workers who underwent health checks in 1989 and again in 1998, *H. pylori* antibodies were measured. Those with intermediate serology were excluded from the study. Information on past history was collected using a questionnaire.

Results. Of the 912 seronegative and 1286 seropositive subjects in 1989, seroconversion was observed in 57 and seroreversion in 91 subjects. Seroconversion and seroreversion rates over the 9-year period were 6.3% and 7.1%, respectively, giving rates per 1000 person-years (with 95% confidence interval) of 7.0 (5.2–8.7) and 7.9 (6.3–9.4), respectively. Subjects that reported abdominal symptoms or gastric fiberscope use showed significantly higher seroconversion rates than controls (8.7 vs. 4.5 and 9.2 vs. 1.6, respectively), which remained significant after adjustment for age and gender. Those with a history of duodenal ulcers, a smoking habit or a drinking habit showed significantly lower seroreversion rates than controls (3.5 vs. 8.9, 5.4 vs. 9.2 and 5.9 vs. 13.3, respectively). After adjustment, the association between seroreversion and smoking habit disappeared, while the associations with history of duodenal ulcers and drinking habit remained.

Conclusions. Those with a history of nonspecific abdominal symptoms and those with a history of gastric fiberscope use showed higher seroconversion rates. Alcohol consumption and duodenal ulcers may inhibit the autoeradication of *H. pylori*, possibly through increased acid secretion.

Keywords. seroconversion, seroreversion, drinking habit, history of duodenal ulcer.

It is thought that infection with *Helicobacter pylori* usually continues throughout life [1]. Recent studies have shown that both seroconversion (i.e. a negative to positive change) and seroreversion (i.e. a positive to negative change) can occur in childhood and in adulthood [2,3]. However, to date few studies have investigated the factors associated with seroconversion or seroreversion.

In Japan, the prevalence of *H. pylori* is known to increase with age [4,5]. There are at least two explanations for this positive relationship. First, new *H. pylori* infections increase its prevalence with increasing age as *H. pylori* infections are thought to continue for a lifetime [1]. Secondly, sanitary conditions during childhood are strongly related to the prevalence of infection, and the improvement of sanitary conditions in Japan over the last 50 years has affected the prevalence of *H. pylori* [7,8]. In discussions of this issue, it is essential that seroconversion and seroreversion frequencies are known, for which there are still insufficient data in Japan.

This study was conducted to evaluate the seroconversion and seroreversion rates in Japanese adults and to investigate the factors that may be related to instances of serochange.

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Methods

The subjects were workers belonging to small- or middle-scale companies who underwent phlebotomy as part of a health check in 1989 and again in 1998. About 9500 workers in 1989 and 8700 workers in 1998 underwent the health checks, of whom 3014 workers underwent health checks in both 1989 and 1998. As *H. pylori* eradication therapy was not paid for by health insurance in Japan before 1999, the subjects did not undergo *H. pylori* eradication during the 9-year period. *H. pylori*-specific immunoglobulin G (IgG) antibodies were measured in residual sera from the health checks in 1989 and 1998 using IgG-GAP™ (Biomerica Co., Newport Beach, CA) according to the manufacturer's instructions. Results were determined as positive, negative or intermediate according to the recommended cut-off values of the test. Sera collected in 1989 had been stored for 8 years at less than −30°C, and sera from 1998 for 1 year at less than −80°C in frozen storage. Seroconversion and seroreversion rates were calculated after excluding subjects with intermediate results in either 1989 or 1998.

Information on the smoking and drinking habits of the subjects was collected in 1989 and in 1998 by questionnaire. The questionnaire in 1998 also asked about abdominal symptoms (epigastric pain, heartburn, fullness of stomach, appetite loss, constipation or other abdominal symptoms) and past history of gastric disease (gastric cancer, gastric ulcer, duodenal ulcer, chronic gastritis or gastric polyps). Relationships between these factors and seroconversion or seroreversion were evaluated. For analysis, subjects were classified into two groups according to smoking habit; that is, those who had continued to smoke and those who did not smoke during the 9-year period. Subjects were also classified into three groups by alcohol consumption; namely, those who continued to drink, those who drank occasionally, and those who did not drink alcohol at all during the 9-year period. For analysis of smoking or drinking habits, those who had changed smoking or drinking habits during the 9-year period were excluded.

Crude relative risks and relative risks adjusted for age and gender were calculated using the χ^2 test and proportional hazard models. Mutually adjusted hazard ratios were then calculated as follows: age, gender and factors giving significant results for seroconversion or seroreversion were put into a proportional hazard model, and a final model was obtained by backward elimination so that all p-values for factors except age and gender were less than 1.0.

Results

Of the 3014 subjects examined, 816 subjects gave intermediate results in either 1989 or 1998 and were excluded from the study. Analyses were carried out using 2198 subjects, whose age and gender distribution is shown in Table 1.

Of the 912 seronegative subjects in 1989, 855 were seronegative and 57 seropositive in 1998. The seroconversion rate during the 9-year period was 6.3%, giving a seroconversion rate per 1000 person-years [with 95% confidence interval (CI)] of 7.0 (5.2–8.7). Of the 1286 seropositive subjects in 1989, 1195 were seropositive and 91 seronegative in 1998. The seroreversion rate during the 9-year span was 7.1%, giving a seroreversion rate of 7.9 (6.3–9.4) per 1000 person-years.

