Jpn. J. Cancer Res. 86, 1210–1215, December 1995

Sensitivity and Specificity of Mass Screening for Gastric Cancer Using the Measurement of Serum Pepsinogens

Yasushi Hattori,[1,3] Hiromi Tashiro,[1] Toshihiro Kawamoto[2] and Yasushi Kodama[2]

[1]*Safety and Environment Department, Yawata Works, Nippon Steel Corporation, 1-1 Tobihata-cho, Tobata-ku, Kitakyushu 804 and* [2]*Department of Environmental Health, University of Occupational and Environmental Health, 1-1 Iseigaoka, Yahatanishi-ku, Kitakyushu 807*

The aim of this study was to estimate the validity of mass screening for gastric cancer using serum pepsinogens (PG test). The study subjects were 4876 workers aged from 40 to 61 years old. Sera were obtained at the time of the health checkup and serum pepsinogen levels (PG I and PG II) were measured at the same time. PG I < 50 ng/ml and PG I/PG II ratio < 3.0 were adopted as the criteria for a positive result for the PG test. PG test-positive subjects were examined, in principle, by endoscopy. Furthermore, all the subjects were followed up for a year to check for occurrence of gastric cancer. Among the total subjects, 911 (18.7%) were positive for the PG test and 650 (71.4%) among the positive subjects underwent further examinations, which revealed 11 cases of gastric cancer. Seven gastric cancer cases were diagnosed during the follow-up period within one year after the PG test. Six out of the 7 cancer cases had been negative in the PG test. When the results of one year's follow-up from the time of screening were defined as the gold standard, the sensitivity and specificity of the PG test were estimated at 66.7% and 81.5%, respectively. The authors conclude that the validity of the PG test as a mass screening method may be comparable to that of X-ray screening, if optimum criteria of a positive test are selected.

Key words: Serum pepsinogen — Gastric cancer — Mass screening — Sensitivity and specificity

Gastric cancer is one of the commonest malignant neoplasms and the mortality rate from gastric cancer, in spite of the recent decline, is still high.[1,2] In Japan, where gastric cancer has been the most lethal cancer, mass screening for gastric cancer by barium X-ray (X-ray) has been carried out for over 30 years in order to detect as many curable gastric cancers as possible in the asymptomatic phase. The widespread application of X-ray screening has contributed to a decrease in mortality from gastric cancer in Japan.[3–6] However, there are several shortcomings to the X-ray screening method; subjects are exposed to X-rays[7] and experience discomfort or the side effect of constipation due to barium ingestion, and the procedure is complex, requiring technical expertise. Therefore, the development of screening tests which are safer and require less expertise than X-ray screening is desirable.[3]

Chronic atrophic gastritis has been considered to be a precursor of gastric cancer, especially of the differentiated type.[8–15] Several investigators[16–19] have suggested that serum pepsinogen I (PG I) and pepsinogen II (PG II) levels are predictive of the histologic status of the gastric mucosa and are well correlated with the severity of chronic atrophic gastritis. Nomura *et al.*[20] have reported that a serum PG I level of < 20 ng/ml is associated with a significantly increased risk of gastric cancer of the differentiated type in subjects of Japanese ancestry. Moreover, Kabuto *et al.*[21] and Fukao *et al.*[22] have shown that the prevalence rates for chronic atrophic gastritis determined from serum pepsinogen levels are significantly correlated with the mortality rates from gastric cancer. Because of these findings, serological screening of gastric cancer has been proposed. Recently, gastric mass screening using measurements of serum pepsinogen levels (PG test) has been conducted by way of experiment in some local communities or workplaces in Japan, and has attracted much attention since several investigators[23,24] have suggested that this new screening is effective. However, little is yet known regarding its diagnostic validity as a mass screening method because of the difficulties in determining false-negative cases. The principal aim of this study was to calculate the sensitivity and specificity[25,26] of the PG test used to examine healthy workers by following up all the screenees.

