Hiroshima J. Med. Sci.
Vol.46, No.2, 81~86, June, 1997
HIJM 46-10

The Usefulness of Gastric Mass Screening Using Serum Pepsinogen Levels Compared with Photofluorography

Masaharu YOSHIHARA[1,2], Koji SUMII[1], Ken HARUMA[1], Kuninushi KIYOHIRA[1], Nobuaki HATTORI[1], Shinji TANAKA[1], Goro KAJIYAMA[1] and Takuso SHIGENOBU[2]

1) First Department of Internal Medicine, Hiroshima University School of Medicine, Hiroshima 734, Japan
2) Health Service Center, Hiroshima University, Higashihiroshima 739, Japan

ABSTRACT

Chronic atrophic gastritis, which is thought to be a high risk for gastric cancer, can be diagnosed by serum pepsinogen levels. We compared the usefulness of the measurement of pepsinogen levels and indirect photofluorography as indicators of gastric cancer in a mass screening involving 5,620 Japanese subjects (mean age: 60.1 years old; male : female = 2,268 : 3,352) in 1991 and 1992. Subjects with a serum pepsinogen I level below 30 μg/liter or a pepsinogen I/II ratio below 2.0 were considered to be at high risk of gastric cancer. The incidence of gastric cancer and the ratio of early cancers detected by pepsinogen levels (0.12%, 4/7) were similar to those detected by photofluorography (0.11%, 4/6). Our results showed that mass screening using pepsinogen levels was as useful as indirect photofluorography for the detection of gastric cancer in Japan. In addition, our results showed that the sensitivity of gastric mass screening was increased when the measurement of serum pepsinogen levels was combined with photofluorography.

Key words: *Serum pepsinogen, Gastric mass screening, Gastric cancer, Photofluorography*

The mortality rate of gastric cancer has been decreasing in Japan, in part because of the introduction of mass screening programs[5,12]. The validity of indirect photofluorography, which is the conventional screening method used in Japan, has been recognized[1,5,12]. However, indirect photofluorography is associated with certain drawbacks that limits its use, such as exposure to radiation and the need for specially trained technicians and special equipment. Therefore, simpler and more effective screening strategies for gastric cancer are needed.

Atrophic gastritis, which is closely related to gastric cancer[2,7,14,15,17,20], can be simply detected by measurement of serum pepsinogen I and II levels[11,13]. Our previous study in a local population[18,21,22] showed the usefulness of the measurement of pepsinogen levels as indicators of gastric cancer in a mass screening. In the present study, we compared the usefulness of measurement of pepsinogen levels and indirect photofluorography in a mass screening program for gastric cancer in a local population in Japan.

SUBJECTS AND METHODS

Measurement of serum pepsinogen (PG method) and indirect photofluorography (X-ray method) were performed on 5,620 subjects (mean age: 60.1 years old; male : female = 2,268 : 3,352) who were residents of two counties in Hiroshima prefecture as part of their annual health check-ups in 1991 and 1992. The mean age (standard deviation) was 60.7 (12.2) years in the men and 59.7 (11.4) years in the women. The percentage of subjects over 60 years of age was 62.5% among the men and 56.7% among the women (Fig. 1).

Most subjects underwent both screening tests on the same day. When tests were not performed on the same day, they were performed within at least six months. Subjects were informed that serum pepsinogen levels were being measured to evaluate the gastric mucosa and identify individuals with a high risk for gastric diseases. Serum samples were kept frozen and the levels of serum pepsinogen I (PGI) and pepsinogen II (PGII) were measured within 3 days by a modified radioimmunoassay method[6] using Riabead Kits (DAINABOT Co, Ltd., Tokyo). A pepsinogen I level below 30 μg/liter or a pepsinogen I/II ratio below 2.0 was considered to indicate a high risk for gas-

Address for correspondence requests: Masaharu YOSHIHARA, First Department of Internal Medicine, Hiroshima University School of Medicine, 1-2-3 Kasumi, Minami-ku, Hiroshima 734, Japan

