

## Clinical Application of Serum Pepsinogen I and II Levels for Mass Screening to Detect Gastric Cancer

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A considerable number of gastric cancers derive from stomach mucosa where chronic atrophic gastritis is severe and extensive. Based on the fact that the serum pepsinogen levels provide a precise measure of the extent of chronic atrophic gastritis, we have devised a mass screening method involving serum pepsinogen measurement to identify subjects at high risk of gastric cancer. In 1991, we screened 4,647 workers (male: 4,113, female: 534, mean age: 49.0 years) at a Japanese company using this method. Out of 875 subjects (18.8%) with a serum pepsinogen I level of less than 50  $\mu\text{g}/\text{liter}$  and a pepsinogen I/II ratio of less than 3.0, 676 subjects (14.5%) were selected for further investigation by endoscopy. This led to the detection of four subjects (0.086%) with gastric cancer (three in an early stage) and four subjects with adenoma. The cancer detection rate of this new screening method was comparable, and in some respects superior, to that of the traditional barium X-ray screening. Since the incidence of test-positive subjects was as low as 10% amongst subjects aged less than 40, this screening method appears to be especially useful for screening of younger generations. The new method is less expensive than the traditional barium X-ray and subjects experience little discomfort. Further, many serum samples can be quickly measured simultaneously. The results of this study have indicated that serum pepsinogen screening provides a valuable method for detecting gastric cancers.

Key words: Pepsinogen — Mass screening — Gastric cancer

Despite a recent worldwide decline in the incidence of gastric cancers, such cancers are still a major cause of death in Japan.<sup>1)</sup> For this reason, much effort has been directed to their early detection, and widespread gastric mass screenings have greatly contributed to reducing the high mortality rate from this disease. To detect gastric cancer, a barium X-ray, using 10×10 cm film, is the traditional first screening step, after which those suspected of having a cancer are further investigated either with a higher quality barium X-ray or by endoscopy. Because those tested have little difficulty with this procedure and the cost is low, most workplaces throughout Japan use this method of screening. However, the sensitivity of the first screening step is by no means high; due to its low resolution, this barium X-ray is usually only indicative of the presence of abnormalities in the stomach mucosa. Further, the use of X-ray examination is attended by certain hazards. Therefore, to improve the effectiveness of gastric cancer screening, we have devised a new screening method that utilizes measurement of serum pepsinogen (pepsinogen I and II) levels. This screening system is based on the finding that many gastric cancers develop in stomach mucosa affected by severe and extensive chronic atrophic gastritis.<sup>2-5)</sup> Several studies have indicated that serum pepsinogen levels reflect the morphological and functional status of the stomach mucosa, so that they serve as a marker of

chronic atrophic gastritis.<sup>6-9)</sup> Thus, serum pepsinogen screening would enable the detection of subjects with extensive atrophic gastritis, and since such subjects have a high risk of developing a cancer, those showing abnormal serum pepsinogen levels should be carefully examined by endoscopy or high-quality barium X-ray. This paper reports the first application of serum pepsinogen measurement for gastric mass screening of workers at a company and compares the result achieved by this new method with that of the traditional barium X-ray screening method.

### SUBJECTS AND METHODS

In 1991, 4,647 company employees (4,113 male, 534 female; mean age, 49.0 years; for distribution of age and sex see Fig. 1) were given an annual periodic health check-up that consisted of an interview to ascertain their general state of health, a physical examination, an electrocardiogram, a chest X-ray and a blood sampling. The blood samples for routine laboratory tests were taken after fasting and aliquots of the separated sera were individually stored at  $-20^{\circ}\text{C}$  until the serum pepsinogens levels were measured by using pepsinogen I and II Riabead Kits (Dinabot Co. Ltd.), a modified radioimmunoassay method that has been described.<sup>10)</sup> Those who had undergone a total gastrectomy were excluded

from this serum pepsinogen screening and examined separately by indirect barium X-ray.