MATERIALS AND METHODS

The study subjects were a total of 4876 workers in the steel industry, aged from 40 to 61 years old, who had undergone the annual health checkup carried out at their company in 1993. At that time, sera were obtained and serum levels of PG I and PG II were measured by immunoradiometric assay using Pepsinogen I/II Riabead kits (Dainabot Co. Ltd., Tokyo). Informed consent was obtained from all subjects. In selecting the criteria for a positive result for the PG test, we referred to previous

[3] To whom correspondence should be addressed.

studies[24, 27] and, taking into consideration the manpower required for the further examination mentioned below, PG I <50 ng/ml and I/II <3.0 was adopted as the criteria. PG test-positive subjects were recommended to undergo further examination, in principle, by endoscopy.

Furthermore, all the subjects who had undergone the PG test were followed up for a year to check for occurrence of gastric cancer. The gastric cancer cases were identified by investigating information regarding deaths or long-term absences among the workers in the company or by studying past histories of the workers obtained from health checkups conducted in the workplace, records of gastric cancer cases diagnosed or operated in the hospital attached to the workplace, and the names of diseases recorded on the health insurance receipts in the company. The diagnosis of gastric cancer was confirmed in each case by histological examination of tissue obtained at the time of a surgical operation or endoscopic biopsy and, if necessary, by personal contact with physicians or surgeons. False-negative cases and true-positive cases were defined as follows: false-negative cases were those whose PG test results had been negative, and for whom gastric cancer was subsequently diagnosed within one year; true-positive cases were those whose PG test results had been positive, and for whom gastric cancer was detected at the following examination or diagnosed within one year after the PG test.

Table I. Age and Sex Distributions of Study Subjects

Age (yr.)	Male	Female	Total (%)
40–44	888	24	912 (18.7)
45–49	526	16	542 (11.1)
50–54	2793	59	2852 (58.5)
55–59	495	15	510 (10.5)
60–	59	1	60 (1.2)
Total	4761	115	4876 (100.0)

RESULTS

Table I shows the age and sex distributions of the 4761 male and 115 female subjects. The major age group was 50 to 54 years of age.

The distributions of PG I and PG II levels and I/II ratios by age are shown in Figs. 1 and 2. The PG II level increased slightly with age ($r=0.102$, $P<0.001$). On the

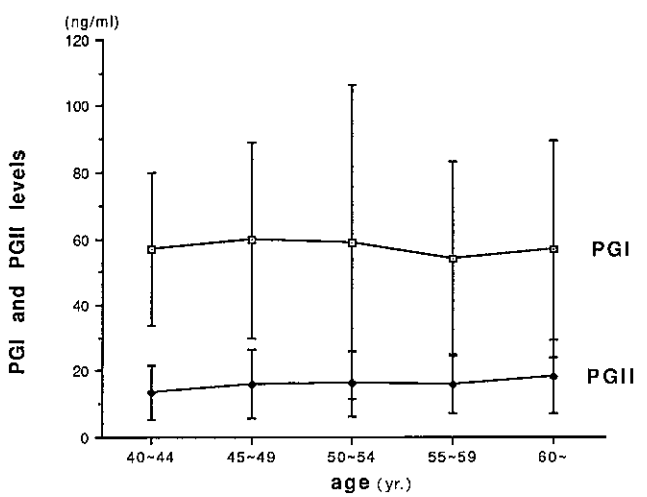

Fig. 1. Distribution of serum PG I and PG II levels by age.

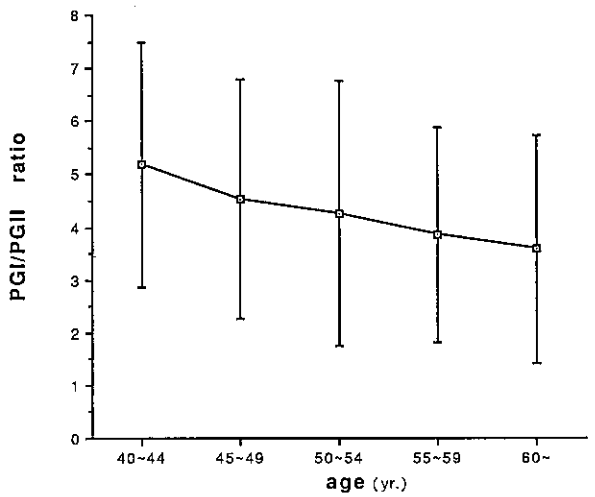

Fig. 2. Distribution of PG I / PG II ratio by age.