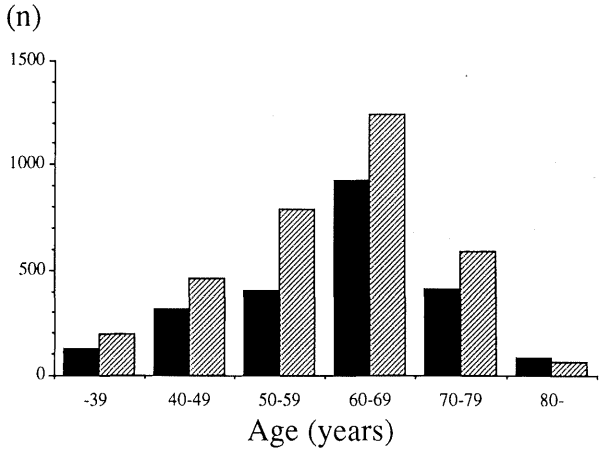

Fig. 1. Sex and age distribution of subjects (male=2,252, female=3,337)
(■ : male, ▨ : female)

tric cancer. Subjects who met either of these criteria were referred for further examination, usually by panendoscopy.

Indirect photofluorography, using 100×100 mm X-ray films, was performed as follows: 1. Prone position with a small amount of barium contrast media; 2. Prone position with full barium; 3. Frontal view in the supine position; 4. Right-anterior-oblique view in the supine position; 5. Left-anterior-oblique view in the supine position; 6. Left-anterior-oblique view in the half standing position; 7. Frontal view in the standing position. The results of indirect photofluorography were interpreted without knowledge of the serum pepsinogen levels. Cases with abnormal (positive) indirect photofluorographic results were referred for further examination regardless of their serum pepsinogen levels. The results of the further examinations were analyzed.

Statistical analysis was performed by Chi-square test and a p value of <0.05 was considered significant.

RESULTS

The rate of positive cases using the PG method was 24.7% compared with 20.4% by the X-ray method (Table 1). There was no significant difference between groups in the positive of in the men, but the rate of positive cases among the women was significantly higher by the PG method than by the X-ray method.

With the PG method, the rate of positive cases increased with age in the men, peaking in the 70-to-79-year-old group (Fig. 2). In the women, the rate of positive cases also increased with age, except for an increase in subjects under 39 years of age. The rate of positive cases was highest in women over 80 years of age.

Table 1. Incidence of positive cases

	Positive case		
	male	female	total
[total subjects]	[2,268]	[3,352]	[5,620]
PG method	551 (24.3)	836 (24.9)*	1,387 (24.7)*
X-ray method	518 (22.8)	630 (18.8)	1,148 (20.4)

Numbers in parentheses represents the percentage of total subjects
*: $p<0.001$ vs. X-ray method

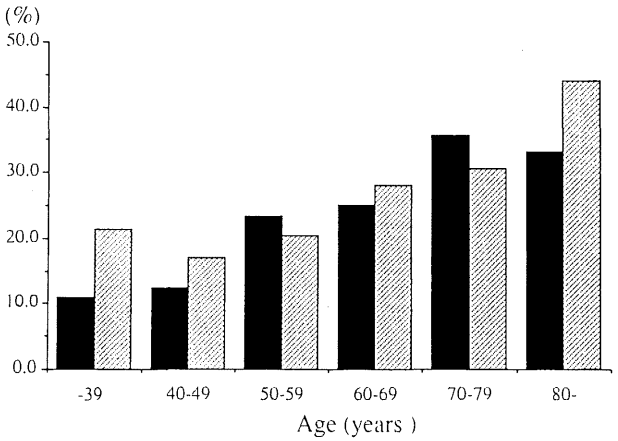

Fig. 2. Incidence of positive cases according to age and sex in PG method
(■ : male, ▨ : female)

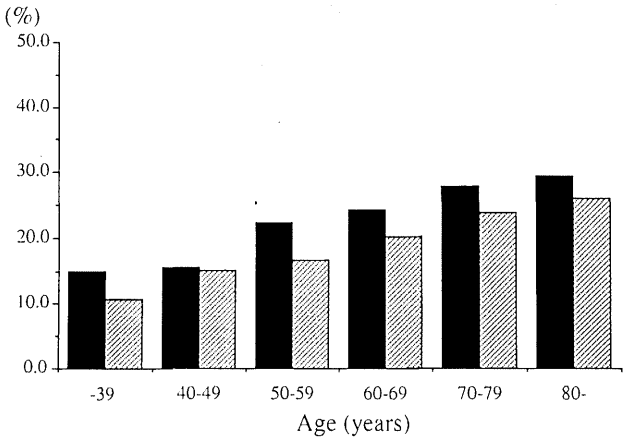

Fig. 3. Incidence of positive cases according to age and sex in X-ray method
(■ : male, ▨ : female)