When calculated according to gender, the seroconversion rate was not found to be significantly higher in male subjects, while the seroreversion rate was significantly higher in female subjects. While age was not related to seroconversion rate, seroreversion rates tended to increase with increasing age, with a p-value of 0.08 (Table 1).

Subjects reporting abdominal symptoms or gastric fiberscope use showed a significantly higher seroconversion rate (8.7 vs. 4.5 and 9.2 vs. 1.6, respectively) than controls (Table 2). This result remained statistically significant after adjustment for age and gender (Table 3). Neither dyspepsia nor history of gastric fiberscope use was associated with seroreversion.

Table 1 Seroconversion and seroreversion rates for *H. pylori* antibody during a 9-year period with reference to age and gender

Class	Seroconversion rate[a] (negative in 1989)	Seroreversion rate[a] (positive in 1989)
Total	7.0 (912)	7.9 (1286)
Gender		
Male	7.5 (724)	6.6 (1058)
Female	4.7 (188)	13.6 (228)
p-value	p = .272	p = .001
Age (years)		
39–44	6.5 (461: 395 + 66)[b]	6.5 (465: 396 + 69)
45–54	6.9 (384: 277 + 107)	8.6 (636: 516 + 120)
55–64	10.7 (52: 40 + 12)	7.8 (156: 125 + 31)
65+	7.4 (15: 12 + 3)	15.3 (29: 21 + 8)
p-value for trend	p = .385	p = .075

[a]Rate per 1000 person-years.
[b](total: male + female).

Table 2 Factors related to the seroconversion and seroreversion of *H. pylori* antibody during a 9-year period

	Seroconversion	Rate[a] (negative in 1989)	RR1[b] (95%CI)[c]	RR2[d] (95%CI)[c]
Dyspepsia	No	4.5 (373)	1.0	1.0
	Yes	8.7 (539)	1.59 (1.03–2.56)	2.01 (1.12–3.63)
History of duodenal ulcer	No	6.8 (818)	1.0	1.0
	Yes	8.3 (94)	1.02 (0.92–1.13)	1.19 (0.54–2.64)
History of gastric fiberscope	No	1.6 (273)	1.0	1.0
	Yes	9.2 (628)	4.45 (1.81–13.93)	5.35 (1.92–14.90)
Smoking	No	4.8 (390)	1.0	1.0
	Yes	7.5 (386)	1.29 (0.88–1.92)	1.43 (0.74–2.77)
Drinking	No	5.9 (132)	1.0 (p = .465[e])	1.0 (p = .815[e])
	Occasionally	5.5 (142)	0.93 (0.37–2.65)	0.93 (0.33–2.65)
	Yes	7.4 (572)	1.23 (0.56–2.81)	1.07 (0.46–2.49)
	Seroreversion	**Rate[a] (positive in 1989)**	**RR1[b] (95%CI)[c]**	**RR2[d] (95%CI)[c]**
Dyspepsia	No	7.2 (761)	1.0	1.0
	Yes	8.9 (524)	0.88 (0.69–1.11)	0.78 (0.52–1.18)
History of duodenal ulcer	No	8.9 (1032)	1.0	1.0
	Yes	3.5 (254)	0.87 (0.81–0.94)	0.43 (0.21–0.89)
History of gastric	No	8.3 (202)	1.0	1.0
fiberscope	Yes	7.7 (1067)	0.94 (0.58–1.58)	1.08 (0.61–1.92)
Smoking	No	9.2 (640)	1.0	1.0
	Yes	5.4 (454)	0.82 (0.70–0.96)	0.68 (0.40–1.16)
Drinking	No	13.3 (200)	1.0 (p = .001[e])	1.0 (p = .022[e])
	Occasionally	9.0 (223)	0.67 (0.37–1.24)	0.70 (0.38–1.30)
	Yes	5.9 (758)	0.44 (0.27–0.73)	0.52 (0.29–0.91)

[a]Rate per 1000 person-years.
[b]Crude relative risk.
[c]95% confidence interval of relative risk.
[d]Relative risk adjusted for age and gender using proportional hazard model.
[e]P-value for trend.

Table 3 Final model using proportional hazard model with backward elimination to assess factors associated with seroconversion of *H. pylori* antibody during a 9-year period

Factors	Hazard ratios (95%CI[a])	p-value
Age (+1 year)	1.02 (0.98–1.06)	.435
Gender		
Male	1.0	.399
Female	0.72 (0.34–1.54)	
Dyspepsia		
No	1.0	.047
Yes	1.82 (1.01–3.30)	
History of gastric fiberscope		
No	1.0	.002
Yes	5.08 (1.82–14.16)	

For more details, see text.
n = 901.
[a]95% confidence interval.