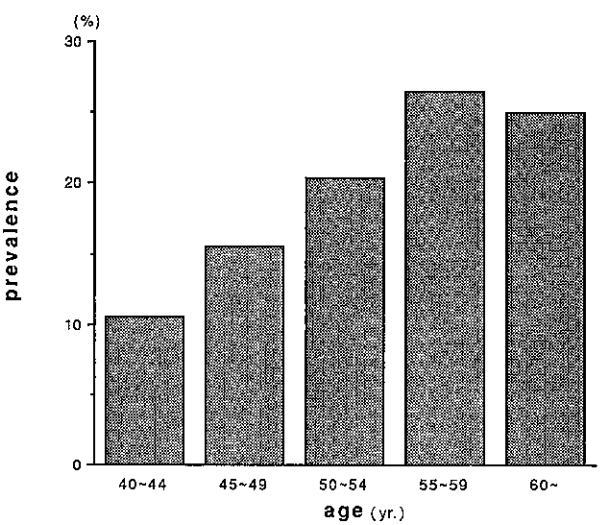

Fig. 3. Prevalence of PG test-positive subjects.

other hand, the PG I level did not change with age. This resulted in a gradual decrease in I/II ratio with age ($r=-0.190$, $P<0.001$). Of the 4876 subjects who underwent the PG test, 911 (18.7%) had positive results. As shown in Fig. 3, the prevalence of positive subjects increased in proportion to age ($P<0.001$).

The results of the mass screening for gastric cancer using serum pepsinogens are shown in Table II. Among the positive subjects, 650 (71.4%) underwent further examinations, including endoscopy and direct roentgenography. Almost all the positive subjects were examined by endoscopy and as a result, 11 cases of gastric cancer were detected in the asymptomatic stage. The detection rate of gastric cancer (No. of cancer cases detected/No. of screened subjects) was 0.23%. Table IIIa lists the gastric cancer cases detected by the PG test. All of the gastric cancer cases were male and most of them were in their fifties. Eight out of the 11 cancer cases were in an

Table II. Results of Gastric Mass Screening Using Serum Pepsinogens and Follow-up

No. of screened subjects	4876 (100.0%)
No. of positive subjects for the PG test	911 (18.7%)
No. of subjects who underwent further examination	650 (13.3%)
No. of gastric cancer cases detected by further examination	11[a] (0.23%)
No. of gastric cancer cases diagnosed during the follow-up period within one year after the PG test	7 (0.14%)
Gastric cancer cases that were positive for the PG test	1 (0.02%)
Gastric cancer cases that were negative for the PG test	6 (0.12%)

Figures in parentheses are prevalences.
a) Includes two cases diagnosed by follow-up endoscopy within one year after the PG test.

