Serum Pepsinogen and Gastric Cancer Screening

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Abstract

Since the 1990's, the test for serum pepsinogen as a marker for chronic atrophic gastritis has been incorporated into gastric cancer screening programs, on a trial basis, to identify people at high risk for gastric cancer. The addition of the serum test to the cancer screening program has been shown to improve the detection rate of cancer and pepsinogen testing is useful in detecting early-stage gastric cancers arising from atrophic gastric mucosa, which macroscopically tend to be elevated and histologically differentiated. Furthermore, the cost for the detection of a single cancer case is much less than that for conventional screening. Thus, with the introduction of pepsinogen testing, complementing barium X-ray, a more efficient screening system is available.

Key words: gastric cancer, screening, pepsinogen, atrophic gastritis, gastric cancer screening, high-risk group

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Introduction

Since the mid-1960s, the Japanese government has advocated gastric cancer screening programs based mainly on double-contrast barium X-ray (1). As a result, a significant reduction in mortality and morbidity from gastric cancer has been attained (2-6). However, the number of people who undergo gastric cancer screening has not increased in recent years. Since the 1990's, the test for serum pepsinogen (PG) as a marker for chronic atrophic gastritis has been incorporated into gastric cancer screening programs, on a trial basis, to identify people who would benefit most from gastric cancer screening (7-12). Ever since PG assay kits became commercially available, numerous centers in Japan have measured serum PG levels as a part of gastric cancer screening. The results have shown that PG testing is useful in detecting early-stage gastric cancer (7-12). After 15 years of experience, the effectiveness of PG testing is receiving wide recognition. The present article summarizes the clinical importance of PG testing and introduces our recent investigations on gastric cancer screening programs incorporating PG testing.

Pepsinogen Testing

Pepsinogen is a precursor for pepsin, a digestive enzyme specifically produced in the gastric mucosa. The human stomach expresses two isozymogens, PGI and PGII, with different biochemical and immunological properties (13). Histological studies based on immunohistochemistry using specific antibodies or *in-situ* hybridization have clearly identified cells that produce PGI and PGII (14-16). While PGI is produced in chief and mucous neck cells, PGII is produced not only in these cells, but also in the cardiac, pyloric, and duodenal Brunner gland cells. The distribution of PGII-producing cells is thus widespread from the entire stomach to the duodenum. Figure 1 shows the distribution of cells producing PGI and PGII in relation with those producing gastric acid and gastrin. Histologically, the localization of PGI-producing cells is limited to an acid-secreting gland, the fundic gland, and that of PGII-producing cells is observed in the fundic and pyloric glands (gastrin-secreting area), and also in the duodenal gland. Figure 1 shows the two-layer structure of PG-producing cell distribution. Pepsinogen is mainly excreted into the stomach lumen, but about 1% of the total enters into the blood stream, although the mechanism is unknown. Studies have clarified that serum PG levels reflect the morphology and function of the gastric mu-

Figure 1. Relationship between the distribution of pepsinogen in gastric mucosa and the secretion of gastric acid and gastrin. 1: Cardiac gland region. 2: Fundic gland region (gastric acid). 3: Pyloric gland region (gastrin). 4: Duodenal Brunner gland region.

cosa and also various pathological conditions such as inflammation (17-23). It is important to note that, during the process of chronic atrophic gastritis, mucosal atrophy advances from the side of the pyloric gland towards the oral side, and that PGI levels and PGI/PGII ratios decrease with advancement in mucosal atrophy (18-20, 23) (Fig. 2). These clinically extremely important changes in serum PG levels are due to the above-mentioned unique distribution of PG-producing cells in gastric mucosal epithelia. In addition, the results of past pathological and epidemiological studies have shown that a strong correlation exists between chronic atrophic gastritis and differentiated gastric cancer development, and thus, chronic atrophic gastritis is considered to be a pre-cancerous lesion (24-27). Pepsinogen testing is based on the correlation between chronic atrophic gastritis and gastric cancer development on the one hand, and the correlation between chronic atrophic gastritis and low PG level on the other. By the introduction of PG testing, which allows the identification of subjects at high risk for gastric cancer, and also by the introduction of endoscopy for the screening of the PG test-positive subjects, the efficiency of gastric cancer detection can be improved dramatically.