Table 4 Final model using proportional hazard model with backward elimination to assess factors associated with seroreversion of *H. pylori* antibody during a 9-year period

Factors	Hazard ratios (95%CI[a])	p-value
Age (+1 year)	1.02 (0.99–1.05)	.229
Gender		
Male	1.0	.442
Female	1.24 (0.72–2.14)	
History of duodenal ulcer		
No	1.0	.020
Yes	0.40 (0.18–0.87)	
Drinking (no/occasionally/yes)[b]	0.73 (0.55–0.96)	.026

For more details, see text.
n = 1181.
[a]95% confidence interval.
[b]No, occasionally and yes were defined as 1, 2 and 3, respectively.

Seroconversion was not associated with history of duodenal ulcer, smoking habit or alcohol consumption (Table 2). However, subjects with a history of duodenal ulcer, smoking or alcohol intake showed significantly lower seroreversion rates (3.5 vs. 8.9, 5.4 vs. 9.2 and 5.9 vs. 13.3, respectively) compared to controls. After adjustment for age and gender (Table 2), the significant association with smoking habit disappeared while the associations with history of duodenal ulcer and drinking habit remained. They remained significantly associated with seroreversion even after mutual adjustment (Table 4). All other factors examined showed no significant associations with seroconversion or seroreversion.

Discussion

To avoid overestimation of serochange, subjects with intermediate *H. pylori* antibody titer levels

in either 1989 or 1998 were excluded from the study. If such subjects had been included, spontaneous intrapersonal changes in antibody titers would have been counted as serochange. Therefore, seroconversion and seroreversion rates in this study can be regarded as reliable estimations of real rates of change in *H. pylori* infection status.

Seroconversion

While the overall seroconversion rate was 7.0 per 1000 person-years, the rate was higher in subjects with dyspepsia or a history of gastric fiberscope use. Age and gender were not associated with seroconversion. A Japanese study using the same commercial assay kit and cut-off values for *H. pylori* antibody titers as the present study reported a seroconversion rate of 10.0 per 1000 person-years between 1986 and 1994 [3], similar to our findings in the present study. Similar results have also been obtained in Denmark [9] and in Brazil [10], with seroconversion rates of 9.0 and 11.0 per 1000 person-years, respectively. However, reported seroconversion rates for New Zealand [11], the Netherlands [12] and Italy [13] were lower than in the present study, with values of 1.0, 3.0 and 3.0 per 1000 person-years, respectively, and North American missionaries showed a higher seroconversion rate of 19.0 per 1000 person-years [14]. As developing countries show higher seroconversion rates than developed countries, seroconversion rates in the adult population may depend on the seroprevalence within the population as well as general sanitary conditions. The present study, and another Japanese study, showed similar seroconversion rates to those in developing countries. This may be attributable to the fact that, although sanitary conditions in Japan are similar to those in developed countries, there is a higher prevalence of *H. pylori* in Japan.

The significant association between nonspecific abdominal symptoms and seroconversion was observed even after mutual adjustment. A possible explanation for the significant association is that the abdominal symptoms accompanied the new *H. pylori* infection that caused the seroconversion in some cases. However, it may not be appropriate to connect the abdominal symptoms with seroconversion, because the precise time when the subjects first experienced abdominal symptoms was not obtained in this study.

Although some studies have shown negative results [15], many studies have found *H. pylori* infections to be associated with the use of gastric fiberscopes [16,17]. Guidelines and recommendations for cleaning and disinfecting gastric fiberscopes have been published [18], and were released in Japan in 1995 [19,20]. The observation period of this study (1989–98) encompassed several years prior to the publication of the guidelines, and even after the guidelines were published there has been some debate over whether the gastric fiberscope cleaning and disinfection methods are completely effective [21–23]. Given these considerations, *H. pylori* infection via the gastric fiberscope during the observation period of our study can explain the positive association between seroconversion and gastric fiberscope use. Nevertheless, it is not possible to draw firm conclusions, because the time at which the subjects underwent examinations with a gastric fiberscope was not clear in this study.

Seroreversion

The seroreversion rate in our study was 7.9 per 1000 person-years. This is similar to the rate of 7.0 observed in Denmark [9], higher than the rate of 2.0 reported for Brazil [10], and lower than the rate of 18.0 per 1000 person-years found in another Japanese study [3]. The small number of reported studies makes it difficult to determine the relationship between geographical location and seroconversion rate. In the present study, the seroreversion rate was associated with age, gender, drinking habit and history of duodenal ulcer. It is possible that the seroreversion rate is more dependent on these individual factors than on country or ethnic group, and that it is the distribution of these factors among a population that affects the overall seroreversion rate.

Age showed a weak association with seroreversion. Atrophic gastric mucosa is thought not to be ideal for *H. pylori* [24], and auto-eradication can occur. Atrophy of the gastric mucosa is more frequent and more severe in older subjects [25,26], and may explain the weak association between age and seroreversion. However, this association disappeared after adjustment for gender, drinking habit and history of duodenal ulcer, and the relationship between age and seroconversion, based on the results of our study, remains unclear.

While gender showed an association with seroreversion, this association also disappeared after adjustment for age, drinking habit and

history of duodenal ulcer. Male/female ratios differed depending on age and, as there was a weak positive association between age and seroreversion, it is possible that age was a confounding factor in the relationship between gender and seroreversion. Drinking habit was strongly associated with gender, and drinking habit also showed an association with seroreversion, so that drinking habit may be another confounding factor. Therefore, the apparent association between gender and seroreversion may be an artifact attributable to the presence of confounding factors.