Table III. Characteristics of the Gastric Cancer Cases

Case No.	Age (yr.)	Sex	Endoscopic diagnosis	Histology	Location	Size (cm)	PG I (ng/ml)	PG II (ng/ml)	I/II
a. Gastric cancer cases detected by gastric mass screening using serum pepsinogens									
1	49	Male	II_a early cancer	Differentiated	Antrum	0.9×0.9	19.2	9.6	2.0
2	60	Male	II_c early cancer (multiple)	Differentiated	Body	1.0×1.0 0.5×0.8	32.4	18.0	1.8
3	56	Male	Borrmann I type advanced cancer	Undifferentiated	Cardia	2.0×2.5	48.2	26.8	1.8
4	53	Male	II_a+II_c like advanced cancer	Undifferentiated	Angulus	4.5×4.0	19.3	14.8	1.3
5	54	Male	II_c early cancer	Differentiated	Body	5.6×5.0	3.8	12.7	0.3
6	51	Male	II_c early cancer	Differentiated	Body	3.0×3.0	26.9	15.8	1.7
7	53	Male	II_c+II_a early cancer	Differentiated	Antrum	6.5×4.0	19.3	7.4	2.6
8	50	Male	II_c early cancer (multiple)	Differentiated	Antrum	1.9×1.0 1.1×0.7	21.1	15.1	1.4
9	55	Male	II_c like advanced cancer	Undifferentiated	Body	3.5×3.5	20.6	20.6	1.0
10	51	Male	II_c early cancer	Differentiated	Angulus	0.5×0.5	2.8	7.0	0.4
11	44	Male	II_c+III early cancer	Differentiated	Antrum	1.5×1.5	17.6	11.7	1.5
b. Gastric cancer cases diagnosed during the follow-up period within one year after the PG test									
12	50	Male	II_c early cancer	Undifferentiated	Angulus	5.0×4.8	64.6	32.3	2.0
13	58	Male	II_c early cancer	Undifferentiated	Antrum	2.0×3.0	156.0	31.2	5.0
14	51	Male	Borrmann IV type advanced cancer	Undifferentiated	Body–Antrum	Whole anterior wall	62.1	44.5	1.4
15	51	Male	II_c early cancer	Differentiated	Antrum	2.0×1.5	49.8	13.5	3.7
16	56	Male	Borrmann III type advanced cancer	Differentiated	Cardia–Body	11.5×8.5	11.9	19.8	0.6
17	46	Male	II_c like advanced cancer	Differentiated	Body	3.7×3.5	66.6	22.2	3.0
18	44	Male	II_c+III early cancer	Undifferentiated	Angulus	2.0×2.0	80.1	17.0	4.7

Endoscopic diagnosis of advanced and early cancer was determined according to the classification of Borrmann and the Japanese Endoscopic Society, respectively.

Table IV. Sensitivity and Specificity of the PG Test According to the Criteria of a Positive Test Based on the Results of a Follow-up

PG test outcome	Cancer		Total
	Positive[a)]	Negative	
a. PG I <50 ng/ml and I/II <3.0			
Positive	12	899	911
Negative	6	3959	3965
Total	18	4858	4876
	Sensitivity $=12/18=66.7\%$		
	Specificity $=3959/4858=81.5\%$		
b. PG I ≤ 70ng/ml and I/II ≤ 3.0			
Positive	15	1243	1258
Negative	3	3615	3618
Total	18	4858	4876
	Sensitivity $=15/18=83.3\%$		
	Specificity $=3615/4858=74.4\%$		
c. PG I ≤ 30ng/ml or I/II ≤ 2.0			
Positive	14	817	831
Negative	4	4041	4045
Total	18	4858	4876
	Sensitivity $=14/18=77.8\%$		
	Specificity $=4041/4858=83.2\%$		

a) Gastric cancer cases diagnosed within one year after the PG test were regarded as cancer positives at the time of the PG test by definition.

early stage (invasion limited to mucosa or submucosa). Three out of the 8 early cancers were less than 1 cm in diameter which is too small to observe by morphological screening. Of the carcinomas, 8 were histologically of the differentiated type and 3 of the undifferentiated type.

In addition to the gastric cancer cases detected at the PG test, 7 gastric cancer cases were subsequently diagnosed during the follow-up period within one year after the PG test (Tables II and IIIb). Six out of the 7 cancer cases had been negative in the PG test. The remaining case (case No. 16), in spite of being positive in the PG test, had not undergone further examination and was diagnosed as advanced cancer 12 months after the PG test. Six out of the 7 cancer cases were diagnosed after symptoms appeared and the remaining case (case No. 15), who had no symptoms, was detected by X-ray screening conducted in a local community 8 months after the PG test. None of the subjects died from gastric cancer during this period.