Using the X-ray method, the rate of positive cases also increased with age in both men and women (Fig. 3). However, the age-associated increase was more gradual than by the PG method

and the difference between the maximum and minimum was smaller. With the X-ray method, the positive rate was higher in the men than in the women in all age groups.

Further examination was performed in 908 (65.5%) of 1,387 positive cases by the PG method and 867 (75.5%) of 1,148 positive cases by the X-ray method ($p<0.001$). Gastric cancer was detected in 7 cases by the PG method and 6 cases by the X-ray method (Table 2). The PG method detected a slightly higher number of gastric cancers than the X-ray method. Three cases were detected by both the PG method and the X-ray method; therefore, the real number of gastric cancers was 10. The percentage of all subjects and of subjects who underwent further examination were slightly higher with the PG method than with the X-ray method.

Table 2. Incidence of gastric cancer

	PG method	X-ray method
Gastric cancer	7	6
% of total	0.12	0.11
% of positive cases	0.50	0.52
% of further examination	0.77	0.69

% of further examination: % of subjects who underwent further examination

All subjects were divided into four groups according to the results of their screening (Table 3): (1) negative by both PG method and X-ray method (PG(-)X-ray(-) group); (2) positive only by PG method (PG(+)X-ray(-) group); (3) positive only by X-ray method (PG(-)X-ray(+) group), and (4) positive by both PG method and X-ray method (PG(+)X-ray(+) group). The numbers and the percentage of total were respectively 3,415 (60.8%), 1,057 (18.8%), 818 (14.6%), and 330 (5.9%). However, the percentage of total subjects was least in the PG(+)X-ray(+) group, where the incidence of gastric cancer was highest. Moreover the incidence in the PG(+)X-ray(-) group was the secondary highest.

The characteristics of gastric cancers, based on the criteria of the Japanese Gastric Cancer Research Association[8], are shown in Table 4. The mean age of cases detected by the PG method

Table 3. Incidence of gastric cancer according to the results of screening

	PG(-)X-ray(-)	PG(+)X-ray(-)	PG(-)X-ray(+)	PG(+)X-ray(+)
Each group (% of total)	3,415(60.8)	1,057 (18.8)	818 (14.6)	330 (5.9)
Further examination (% of subjects)		655 (62.0)	614 (76.7)	253 (76.7)
Gastric cancer		4	3	3
% of each group		0.38	0.37	0.91
% of further examination		0.61	0.49	1.19

Table 4. Cases with gastric cancer

No	Year	sex	age	PGI	PGII	I/II ratio	PG	X-ray	Location	Site	Gross Shape	Depth	Pathology
1	1991	male	67	22.3	23.9	0.93	(+)	(-)	C	L	Borr 3	mp	dif
2	1992	male	72	15.4	17.6	0.87	(+)	(-)	CM	A	IIa	m	dif
3	1992	male	66	60.8	42.2	1.44	(+)	(-)	M	G	III+IIc	sm	dif
4	1992	male	71	11.5	7.8	1.47	(+)	(-)	MC	A	Borr 5 (IIa+IIc-like)	mp	undif
5	1991	male	73	15.9	6.3	2.53	(+)	(+)	A	L	IIa+IIc	sm	dif
6	1992	female	65	19.1	22.7	0.84	(+)	(+)	M	PL	I	m	dif
7	1992	female	81	14.0	16.5	0.84	(+)	(+)	MC	A	Borr 5 (IIc-like)	mp	dif
8	1991	female	67	90.0	31.8	2.80	(-)	(+)	A	L	IIc	m	undif
9	1992	male	70	47.7	13.8	3.45	(-)	(+)	C	L	IIc	sm	dif
10	1992	female	65	65.4	25.6	2.55	(-)	(+)	M	P	Borr 5 (IIc-like)	mp	undif