Smoking habit showed an association with seroreversion, which disappeared after age and gender adjustment. However, those with drinking habits or a history of duodenal ulcers showed less frequent seroreversion and both associations remained in the final model. Although few studies have analyzed the relationship between alcohol consumption and seroreversion, a prospective study has shown that seroreversion is rare amongst those with duodenal ulcers [27], which is consistent with the results of our study. A common feature of drinking habit [28,29] and history of duodenal ulcers [30] is that both factors are characterized by increased gastric acid secretion.

Fermented alcoholic beverages containing low or moderate concentrations of alcohol stimulate gastric acid secretion, whereas high alcohol concentrations do not stimulate acid secretion [31]. As consumption of distilled alcohol without dilution is rare in Japan, most subjects with a drinking habit in the present study are expected to have consumed low to moderate concentrations of alcohol, with consequent upregulation of acid secretion. Duodenal ulcer patients show a high prevalence of *H. pylori* infection [32]. The inflammation caused by *H. pylori* infection provokes hyperacidity, which is a cause of duodenal ulcers [33,34]. A recent study revealed that polymorphism of the interleukin-1 beta gene is related to duodenal ulcer risk [35]. As the polymorphism is a genetic factor, those with a history of duodenal ulcers tend be genetically predisposed to upregulated gastric juice secretion.

Increased acid secretion has the effect of diluting and washing off substances contained in food and drink, including substances with bactericidal or bacteriostatic effects. In addition, hyperacidity can inhibit the effect of antibiotics, which is why proton pump inhibitors or H2-blockers are prescribed with antibiotics for the eradication of *H. pylori* [36,37]. Although we do not have any information regarding the antibiotic use of the subjects during the 9-year period, antibiotics are often prescribed for the common cold in Japan. Thus, it is possible that antibiotic use may have exaggerated the inhibitory effect of increased acid secretion on seroreversion.

An inverse relationship between alcohol consumption and *H. pylori* prevalence has been reported in a number of studies [38], including our previous study [39]. The results of the present study suggest that the eradicating effect of alcohol on *H. pylori* infection does not appear to underlie the inverse association observed in cross-sectional studies. Eradication therapies against *H. pylori* in those with drinking habits tend to show higher success rates [40], which at first sight is not consistent with the results of our study. However, as eradication therapies also contain proton pump inhibitors [36] or H2-blockers [37], the presence of these compounds may alter the effect of alcohol intake. Thus, while alcohol consumption may prevent infection with *H. pylori*, it may also inhibit its spontaneous eradication.

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Original article

Trends in the incidence of gastric cancer in Japan and their associations with *Helicobacter pylori* infection and gastric mucosal atrophy

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Abstract

Background. **Although age-adjusted mortality from gastric cancer has been decreasing in Japan, the crude incidence of gastric cancer shows a slight increase.**

Methods. **We have observed trends in the incidence of gastric cancer by sex and 20-year age groups over the past two decades (1976–1996). Source data were obtained from the cancer statistics materials provided by the Research Group for Population-Based Cancer Registration in Japan. Simultaneously, we observed changes in the prevalence of *Helicobacter pylori* infection and in serological atrophy of the gastric mucosa, and compared the results with those involving changes in the incidence of gastric cancer.**

Results. **A slight decline was observed in all age groups over 40 years old, in both men and women, between 1986 and 1996. However, a marked decline in incidence was observed for those aged 20–39 years. The prevalence of *H. pylori* infection declined in both sexes between 1989 and 1998. The frequency of serological atrophy of the gastric mucosa significantly declined in all age groups between 1989 and 1996, with young age groups experiencing a more marked decrease.**

Conclusion. **The marked decline in gastric cancer incidence observed in the young population will also begin to occur in the elderly population in the future.**

Key words Gastric cancer incidence · *Helicobacter pylori* · Pepsinogen · Gastric mucosal atrophy

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Introduction

Despite a marked decline in the incidence of gastric cancer in many industrialized countries, gastric cancer is still the second most common cause of cancer-related deaths in Japan [1–4]. Based on regional cancer registrations, the incidence of gastric cancer in Japan in 1997 was 99318 (male, 66307 and female, 33011), accounting for 20.7% of the total cancer incidence in the same year [5]. The number of gastric cancer deaths in 1997 was 49739 (male, 32218 and female, 17521) based on vital statistics [6]. Age-adjusted mortality has been decreasing in both men and women, although crude mortality has not changed. Gastric cancer mortality is about half of the incidence, due to improved diagnostic and therapeutic techniques.

It is well known that *Helicobacter pylori* infection is one of the major risk factors for gastric cancer, and that low values of the pepsinogen (PG) I-to-II ratio can be a marker for atrophy of the gastric mucosa, as well as a marker for gastric cancer risk [7–10]. Therefore, the prevalence of *H. pylori* infection and the frequency of gastric mucosal atrophy may influence the incidence of gastric cancer.