Table IVa shows the results of the follow-up in a 2×2 table based on our definition. Twelve out of 18 subjects with gastric cancer were true positive, and 3959 out of 4858 subjects without gastric cancer were true negative, resulting in a sensitivity of 66.7% and a specificity of 81.5%. Twelve out of 911 subjects that were positive for the PG test had gastric cancer, resulting in a positive predictive value[25)] of 1.3%. The sensitivity and specificity of the PG test were also calculated when the following two criteria of a positive test were adopted. According to the criteria defined by Miki[28)] (PG I ≤ 70 ng/ml and I/II ≤ 3.0), the sensitivity and specificity was estimated at 83.3% and 74.4%, respectively (Table IVb). When the criteria defined by Watanabe[23)] (PG I ≤ 30 ng/ml or I/II ≤ 2.0) were adopted, the sensitivity and specificity was estimated at 77.8% and 83.2%, respectively (Table IVc).

DISCUSSION

The increasing trend in the prevalence of positive results of the PG test with age (Fig. 3), which is in accord with previous studies,[24, 27)] is likely to reflect the chronological oral-ward expansion of chronic atrophic gastritis.[29)]

The detection rate of gastric cancer achieved by the PG test in the current study (0.23%) was about two-fold higher than that by X-ray screening over the last four years in this workplace (0.12%). Since the yield of cases is greatest at the first screening examination,[25)] it is likely that the high rate in the current study was mostly due to the first application of serum pepsinogen measurements to gastric mass screening of workers in this workplace.

Sensitivity and specificity of the PG test for detecting gastric cancer were determined in this study. Although several studies[18, 20, 30–35)] have been conducted on the diagnostic validity of the PG test, they were all based on the procedure of testing retrospectively a group of patients diagnosed on the basis of clinical symptoms, or otherwise known to have gastric cancer. This procedure is flawed in that people with a manifest clinical disease do not have the condition that is the object of the screening.[25, 26)] A few studies[23, 24)] have so far been reported on the validity of the PG test used to examine healthy persons in a screening setting. But false-negative cases were not determined correctly in these studies. To determine false-negative cases, we followed up all the screenees for a year after the PG test and observed how many cancers eventually occurred among them. Because the study subjects of the current study were all workers belonging to a single company and, except for the small number who had retired from the company before retirement age, formed a rather accessible population, we could follow up all the screenees and identify occurrences of gastric cancer among them quite easily. As to the duration of the follow-up, the period of one year is arbitrary and may be too short to identify occult prevalent cancers, because we do not know the natural history of gastric cancer completely. In addition, the number of screened subjects in the current study was relatively small and not all the positive subjects in the PG test agreed to further examination. Regardless of the shortcomings of the methods mentioned above, this is the first paper to estimate the

validity of the PG test used to examine healthy workers in a screening setting.

In regard to histological findings, the differentiated type of gastric cancer was predominant in cancers detected by the PG test, while four out of the 6 false-negative cases were histologically of the undifferentiated type. If we calculate the sensitivity of the PG test for detecting the histologically different types of gastric cancer separately, that for the differentiated gastric cancers would be 81.8% and that for the undifferentiated gastric cancers would be 42.9%. There is some likelihood that undifferentiated gastric cancers would be missed by the PG test, since they might not arise in areas of chronic atrophic gastritis.

It is important to select optimum criteria for a positive result for the PG test. However, there is so far no agreement on this. Using criteria of PG I $\leqq$70 ng/ml and I/II $\leqq$3.0 (Table IVb), we found a considerable improvement in the level of sensitivity with a considerable decrease in specificity. With criteria of PG I $\leqq$30 ng/ml or I/II $\leqq$2.0 (Table IVc), there was an improvement in the level of sensitivity without any loss of specificity, which is inconsistent with the findings by Sasamori *et al.*[27] that the use of the criteria of PG I $\leqq$30 ng/ml or I/II $\leqq$2.0 resulted in the lowest level of both sensitivity and specificity. Because serum pepsinogen levels change depending on age and sex,[23, 27, 36, 37] and show geographical differences,[21, 22] the criteria should be defined separately by age, sex and area. If we give priority to the sensitivity, the criteria of PG I $\leqq$70 ng/ml and I/II $\leqq$3.0 are considered to be the most appropriate for this population.