A previous study has clearly shown that a reduction in the area of the fundic gland occurs with the progression of chronic atrophic gastritis, and that this correlates with a stepwise reduction in the serum pepsinogen I level and the pepsinogen I/II ratio.<sup>9)</sup> Further, another study has revealed that the serum levels of patients with gastric cancer are significantly lower than those of cancer-free subjects, the low levels reflecting the presence of coexisting extensive chronic atrophic gastritis.<sup>11)</sup> Given these facts, the next step was to establish criteria for confirming the presence of severe atrophic gastritis associated with gastric cancer by this new method, and to achieve this we analyzed the serum pepsinogen levels of 3,738 cancer-free subjects and 178 subjects with gastric cancer.<sup>12)</sup> Another point that had to be considered in establishing the criteria is the manpower required for the second screening step (the endoscopic inspection of those suspected of having a gastric cancer), since when using the traditional barium X-ray gastric mass screening method, nearly 20% of the initially screened subjects generally require a more thorough follow-up examination with endoscopy and this can involve a great deal of time and labor. Thus, the cutoff level should be such that the

positive rate in the screened subjects be less than 20% and that the sensitivity of this method for detecting cancers be as high as possible. Taking all these factors into consideration, a pepsinogen I level of less than 50  $\mu\text{g/liter}$ , together with a I/II ratio of less than 3.0, was used as the cutoff level; this gave a positive predictive value of 58.6% and a specificity of 78.9%.<sup>11)</sup> Based on these cutoff values, subjects showing low serum pepsinogen levels were considered to be positive for extensive chronic atrophic gastritis and were further investigated by endoscopy using a panendoscope (Olympus GIF-P20).

## RESULTS

The results of the gastric mass screening using serum pepsinogen measurement are shown in Table I. Of the 4,647 subjects who underwent the screening, 875 (18.8%) had positive serum tests. The percentage of positive subjects increased with age, which is in accord with previous studies<sup>10, 12)</sup> and with the fact that chronic atrophic gastritis is linked with the aging process<sup>13)</sup> (Fig. 2). The positive ratio in those more than 50 years old was about 30% and that in those less than 40 years was just below 10%. Among the positive subjects, 676 (14.5%)

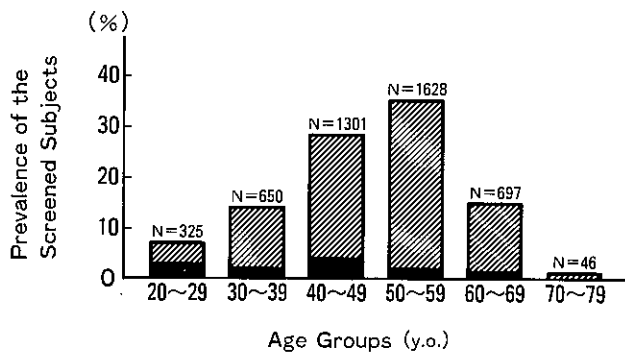


Fig. 1. Distribution of the serum pepsinogen-screened subjects, according to age and sex. □, male; ■, female.

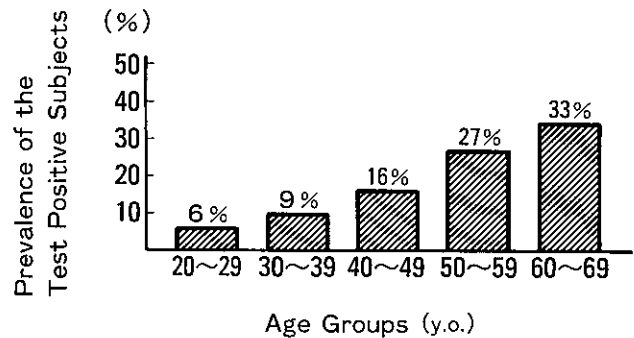


Fig. 2. Age distribution of serum pepsinogen test-positive subjects.

Table I. Results of the Serum Pepsinogen Screening Method (1991)

No. of cases screened	4,647
Cutoff levels of pepsinogen I and the I/II ratio	50 ( $\mu\text{g/liter}$ ) and 3.0
Positive cases (incidence)	875 (18.8%)
No. of subjects examined with endoscopy (incidence)	676 (14.5%)
No. of gastric cancers detected (incidence)	4 (0.086%)
Early cancer/advanced cancer	3/1
No. of adenomas detected (incidence)	4 (0.086%)

Table II. Results of Mass Screening Using the Traditional Barium X-Ray Method Over the Last Five Years (1986-1990)