In this study, we analyzed trends in the incidence of gastric cancer over the past two decades, by sex and 20-year age groups. At the same time, we observed changes in the prevalence of *H. pylori* infection and in serological atrophy of the gastric mucosa, and compared them with changes in the incidence of gastric cancer.

Methods

Cancer incidence figures in Japan are available from the Research Group for Population-Based Cancer Registration of the Ministry of Health, Labour, and Welfare, Japan, which issues annual cancer statistical data. We analyzed trends in the incidence of gastric cancer from 1976 to 1996. The figures from 1985 to 1989 were acquired from the published data [11] that this research group had reported, and the pre-1984 data were from the group's website. The gastric cancer incidence in four 20-year age groups (20–39, 40–59, 60–79, and 80 and over) from 1975 to 1996 was calculated using these data. Mortalities from gastric cancer in 1986 and 1996 were acquired from published data [6] from the Statistics and Information Department, Minister's Secretariat, Ministry of Health, Labour, and Welfare, Japan. To observe trends in gastric cancer incidence and its mortality, the 1996/1986 ratios of incidence and mortality were calculated by dividing the value in 1996 by the one in 1986. In order to compare findings with the results for frequency of serological atrophy of the gastric mucosa, the 1996/1989 ratios of the incidence were also calculated.

For our analysis of the frequency of serological atrophy of the gastric mucosa, subjects were recruited from a workplace in the Kanto-shin-etsu area of Japan; 4486 of the subjects had participated in a health checkup program in 1989, and 4506 had participated in 1996. Serum PG I and serum PG II values were measured using residual sera from the health checkup programs in those 2 years. Measurements were carried out by immunoradiometric assay, with Pepsinogen I/II Riabead kits (Dainabot, Tokyo, Japan). When the serum PG I level was 70 ng/ml or less and the PG I/II ratio was 3.0 or less, it was defined as "serological atrophy" of the gastric mucosa [12].

To determine the prevalence of *H. pylori*, the subjects were selected from workers who belonged to a group of companies in the Tokyo area who were aged 50–59. Six hundred and seventy-six (male, 532; female, 144) of them took part in a general health checkup program in 1989, and 1916 (male, 1580; female, 336) took part in 1998. The sera in 1989 had been frozen for 10 years at −30 °C, and those in 1998 had been frozen for 1 year at −30 °C before the measurements. Serum *H. pylori* antibodies were measured using both the 1989 and 1998 sera. The measurements were carried out by enzyme-linked immunosorbent assay (ELISA) with Pilika-Plate G Helicobacter II, produced by Biomerica (Newport Beach, CA, USA).

All statistical analyses were conducted using a commercial program for statistical analysis obtained from Halwin Gendai-Sugakusha (Kyoto, Japan). Our studies were approved by the Ethics Committee, Aichi Medical University School of Medicine.

Results

Figure 1 shows changes in gastric cancer incidence by sex in the 20-year age groups. A gradual decline in incidence was observed in all age groups, in both men and women, and the steepest decline was in the 20–39 age group. No clear change was observed before 1986, and a clear decline was observed only between 1986 and 1996, the trend of which was linear and statistically significant in each age group.

The 1996/1986 ratios of gastric cancer incidence for the age groups (Fig. 2) showed that the decline in younger age groups was more conspicuous than that in older age groups. The 1996/1989 ratios gave similar results, but the effect of age was not so clear in the age groups over 40 years.

On the other hand, the 1996/1986 ratios of gastric cancer mortality were in men, 0.516 for those aged 20–39; 0.667 for those aged 40–59; 0.759 for those aged 60–79; and 0.923 for those aged 80 or more. Similarly, in women, the ratios were 0.445, 0.689, 0.652, and 0.849, respectively. The 1996/1986 ratios of gastric cancer mortality showed a trend of decline that was more conspicuous in younger age groups than in older ones.

Figure 3 shows the frequency of serological atrophy of the gastric mucosa in 1989 and 1996. During the 7-year period, the frequency of serological atrophy of the gastric mucosa significantly declined in all age groups, with young age groups experiencing a more notable decrease.

Figure 4 shows the seroprevalence of *H. pylori* among those aged 50–59, in 1989 and 1998. The prevalence of *H. pylori* infection declined significantly in both sexes over the 9-year period of this study.

Discussion

Because the incidence of gastric cancer is low in people under 40 years of age, and because analysis by 20-year groups can maintain the stability of data, we examined the trends in mortality and incidence by 20-year age groups. A decrease in gastric cancer incidence was revealed, with those aged 20 to 40 showing the most rapid decrease, in both men and women. The decrease was observed only after 1986. Highly salted food intake, smoking, and drinking are enumerated as three major risk factors for gastric cancer, other than *Helicobacter pylori* infection and gastric mucosal atrophy. However, these three risk factors do not seem to explain the decrease sufficiently, for the following reasons. Firstly, although a change in the whole amount of salt intake does not necessarily correlate with a change in the dietary intake of highly salted foods, it is unlikely that the dietary intake of highly salted foods fell rapidly, because it