Location: C: cardial portion of stomach; M: middle portion of stomach; A: antral portion of stomach
Site: L: lesser curvature; G: greater curvature; A: anterior wall; P: posterior wall
Gross Shape: Borr: Borrmann
Pathology: dif: differentiated-type adenocarcinoma containing tubular and papillary adenocarcinoma
undif: undifferentiated-type adenocarcinoma containing poorly differentiated adenocarcinoma and signet ring cell carcinoma

was 70.7 years (male: female=5:2). The mean age of cases detected by the X-ray method was 70.2 years (male: female=2:4). Of the 7 cancers detected by the PG method, 4 (57.1%) were early gastric cancers. Of the 6 cases detected by X-ray method, 4 (66.7%) were early gastric cancers. Differentiated-types of adenocarcinoma accounted for 6 of 7 cases detected by the PG method and 4 of 6 cases detected by the X-ray method. Undifferentiated-type adenocarcinoma accounted for 2 of the 3 cases detected only by the X-ray method (No.8, 10). The rate of differentiated-type adenocarcinoma was greater using the PG method rather than in the X-ray method.

DISCUSSION

Since the institution of gastric mass screening in Japan, several million people have annually undergone indirect photofluorography[5]. The usefulness of this method of mass screening for the detection of gastric cancer has been recognized[1,5,12] in Japan. Indirect photofluorography is performed in mobile X-ray vans and requires seven films. Thus, the specialized technique and expensive apparatus necessary are drawbacks to its use for mass screening. On the other hand, the serum test does not need such specialized techniques nor apparatus, so we investigated the clinical application of serum pepsinogen levels for gastric mass screening.

Atrophic gastritis is generally believed to be an associated lesion of gastric carcinoma[2,7,14,15,17]. Atrophic gastritis is common in patients with gastric carcinoma, especially in the intestinal type of gastric carcinoma[14,15,20]. Although atrophic gastritis can be diagnosed by morphological, histological or functional examinations, the most convenient reliable diagnostic method is the measurement of serum pepsinogen levels[11,13]. Moreover, the correlation between the prevalence rates for atrophic gastritis determined by serum pepsinogen levels and the mortality rates for gastric cancer in Japan has been clarified[3,9]. Accordingly, subjects with atrophic gastritis determined by pepsinogen levels are considered to have a high risk for gastric cancer.

As a result, measurement of pepsinogen levels may be a useful method for screening for gastric cancer[10,16], and it also is simpler and less expensive than indirect photofluorography. We initially investigated the usefulness of this screening method in a local area in 1989[18,22]. At first the cutoff level for the risk of gastric cancer was defined as a pepsinogen I/II ratio below 2.0[18], based on the data of Stemmermann et al[16]. In 1990, we revised this definition to a PGI level below 30 μg/liter or a pepsinogen I/II ratio below 2.0 to increase sensitivity based on our initial results[18]. Of 8,115 subjects who underwent screening over a 3-year period, 16 were found to have gastric cancer based on their pepsinogen levels[22], yielding a 0.20% incidence of gastric cancer. Early gastric cancer accounted for 56.3% of the cancers detected[22]. This result was similar to the results of a national gastric screening using indirect photofluorography conducted in 1990 (3,446,365 subjects underwent gastric mass screening; 13.8% positive cases; 0.15% incidence of gastric cancer; early gastric cancers : 54.3%)[19]. Thus, screening based on serum pepsinogen levels appears to be as useful as screening based on indirect photofluorography[21,22]. However, in these previous studies the results of the PG method and the X-ray method were assessed in separate groups of subjects[22] or the X-ray method was different in each year[21]. In the present study we assessed these methods in subjects who underwent both methods under fixed conditions.