From the perspective of complementing conventional radiography, the following four methods for gastric cancer screening utilizing PG testing have been proposed (Fig. 3). In the Concurrent Method, both PG testing and X-ray imaging are performed at the same time, and while this method is ideal for early detection because the two tests have different mechanisms of detection, it is expensive and the number

Figure 2. Serum pepsinogen I/II ratio and gland boundary as assessed by endoscopic Congo red staining

of subjects requiring further examination by endoscopy is larger than in the other three methods. In the Two-stage Method, PG testing is performed to detect early-stage cancer and X-ray imaging is performed to pick up PG-negative cancer, that is, cancer that will develop from the stomach with mild atrophic gastritis. With this method, the results of PG testing should ideally be available quickly so that X-ray imaging can be performed on the same day if necessary. Third, as the Alternative Method, PG testing and X-ray imaging are performed on alternative years. This method is not useful for dynamic populations, such as regional screenings in big cities, but is useful for static populations, such as in the workplace in our country. Finally, the last one is the Single PG Method. This method does not include barium X-ray screening, and the cancer screening can be combined with a general health check-up that can be carried out by analyzing blood samples. However, as described above, there does exist PG-negative gastric cancer accounting for about 30-40% of total gastric cancer, and these cancers easily escape diagnosis by the serum tests. Nonetheless, this method is useful for encouraging people to undergo gastric cancer screenings in areas where the number of people receiving the conventional cancer screening remains relatively constant. This method may also be useful as part of the screening programs that are carried out for patients 30 years old and every 5-10 years thereafter, such as the screening carried out by the municipal government in our country.

Actual State of Gastric Cancer Screening Utilizing Serum PG Testing

Of the above four methods, we have developed a gastric cancer screening program that concurrently performs PG testing and barium digital radiography (DR), and have conducted research to establish an efficient gastric cancer screening program (28). In other words, over a period of 7 years from 1995 to 2002, a total of 17,647 men with a

Figure 3. Pepsinogen test procedures.

mean age of 50.4 ± 5.4 years (range, 40-60 years) received gastric cancer screenings at their workplaces. In the primary screening, serum PG testing and barium X-ray with DR were combined, and if either or both of the two screening methods were positive, the subject was further screened by upper gastrointestinal endoscopy. Serum PG levels were measured by radioimmunoassay (RIA) (29). After taking into account the manpower necessary for gastroscopy, the cutoff values for the PG test were set at $\text{PGI} \leq 50 \mu\text{g/l}$ and $\text{PGI/II ratio} \leq 3.0$; these criteria give a positive rate of approximately 20% in all subjects. The detection rate of gastric cancer during the observation period was 0.28%, markedly higher than that by conventional barium X-ray with photofluorography (0.1%) (30), clarifying that this concurrent method more efficiently detects gastric cancer than the conventional screening method. Of the gastric cancers detected, 63.3% were PG-positive and 69.4% were DR-positive, but only 32.7% were both PG- and DR-positive. Of the gastric cancers detected, 88% were early-stage gastric cancer. Early-stage cancer accounted for 100% of cancers detected by PG, 83% of cancers detected by DR, and 81% of cancers detected by both PG and DR. In addition, the size of cancer detected by PG was significantly smaller than that detected by DR, and 89% of these cancers were intramucosal tumors. Conversely, intramucosal cancers only accounted for about half of the cancers detected by DR. Pepsinogen testing is thus useful in detecting small cancers arising from atrophic gastric mucosa, which macroscopically tend to be elevated and histologically differentiated. As a result, the method is superior for detecting early-stage cancer. All tumors were completely removed by surgery or endoscopic mucosal resection (EMR). The latter procedure is particularly suited for small, differentiated mucosal cancer (especially elevated types) (31). In fact, 44% of cancers detected by PG were treated by EMR, and this figure was higher when compared to the other groups (DR, 22%; Combined, 12%). In this manner, PG testing greatly improves the quality of life of patients, because gastric cancer can be