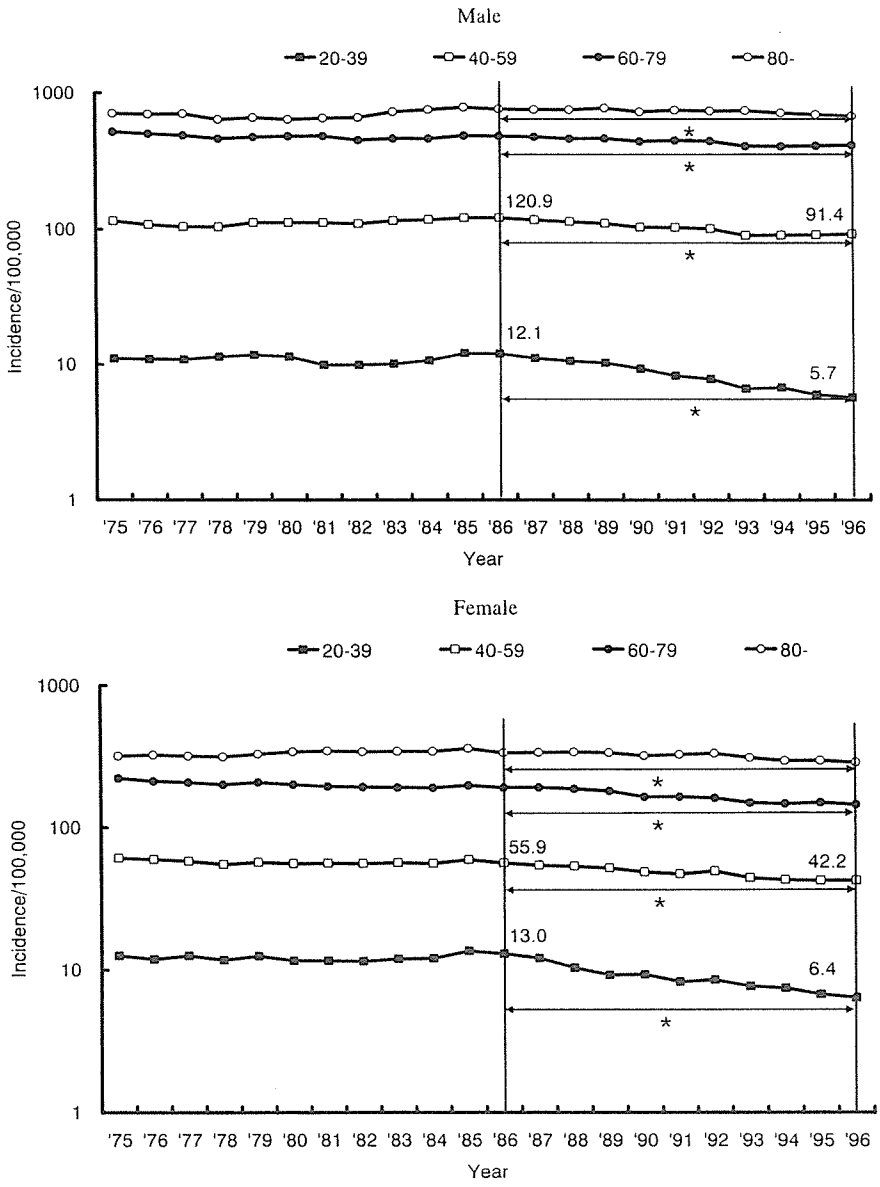

Fig. 1. Changes in gastric cancer incidence according to age are shown. A decline in incidence was observed in all 20-year age groups of both sexes between 1986 and 1996, and the decline in those aged 20–39 years was the steepest. *P*-value for trends, <0.001

has been shown that the amount of salt intake has almost leveled off, according to the National Nutrition Survey in Japan [13]. Secondly, the smoking rate has been decreasing in men and has leveled off in women, but is increasing in young women. The drinking trends have been similar to the smoking trends [14]. Therefore, these three factors do not seem to be major causes of the observed decline in gastric cancer incidence. Thus, among the possible factors contributing to the decrease, two in particular appear to be involved, i.e., changes in the prevalence of *H. pylori* infection, and the diminishing frequency of serological atrophy of the gastric mucosa.

Changes in the prevalence of H. pylori *infection*

Numerous epidemiological and experimental studies using animals have shown that *H. pylori* infection is a causal risk factor for gastric cancer [15,16]. *H. pylori* infection occurs mostly in childhood [17–23] and continues for almost the entire life of the patient. Its overall prevalence is strongly correlated with socioeconomic factors, such as living conditions [24–26], water supply, and sewerage [27,28], which may be especially important in developing countries. In many cross-sectional studies, an increase in the prevalence of *H. pylori* with age has been observed, for which there are two hypotheses: one is that new infections in the aging population increase the gradient of the prevalence; the other is that the gradient is influenced by a cohort effect,