In the present study, the PG method yielded a slightly higher percentage of positive cases than the X-ray method (24.7% vs. 20.4%). In a workplace survey conducted by Miki et al[10], the rate of positive cases was below 20%. The percentage of positive subjects increased with age both in the present study and the study by Miki et al, except for a slight decrease in male subjects over 80 years of age and an unexplained increase in women under the age of 40 in the present study. Our investigation included subjects older than those in the survey by Miki et al[10], which may explain why the number of positive cases was greater in our survey. The incidence of atrophic gastritis was also thought to be higher in our study than in that of Miki et al. The highest positive rate was observed in men in their 70s and women over the age of 80. The mortality rate of gastric cancer is higher in men than in women, but the rate of positive cases detected by the PG method was similar in men and women, suggesting that there may have been more false-positive cases in the women. It remains to be determined if different cutoff levels should be used in men and women.

We detected 10 gastric cancers. There was no significant difference in the incidence of gastric cancer or the number of cases of early gastric cancer between the PG method and the X-ray method. The incidence of gastric cancer was somewhat higher with the PG method than the X-ray method, though the difference was not significant. Although the number of cases with positive results by both methods (PG(+)X-ray(+) group) was smaller than the number of positive cases by either method alone, the incidence of gastric cancer was highest in this group. In addition, our results showed that the sensitivity of gastric mass screening was increased when the PG method was combined with photofluorography.

Of the 7 gastric cancers detected by the PG

method, 6 were differentiated-types of adenocarcinoma. The intestinal type of gastric cancer (differentiated type) is closely related to atrophic gastritis[14,15] and associated with low pepsinogen levels[4,20]. Of the three gastric cancers detected only by the X-ray method, two were undifferentiated-types of adenocarcinoma. Thus, the PG method and the X-ray method tended to detect different histological types of gastric cancer because they employ different criteria for positive.

The number of false-negative cases was three of 10 with the PG method and four of 10 with the X-ray method.

In conclusion, the PG method is as useful as indirect photofluorography for the detection of gastric cancer in Japan. Measurement of pepsinogen levels is simpler than photofluorography and thus could facilitate mass screening for gastric cancer.

ACKNOWLEDGMENTS

The authors thank Drs. C. Watanabe (Hiroshima Prefectural Hospital), A. Kodoi (Hiroshima Red Cross Hospital), A. Kishi (Kake Hospital, Hiroshima) and S. Tange (Togochi-cho, Hiroshima) who helped conduct the mass screening.

(Received January 22, 1997)
(Accepted May 27, 1997)