Concerning the X-ray screening, previous studies[38–41] on its validity as a mass screening method have been conducted by following up the screenees by means of a record linkage to a population-based cancer registry, and the results of a 1-year follow-up from the time of screening were defined as the gold standard, from which the validity values were calculated. According to the results of these studies, X-ray screening had a sensitivity of between 69.3% and 89.6% and a specificity of between 83.4% and 92.0%. Comparing these values with those obtained from our study, we conclude that the validity of the PG test as a mass screening method can be comparable to that of X-ray screening, if optimum criteria of a positive test are adopted.

(Received June 19, 1995/Accepted September 12, 1995)

REFERENCES

1) Parkin, D. M., Läärä, E. and Muir, C. S. Estimates of the worldwide frequency of sixteen major cancers in 1980. *Int. J. Cancer,* **41,** 184–197 (1988).
2) Howson, C. P., Hiyama, T. and Wynder, E. L. The decline in gastric cancer: epidemiology of an unplanned triumph. *Epidemiol. Rev.,* **8,** 1–27 (1986).
3) Chamberlain, J., Day, N. E., Hakama, M., Miller, A. B. and Prorok, P. C. UICC workshop of the project on evaluation of screening programmes for gastrointestinal cancer. *Int. J. Cancer,* **37,** 329–334 (1986).
4) Oshima, A., Hirata, N., Ubukata, T., Umeda, K. and Fujimoto, I. Evaluation of a mass screening program for stomach cancer with a case-control study design. *Int. J. Cancer,* **38,** 829–833 (1986).
5) Yamazaki, H., Oshima, A., Murakami, R., Endoh, S. and Ubukata, T. A long-term follow-up study of patients with gastric cancer detected by mass screening. *Cancer,* **63,** 613–617 (1989).
6) Oshima, A., Hanai, A. and Fujimoto, I. Evaluation of a mass screening program for stomach cancer. *Natl. Cancer Inst. Monogr.,* **53,** 181–186 (1979).
7) Maruyama, T., Noda, Y., Kumamoto, Y., Nishizawa, K., Furuya, Y., Iwai, K., Urahashi, S., Kurihara, R., Kamata, R. and Sakata, S. Estimation of frequency, population doses and stochastic risks in stomach mass screening examinations in Japan, 1980. *Nippon Acta Radiol.,* **47,** 971–982 (1987) (in Japanese).
8) Correa, P. The gastric precancerous process. *Cancer Surv.,* **2,** 437–450 (1983).
9) Morson, B. C. Carcinoma arising from areas of intestinal metaplasia in the gastric mucosa. *Br. J. Cancer,* **9,** 377–385 (1955).
10) Sipponen, P., Kekki, M. and Siurala, M. Atrophic chronic gastritis and intestinal metaplasia in gastric carcinoma. *Cancer,* **52,** 1062–1068 (1983).
11) Imai, T., Kubo, T. and Watanabe, H. Chronic gastritis in Japanese with reference to high incidence of gastric carcinoma. *J. Natl. Cancer Inst.,* **47,** 179–195 (1971).
12) You, W., Blot, W. J., Li, J., Chang, Y., Jin, M., Kneller, R., Zhang, L., Han, Z., Zeng, X., Liu, W., Zhao, L., Correa, P., Fraumeni, J. F. and Xu, G. Precancerous gastric lesions in a population at high risk of stomach cancer. *Cancer Res.,* **53,** 1317–1321 (1993).
13) Siurala, M. and Seppälä, K. Atrophic gastritis as a possible precursor of gastric carcinoma and pernicious anemia. *Acta Med. Scand.,* **166,** 455–474 (1960).
14) Cheli, R., Santi, L., Ciancamerla, G. and Canciani, G. A clinical and statistical follow-up study of atrophic gastritis. *Dig. Dis.,* **18,** 1061–1066 (1973).
15) Kato, I., Tominaga, S., Ito, Y., Kobayashi, S., Yoshii, Y., Matsuura, A., Kameya, A., Kano, T. and Ikari, A. A prospective study of atrophic gastritis and stomach cancer risk. *Jpn. J. Cancer Res.,* **83,** 1137–1142 (1992).
16) Bock, O. A. A., Arapakis, G., Witts, L. J. and Richards, W. C. D. The serum pepsinogen level with special reference to the histology of the gastric mucosa. *Gut,* **4,** 106–