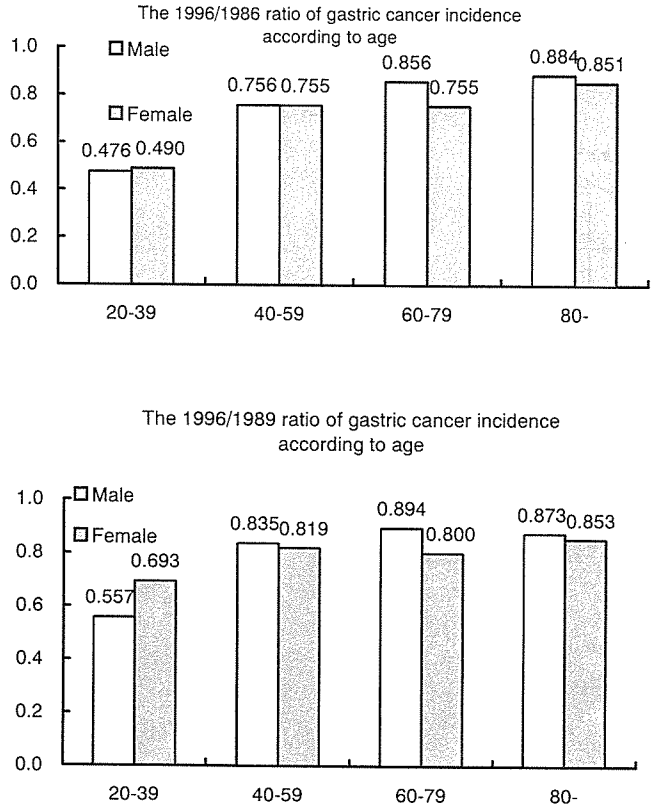

Fig. 2. The 1996/1986 ratios of gastric cancer incidence (over a 10-year period) for each age group showed that the decline was more conspicuous in young age groups than in old age groups. Similar results were observed in the 1996/1989 ratios (over a 7-year period), but the effect of age was not so clear among the age groups aged over 40 years

reflecting more widespread transmission contemporaneous with the childhood years of earlier birth cohorts [19,29,30].

In order to clarify which hypothesis is correct, we compared the prevalence of *H. pylori* between the subjects aged 50–59 years in 1989 and those aged 50–59 years in 1998 in a workers' group and found a decline in seroprevalence over the 9-year period. Although the subjects were only from the Tokyo region, another study with subjects from other areas throughout Japan (Nagano, Niigata, Gunma, Toyama, Shizuoka, Mie, and Miyagi prefectures) has reported the same results [31]. Although these results may not be sufficiently representative of conditions in Japan as a whole, no contradictory results have been found, as far as we can discover, suggesting that the cohort effect of improved hygiene exerts a greater influence on the overall rate of prevalence than new infections with aging [32–34].

Although hygiene conditions in Japan were poor just after World War II, they have gradually improved since about 1950, which seems to support the conclusion mentioned above. If the prevalence of *H. pylori* mainly depends on hygiene conditions in childhood, a decline in *H. pylori* prevalence owing to improved hygiene conditions must occur first in the younger population. These explanations seem to be consistent with the observed decrease in gastric cancer incidence in that young population.

Frequency of serological atrophy of the gastric mucosa

It has been established that people with atrophic gastritis have a high risk for gastric cancer [26,35]. Previous studies have shown that serum PG values were strongly associated with gastric cancer [36]. In people under 40 years of age, the PG II level, as well as the PG I/II ratio, showed a strong association with the risk for gastric cancer [37]. Among those over 40, a strong association was also observed between the gastric cancer risk and serological atrophy of the gastric mucosa [10]. In addition, the relation between atrophic gastritis and gastric cancer has been confirmed by endoscopic studies [38].

Serum PGs are markers for atrophic gastritis and gastric mucosal atrophy. A low serum PG I level and a low PG I/II ratio are related to atrophy of the gastric mucosa, as well as being related to inflammation of the gastric mucosa [39,40]. Therefore, we defined low values for serum PGs (serum PG I level of 70 ng/ml or less and PG I/II ratio of 3.0 or less) as serological atrophy. These low levels are also related to the risk for gastric cancer and are sometimes used in screening programs for gastric cancer [12]. If gastric mucosal atrophy is related to the risk for gastric cancer, a consistent change in the prevalence of gastric mucosal atrophy might be expected in conjunction with the observed decline in the gastric cancer incidence. We observed a change in the frequency of serological atrophy of the gastric mucosa over a 7-year period, and compared it with the change in gastric cancer incidence over the same period.

The frequency of serological atrophy of the gastric mucosa decreased over that 7-year period. The marked decline in frequency of the atrophy cannot be explained without considering the possibility of reversible change in serological atrophy. Indeed, 63% of the subjects experienced an increase or no change in the PG I/II ratio over the 7-year period [39,40], indicating that serological atrophy of the gastric mucosa is reversible.

The decline in young age groups was more conspicuous than that in older groups. Although the subjects did not necessarily represent the Japanese population as a whole, they were, in fact, from relatively wide spread areas: Niigata, Nagano, Gunma, Tochigi, Ibaraki, Saitama, and Tokyo.