Year	No. of cases screened	No. of gastric cancers detected	Incidence	No. of early cancers detected	No. of advanced cancers detected
1986	2,595	2	0.077	1	1
1987	2,805	3	0.107	2	1
1988	2,507	4	0.160	3	1
1989	3,468	0	0	0	0
1990	3,675	1	0.027	1	0
Total	15,050	10	0.066	7	3

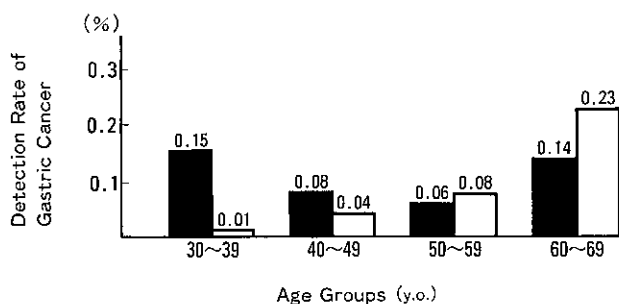


Fig. 3. A comparison of gastric cancer detection rate between the serum pepsinogen screening method and traditional barium X-ray screening. ■, serum pepsinogen tests; □, traditional indirect barium X-ray. The detection rate of the barium X-ray is based on the mean of five years' data (1986-1990) from Kanagawa Health Service Association.

underwent endoscopic examination and as a result, 4 cases of gastric cancer (0.086%) and 4 cases of gastric adenoma (0.086%) were detected.

Table II shows the results of gastric mass screening using the traditional barium X-ray method in workers at the same company from 1986 to 1990. Using traditional screening, the cancer detection rate was less than 0.16% (mean: 0.066%). Thus, the cancer detection rate of the

new serum pepsinogen screening method was found to be at least comparable. The incidence of detected cancers for each age group by both methods is shown in Fig. 3. The percentages of detected cancers by the new pepsinogen method were 0.15% for those in their 30s, 0.08% for those in their 40s, 0.06% for those in their 50s and 0.14% for those in their 60s, and in patients who were young, these values are higher than the detection rate of the traditional barium X-ray screening (data from the Kanagawa Health Service Association from 1986 to 1990<sup>14)</sup>), specifically 15 times higher for those in their 30s and two times higher for those in their 40s. However, gastric cancer detection by the serum pepsinogen screening method was lower in older people, especially those in their 60s.

All of the cancers detected by serum pepsinogen screening were in subjects who showed no other symptoms, and three of them (75%) were in the early stage (Table III). It is interesting to note that two of these three cancers were relatively small and it was quite difficult to visualize these lesions in further investigation using high-quality barium X-ray. The proportion of early-stage cancers detected by the serum pepsinogen screening method was higher than that detected by the traditional screening method (50%). A histological study revealed that of the four cancers detected, two were well-differentiated adenocarcinomas and two were

Table III. Gastric Cancers Detected by the Serum Pepsinogen Screening Method

Case	Age (yr)	Sex	Endoscopic diagnosis (histology)	Location size (cm)	Pepsinogen	
					I ( $\mu\text{g}/\text{liter}$ ),	I/II ratio
1	33	Male	IIC-like advanced cancer	Body (2.5×3.8)	44.9	3.0
2	40	Male	IIC early cancer	Body (3.0×4.0)	8.5	0.4
3	57	Male	IIB+IIC early	Body (1.0×1.0)	27.3	1.3
4	66	Male	IIC early cancer	Antrum (0.5×0.5)	31.3	1.4

poorly differentiated adenocarcinomas. These four cancers were surgically resected and postoperative evaluation of each patient's stomach confirmed the complete removal of each cancer. All four cancers, which were confirmed by endoscopic biopsies to be gastric adenomas, were less than 1 cm in diameter, and each was completely removed by the technique known as strip biopsy, i.e., an endoscopic mucosal resection.<sup>15)</sup>