111 (1963).
17) Samloff, I. M., Varis, K., Ihamaki, T., Siurala, M. and Rotter, J. I. 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 (1982).
18) Miki, K., Ichinose, M., Shimizu, A., Huang, S., Oka, H., Furihata, C., Matsushima, T. and Takahashi, K. Serum pepsinogens as a screening test of extensive chronic gastritis. *Gastroenterol. Jpn.,* **22,** 133–141 (1987).
19) Haruki, K., Kurokawa, K., Adachi, H. and Obata, H. Serum and gastric mucosal pepsinogens in atrophic gastritis, particularly in type A gastritis associated with pernicious anemia in Japanese. *Gastroenterol. Jpn.,* **28,** 359–366 (1993).
20) Nomura, A. M. Y., Stemmermann, G. N. and Samloff, I. M. Serum pepsinogen I as a predictor of stomach cancer. *Ann. Intern. Med.,* **93,** 537–540 (1980).
21) Kabuto, M., Imai, H., Tsugane, S. and Watanabe, S. Correlation between atrophic gastritis prevalence and gastric cancer mortality among middle-aged men in 5 areas in Japan. *J. Epidemiol.,* **3,** 35–39 (1993).
22) Fukao, A., Hisamichi, S., Ohsato, N., Fujino, N., Endo, N. and Iha, M. Correlation between the prevalence of gastritis and gastric cancer in Japan. *Cancer Causes Control,* **4,** 17–20 (1993).
23) Watanabe, C. A clinical study on gastric mass assessment using serum pepsinogen I and II in a local population survey. *J. Gastroenterol. Mass Surv.,* **97,** 42–50 (1992) (in Japanese).
24) Miki, K., Ichinose, M., Ishikawa, K. B., Yahagi, N., Matsushima, M., Kakei, N., Tsukada, S., Kido, M., Ishihama, S., Shimizu, Y., Suzuki, T. and Kurokawa, K. Clinical application of serum pepsinogen I and II levels for mass screening to detect gastric cancer. *Jpn. J. Cancer Res.,* **84,** 1086–1090 (1993).
25) Cole, P. and Morrison, A. S. Basic issues in population screening for cancer. *J. Natl. Cancer Inst.,* **64,** 1263–1272 (1980).
26) Love, R. R. and Camilli, A. E. The value of screening. *Cancer,* **48,** 489–494 (1981).
27) Sasamori, N., Tamura, M., Iwasaki, M., Suzuki, T., Kiyose, K., Andoh, Y., Hinohara, S., Matsuda, M. and Tohkake, S. Evaluation of serum pepsinogen tests at MHTS: a new method of gastric cancer screening. *Jpn. J. MHTS,* **20,** 343–354 (1993) (in Japanese).
28) Miki, K. Gastric cancer screening using serum tests (stomach dry dock) — Study of the systems of the first screening for cancer-susceptible subjects by serum pepsinogen levels and the secondary close-examination by every-other-year panendoscopy. *J. Gastroenterol. Mass Surv.,* **107,** 19–30 (1994) (in Japanese).
29) Kimura, K. Chronological transition of the fundic-pyloric border determined by stepwise biopsy of the lesser and greater curvatures of the stomach. *Gastroenterology,* **63,** 584–592 (1972).
30) Stemmermann, G. N., Samloff, I. M., Nomura, A. M. Y. and Heilbrun, L. K. Serum pepsinogens I and II and stomach cancer. *Clin. Chim. Acta,* **163,** 191–198 (1987).