detected in the early stages. In addition, the cost for the detection of a single cancer case was much less than that for conventional screening (¥4,408,543 [\$37,360] by conventional screening vs. ¥2,275,387 [\$19,282] by PG testing). Figure 4 shows an example of early-stage gastric cancer as detected by PG or DR. In a PG-negative DR-positive patient (case A), a 10-mm type IIc + III lesion was located in the lesser curvature of the gastric angle. Partial gastrectomy was then performed and histopathological examination of the excised tissue specimen showed diffuse-type mucosal cancer. In a PG-positive DR-negative patient (case B), endoscopy revealed an 8-mm IIa lesion in the lesser curvature of the proximal antrum, and histological analysis of a biopsy specimen showed intestinal-type mucosal cancer. The cancer was subsequently removed by EMR. Both patients were asymptomatic, and it is noteworthy to add that if only PG or DR had been performed, these lesions could have been missed. Because PG and DR detect gastric cancer based on different clinicopathological mechanisms, a combination of the two methods can improve the efficacy of screening and may lower the mortality rate for gastric cancer in the long run. To further refine this screening program, studies should be done to ascertain how and on which groups of subjects the two tests should be performed.

Gastric Cancer Screening Based on Individual Cancer Risk

Over a period of about 8 years, we followed about 5,000 middle-aged men to ascertain the significance of atrophic gastritis as a risk factor for gastric cancer in relation to *Helicobacter pylori* (HP) infection (32). *H. pylori* infection was assessed based on serum anti-HP IgG antibody, while advancements in chronic atrophic gastritis were assessed based on the PG test; test-positive criteria were $\text{PGI} \leq 70 \mu\text{g/l}$ and $\text{PGI/II ratio} \leq 3.0$. Furthermore, based on the results of both tests, the subjects were divided into four groups according to the severity of chronic atrophic gastritis: Group A, HP(-)

Figure 4. Representative stomach cancers detected by gastric cancer screening. Case A: DR-positive and PG-negative 10-mm type IIc + III lesion located in the lesser curvature of the gastric angle. Serum PGI was 44.6 $\mu\text{g/l}$ and the PG I/II ratio was 3.3. Case B: DR-negative and PG-positive 8-mm type IIa lesion located in the lesser curvature of the proximal antrum as indicated by the arrowheads. Serum PGI was 39.5 $\mu\text{g/l}$ and the PG I/II ratio was 1.

	Group A	Group B	Group C	Group D
	HP(-) PG(-)	HP(+) PG (-)	HP(+) PG(+)	HP(-) PG(+)

Annual incidence of stomach cancer	0%	Approximately 0.1%	Approximately 0.25%	Approximately 1%
Ratio to total population	20%	50%	30%	0.7%
Screening method	Possible to exclude from stomach cancer screening	X-ray imaging	Endoscopy	

Figure 5. Improving the efficiency of gastric cancer screening. Hp: serum anti-*H.pylori* antibody; Pg: serum pepsinogen. * excluding eradicated cases.

PG(-); Group B, HP(+) PG(-); Group C, HP(+) PG(+); and Group D, HP(-) PG(+). In other words, Group A included subjects who were without HP infection and with healthy stomach, Group B included subjects with HP infection but without atrophic gastritis, Group C included subjects who had atrophic gastritis induced by HP infection, and Group D included subjects with extensive atrophic gastritis together with widespread intestinal metaplasia, which led to a reduction in HP load in the stomach and finally to spontaneous eradication. Thus, group D comprised a group of subjects with metaplastic gastritis (Fig. 5). The annual incidence of gastric cancer in Group A was 0%, in Group B 0.1%, in Group C 0.25%, and in Group D 1%, and the hazards ratio of gastric cancer significantly increased with the progression of gastritis (32). The results also clarified that gastric cancer was extremely rare in Group A (subjects with healthy stomachs and without HP infection). While further investigations are needed, Group A may be excluded from gastric cancer

screening. In other words, the efficacy of gastric cancer screening can be improved by testing only Groups B-D. Because double contrast barium X-ray is efficient at detecting lesions with a depressed or ulcerated morphology (33, 34), we believe that barium X-ray should be performed on Group B subjects, in which acid secretion is not reduced and cancerous lesions tend to be depressed or ulcerated (35, 36). In contrast, endoscopy should be performed on Groups C and D (high-risk groups), in which acid secretion is reduced and the cancers tend to have elevated morphology (35, 36).

These findings suggest that, in the future, gastric cancer screening should be performed after assessing individual cancer risk based on the combination of serum PG levels and HP antibody. Needless to say, highly sensitive radiography such as DR will improve the efficiency of gastric cancer screening.

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