REFERENCES

1. **Chamberlain, J., Day, N.E., Hakama, M., Miller, A.B. and Prorok, P.C.** 1986. UICC workshop of the project on evaluation of screening programs for gastrointestinal cancer. Int. J. Cancer **37:** 329–344.
2. **Correa, P.** 1988. A human model of gastric carcinogenesis. Cancer Res. **48:** 3554–3560.
3. **Fukao, A., Hisamichi, S., Ohsato, N., Fujino, N., Endo, N. and Iha, M.** 1993. Correlation between the prevalence of gastritis and gastric cancer in Japan. Cancer Causes and Control **4:** 17–20.
4. **Haruma, K., Yoshihara, M., Sumii, K., Tari, A., Watanabe, C., Kodoi, A. and Kajiyama, G.** 1993. Gastric acid secretion, serum pepsinogen I, and serum gastrin in Japanese with gastric hyperplastic polyps or polypoid-type early gastric carcinoma. Scand. J. Gastroenterol. **28:** 633–637.
5. **Hisamichi, S., Sugawara, N. and Fukao, A.** 1988. Effectiveness of gastric mass screening in Japan. Cancer Detect. Prev. **11:** 323–329.
6. **Ichinose, M., Miki, K., Furihata, C., Kageyama, T., Hayashi, R., Niwa, H., Matsuhima, T. and Takahashi, K.** 1982. Radioimmunoassay of serum group I and group II pepsinogens in normal controls and patients with various disorders. Clin. Chim. Acta **126:** 183–191.
7. **Imai, T., Kubo, T. and Watanabe, H.** 1971. Chronic gastritis in Japanese with reference to high incidence of gastric carcinoma. J. Nat. Cancer Inst. **47:** 179–195.
8. **Japanese Research Society for Gastric Cancer.** 1993. The general rules for gastric cancer. 12th ed., pp.2–33. Kanehara Publication, Tokyo (in Japanese).
9. **Kabuto, M., Imai, H., Tsugane, S. and Watanabe, S.** 1993. Correlation between atrophic gastritis prevalence and gastric cancer mortality among middle-aged men in 5 areas in Japan. J. Epidemiol. **3:** 35–39.
10. **Miki, K., Ichinose, M., Ishikawa, K.B., Yahagi, M., Matsushima, M., Kakei, N., Tsukada, S., Kido, M., Ishihama, S., Shimizu, Y., Suzuki, T. and Kurokawa, K.** 1993. Clinical application of serum pepsinogen I and II levels for mass screening to detect gastric cancer. Jpn. J. Cancer Res. **84:** 1086–1090.
11. **Miki, K., Ichinose, M., Shimizu, A., Huang, S.C., Oka, H., Furihata, C., Matsushima, T. and Takahashi, K.** 1987. Serum pepsinogens as a screening test of extensive chronic gastritis. Gastroenterol. Jpn. **22:** 133–141.
12. **Ohshima, A., Hirata, N., Ubukata, T., Umeda, K. and Fujimoto, I.** 1986. Evaluation of a mass screening program for stomach cancer with a case-control study design. Int. J. Cancer **38:** 829–833.
13. **Samloff, I.M., Varis, K., Ihamaki, T., Siurala, M. and Rotter, J.I.** 1982. Relationships among serum pepsinogen I, serum pepsinogen II, and gastric mucosal histology - a study in relatives of patients with pernicious anemia. Gastroenterology **83:** 204–209.
14. **Sipponen, P., Kekki, M. and Siurala, M.** 1983 Atrophic chronic gastritis and intestinal metaplasia in gastric carcinoma. Cancer **52:** 1062–1068.
15. **Sipponen, P., Kekki, M. and Siurala, M.** 1984. Age-related trends of gastritis and intestinal metaplasia in gastric carcinoma patients and in controls representing the population at large. Br. J. Cancer **49:** 521–530.
16. **Stemmermann, G.N., Samloff, I.M., Nomura, A.M.Y. and Heilbrun, L.K.** 1987. Serum pepsinogens I and II and stomach cancer. Clin. Chim. Acta **163:** 191–198.
17. **Walker, I.R., Strickland, R.G., Ungar, B. and Macky, I.R.** 1971. Simple atrophic gastritis and gastric carcinoma. Gut **12:** 906–911.
18. **Watanabe, C.** 1992. A clinical study on gastric mass assessment using serum pepsinogen I and II in a local population survey. J. Gastroenterol. Mass Survey **97:** 42–50 (in Japanese).
19. **Yamada, T., Doi, H., Iwasaki, M., Arisue, T., Hisamichi, S., Yoshikawa, K., Kita, S., Koga, M., Ono, Y. and Hojo, K.** 1993. Current statistics of the gastric mass survey in Japan - an annual report in 1990. J. Gastroenterol. Mass Survey **31:** 90–107 (in Japanese).
20. **Yoshihara, M., Haruma, K., Sumii, K., Watanabe, C., Kiyohira, K., Kawaguchi, H., Tanaka, S. and Kajiyama, G.** 1995. The relationship between gastric secretion and type of early gastric carcinoma. Hiroshima J. Med. Sci. **44:** 79–82.

21. **Yoshihara, M., Sumii, K., Haruma, K., Kodoi, A., Kawaguchi, H., Watanabe, C., Kohmoto, K., Fujimura, J., Yamanaka, H., Tsuda, T., Tanaka, S., Sumii, M., Kajiyama, G., Shigenobu, T., Sekito, M. and Kishi, A.** 1994. Evaluation on gastric mass survey using serum pepsinogen - comparison with gastric mass screening using photofluorography-. J. Gastroenterol. Mass Survey **32:** 15–20 (in Japanese).

22. **Yoshihara, M., Sumii, K., Haruma, K., Watanabe, C., Okamoto, S., Kodoi, A., Kawaguchi, H., Kohmoto, K., Tanaka, S., Sumii, M., Takehara, Y., Kajiyama, G., Shigenobu, T., Sekito, M. and Kishi, A.** 1993. Evaluation on gastric mass survey using serum pepsinogen in a local area for three years. J. Gastroenterol. Mass Survey **31:** 24–29 (in Japanese).