So far, many studies have noted the prevalence of gastric mucosal atrophy, but few have examined the

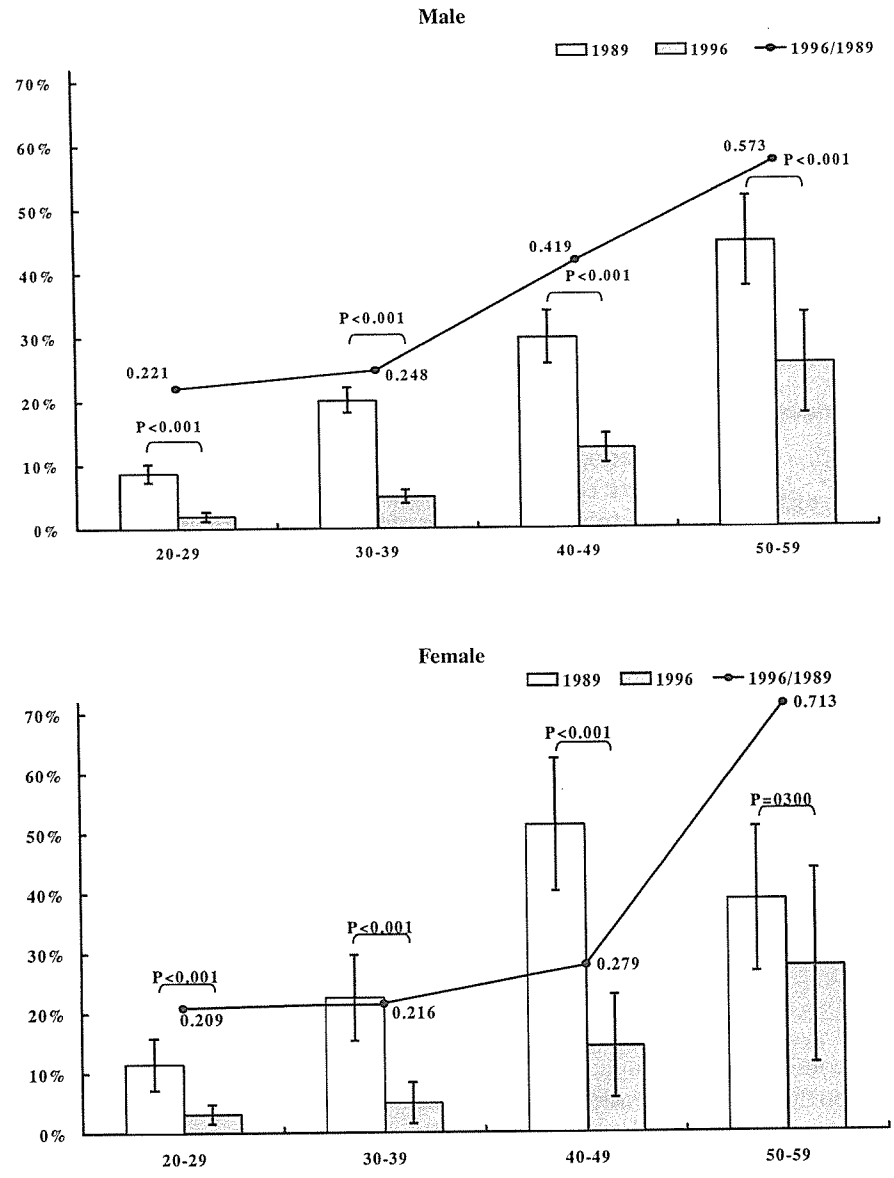

Fig. 3. Frequencies of serological atrophy of the gastric mucosa in 1989 and in 1996. During the 7-year period, the frequency of serological atrophy of the gastric mucosa significantly declined in all age groups, with younger age groups showing a particularly marked decrease

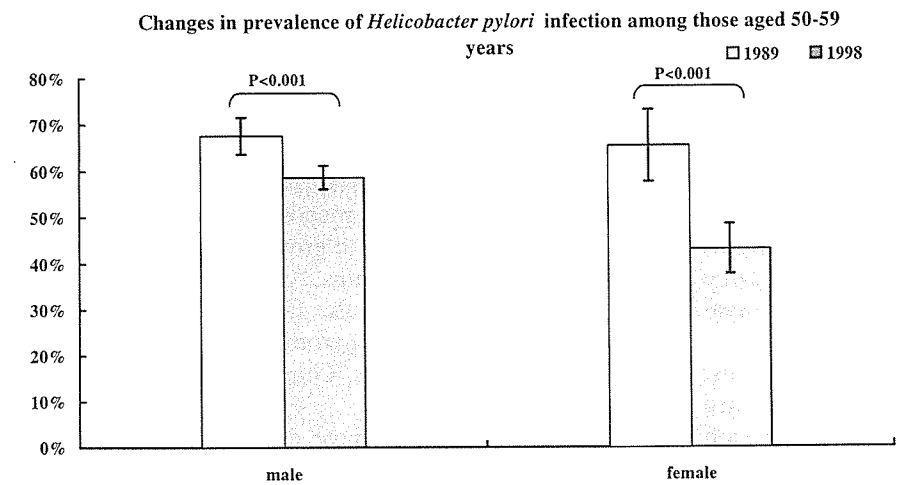

Fig. 4. The prevalence of *Helicobacter pylori* infection declined in both sexes between 1989 and 1998