## DISCUSSION

Mass screenings to detect gastric cancers have been conducted in Japan for about a quarter of a century, and over six million people are screened annually, mainly by barium X-ray examination. To improve the efficiency of gastric mass screening, it should be focused on subjects at high risk of developing gastric cancer. However, in spite of numerous studies aimed at identification of the environmental agents involved in the development of a gastric cancer, no major risk factor is known.<sup>15)</sup> Still, there is general agreement that intestinal metaplasia, a possible precancerous condition of the stomach, increases in frequency and extent with the progression of chronic atrophic gastritis.<sup>2-5)</sup> Indeed, there is evidence indicating a statistically significant increase in the risk of gastric cancer among populations where chronic atrophic gastritis is widespread<sup>4,5)</sup> and follow-up studies have indicated that the cancer is much more likely to arise in a gastritic stomach.<sup>16-18)</sup> Thus, the population in which chronic atrophic gastritis is widespread appears to form a high-risk group. As has been indicated in our previous study, serum pepsinogen levels provide a precise measure of the extent of chronic atrophic gastritis; the method is even more sensitive and accurate than gastric intubation.<sup>9)</sup> Thus, the high reliability of this serum test to detect chronic gastritis led us to consider its application to mass screenings to detect gastric cancer, since the serum pepsinogen levels of gastric cancer patients, particularly the pepsinogen I level and the I/II ratio, are significantly lower than in cancer-free subjects.<sup>12)</sup>

This paper reports the results of the first application of this serum pepsinogen screening method to mass screening of 4,647 employees of a Japanese company. In this screening series, four gastric cancers (0.086%) were detected in four separate subjects, including three still at an early stage. Workers at the same company had previously been screened by the traditional barium X-ray method, and the cancer detection rate of this new serum pepsinogen screening method is comparable to that of the traditional method over the past five years. However, it must be noted that the cancer detection rate achieved by the traditional screening method had been decreasing, the mean value for the last two years being 0.014%, probably as a result of the company's annual screening program.

Thus, it may be that the relatively high cancer detection rate achieved by serum pepsinogen screening may be due not only to the high sensitivity of this method, but also to the change in the screening method used, from conventional morphological screening to one using biochemical markers. Further, the percentage of early cancers detected by the pepsinogen screening method was higher than the results achieved by the traditional screening method over the last five years. It should also be noted that the results of the serum pepsinogen screening were far better than the mean detection rate of gastric mass screenings in workplaces all over Japan (the mean value for the incidence of cancers detected in workplaces all over Japan is 0.03%, and the percentage of early cancers detected is nearly 50%, according to the Annual Report on Gastric Mass Screenings in Japan from the Japanese Society of Gastroenterological Mass Survey in 1989<sup>19)</sup>). In comparison with the traditional screening, the detection rate of the cancer is higher in the younger generations, especially in subjects in their 20s, 30s and 40s. In addition, the numbers of test-positive subjects are relatively low in these generations. Considering the facts that the subjects in these generations are more susceptible to X-ray hazards and their risks of the cancer are relatively less, this non-invasive screening method should be valuable for detecting young subjects at high risk. In contrast, this screening method seems to be less effective in the screening of older subjects. Since the strategy of the method is based on the detection of the subjects with extensive chronic atrophic gastritis, which is a process closely linked with aging of the stomach mucosa, one would expect that the number of false-positive cases might increase as the age of the screened subjects increases. Therefore, more studies are required to check the validity of the method in the screening of older subjects, and we may have to be cautious in applying the method to older subjects. We also have to consider the false-negative rate in evaluation of the screening method. After a one-year period, two cases of early cancer were detected among the subjects determined to be negative. One of the two cases was found in the next year, 1992, by gastric mass screening using the serum test, because his serum pepsinogen levels decreased during the year. The other case underwent endoscopic examination by chance in the clinic of the company 6 months after the screening and was diagnosed as early gastric cancer. We have set up a five-year program for following up the subjects screened by the method in order to evaluate it properly.

In conclusion, this serum pepsinogen screening method has proven to be comparable, and in some ways superior, to the traditional barium X-ray mass screening method. This new screening method has many advantages: (1) the procedure is easy and subjects experience no discomfort; (2) no X-ray hazards are incurred and no side effects are

experienced due to barium ingestion; (3) it is less expensive (about a half the cost of barium X-ray screening); and 4) the procedure is quick and many serum samples can be measured simultaneously. Thus, the initial step of the screening procedure can be completed rapidly. Our results indicate that serum pepsinogen screening is a

valuable method to detect gastric cancers in the Japanese population, and it may be equally effective for the screening of the inhabitants of other countries at high risk of the cancer.

(Received April 20, 1993/Accepted July 21, 1993)

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