31) Miki, K., Ichinose, M., Kawamura, N., Matsushima, M., Ahmad, H. B., Kimura, M., Sano, J., Tashiro, T., Kakei, N., Oka, H., Furihata, C. and Takahashi, K. The significance of low serum pepsinogen levels to detect stomach cancer associated with extensive chronic gastritis in Japanese subjects. *Jpn. J. Cancer Res.,* **80,** 111–114 (1989).
32) Kimura, Y., Fujii, T., Hamamoto, K., Miyagawa, N., Tsuda, K., Tanada, S. and Iio, A. Evaluation of serum pepsinogen I and II of patients with gastric cancer. *Nucl. Med.,* **26,** 1127–1133 (1989) (in Japanese).
33) Kodoi, A., Yoshihara, M., Sumii, K., Haruma, K., Watanabe, C., Okamoto, S., Kawaguchi, H., Kawamoto, K., Tanaka, S., Tsuda, T. and Kajiyama, G. An evaluation of screening for asymptomatic gastric cancer using serum pepsinogen I and II. *J. Gastroenterol. Mass Surv.,* **106,** 21–27 (1994) (in Japanese).
34) Kikuchi, S., Wada, O., Miki, K., Nakajima, T., Nishi, T., Kobayashi, O. and Inaba, Y. Serum pepsinogen as a new marker for gastric carcinoma among young adults. *Cancer,* **73,** 2695–2702 (1994).
35) Tabuchi, T., Soma, T., Nakada, I., Sato, S., Ubukata, H., Goto, Y., Watanabe, Y., Nagayama, Y., Umeda, K., Ebine, S. and Nishikawa, T. A mass screening for gastric cancer using serum pepsinogen I and II. *J. Gastroenterol. Mass Surv.,* **108,** 18–24 (1994) (in Japanese).
36) Aoki, K., Goto, T., Kudo, M., Yasui, T., Shimaoka, A. and Misumi, J. A study on the distributions of serum pepsinogens in general population. *Jpn. Med. J.,* **3576,** 43–48 (1992) (in Japanese).
37) Kikuchi, S., Inaba, Y., Wada, O., Miki, K., Tenjin, H., Kaneko, E. and Mizukoshi, H. Should age, sex, subjective symptoms in the stomach and past history of peptic ulcer be regarded in the evaluation of efficacy of serum pepsinogen values for use in gastric cancer mass-screening? *J. Epidemiol.,* **3,** 71–76 (1993).
38) Ubukata, T., Oshima, A., Morii, T., Nakanishi, K., Umeda, K. and Fujimoto, I. Estimation of the validity of mass screening programs for stomach cancer and the method for that. *J. Gastroenterol. Mass Surv.,* **63,** 65–72 (1984) (in Japanese).
39) Murakami, R., Tsukuma, H., Ubukata, T., Nakanishi, K., Fujimoto, I., Kawashima, T., Yamazaki, H. and Oshima, A. Estimation of validity of mass screening program for gastric cancer in Osaka, Japan. *Cancer,* **65,** 1255–1260 (1990).
40) Fukao, A., Hisamichi, S., Takano, A. and Sugawara, N. Accuracies of mass screening for gastric cancer: test sensitivity and program sensitivity. *J. Gastroenterol. Mass Surv.,* **97,** 59–63 (1992) (in Japanese).
41) Miki, N., Oshima, A., Kawashima, T., Yamazaki, H., Miyamoto, M., Endo, S., Okano, Y., Morii, T., Nakao, M. and Murakami, R. Estimation of mass screening for gastric cancer by means of a record linkage to the Osaka cancer registry. *J. Gastroenterol. Mass Surv.,* **97,** 64–68 (1992) (in Japanese).