Gastric Cancer (2013) 16:280–281
DOI 10.1007/s10120-012-0199-5

EDITORIAL

Can a serological test for selecting high-risk groups before endoscopy reduce gastric cancer deaths?

Osamu Hosokawa

Published online: 28 September 2012

Each year 700,000 patients die from gastric cancer around the world. The incidence of gastric cancer death varies among countries and populations. East Asia, Eastern Europe, and parts of Central and South America have higher gastric cancer death rates. For advanced disease, operation combined with chemotherapy using new drugs has become the standard treatment in all countries. However, the prognosis still remains poor and, therefore, early detection and early treatment via screening are considered useful strategies to reduce gastric cancer death rates. An efficient and cost-effective practical mass screening method is necessary. The majority of countries, even those with high rates of the disease, have no national guidelines or recommendations for gastric cancer screening. A mass screening method for gastric cancer is used in only two countries, Japan and Korea.

In Japan, population screening with X-ray examination began in 1964. More than six million individuals annually participate in the organized X-ray screening programs and about six thousand patients with gastric cancer have been diagnosed via the screening. A meta-analysis of three case–control studies showed that X-ray screening resulted in reduced mortality from gastric cancer. Japanese guidelines [1] were established in 2006 and recommended population gastric cancer screening using X-ray. In 1999, Korea began screening for gastric cancer as a part of the National Cancer Screening Program. The program recommends biennial upper gastrointestinal (GI) X-ray or upper endoscopic gastric cancer screening for men and women older than 40 years. Between 2002 and 2004, 1,503,646 people took part in the program. Of those, 71 % were screened using upper GI X-ray and 29 % were screened with endoscopy [2]. The probability of detecting gastric cancer via endoscopic screening was more than twofold higher than that via X-ray screening. Moreover, the tumors in the endoscopic group were detected earlier than those in the X-ray group. Endoscopic examinations accounted for a considerable number of screenings in the Korean screening program, but these examinations were used in only 4 % of screenings in Japan.

The first reason why endoscopic screening was not widely used in Japan was the absence of published studies that evaluated the efficacy of endoscopic screening in terms of mortality reduction. The Japanese guidelines [1] did not recommend endoscopy as a method for population screening instead of X-ray examination. In a previous study [3], we compared two screening methods and found that the mortality rate from gastric cancer was lower in the endoscopy group compared with that in the X-ray group, indicated by the hazard ratio of 0.23, adjusted for sex and age. It is thought that the problem of endoscopy versus X-ray as the best means of screening would have already been solved. Secondly, despite the diagnostic advantages of endoscopy, it is more expensive and requires more staff and technological expertise than X-ray screening. In financial terms, endoscopic screening is not as effective if the cost is high.

In the process of gastric carcinogenesis, especially that of intestinal-type gastric carcinomas, it has been proposed that the gastric mucosa evolves through the stages of mucosal atrophy and then intestinal metaplasia before developing into gastric cancer. Serum pepsinogen was thought of as a biomarker of gastric mucosal status. Pepsinogen can be used in the diagnosis of advanced atrophic

This editorial refers to the article doi:10.1007/s10120-012-0185-y.

O. Hosokawa (✉)
Yokohama Sakae Kyosai Hospital, Federation of National Public Service Personnel Mutual Associations, Yokohama, Japan
e-mail: osa.hosokawa@gmail.com

gastritis, and its presence is a high risk factor for gastric cancer and may be useful in gastric cancer screening. In population screening for gastric cancer, its use would reduce the number of endoscopy candidates by selecting only those at high risk of gastric cancer. Pepsinogen testing before endoscopy might be attractive as a method to reduce costs in population screening.

However, several factors affect the efficacy of pepsinogen tests as a biomarker of gastric cancer, including *Helicobacter pylori* infection, gender, the histological type of gastric cancer, and the distribution of the gastric cancer. The pepsinogen test results differ before and after *H. pylori* eradiation. It was reported that pepsinogen test results changed from positive to negative in 80 % of pepsinogen test-positive cases following successful eradication of *H. pylori*. Also, the efficacy of pepsinogen testing was found to be different between the genders. It is known that the risk of gastric cancer increased significantly at a lower level of the serum pepsinogen test for men (positive level) than for women (strong-positive level). It might be preferable to vary the cutoff level according to sex. When cancer was separated into two groups by histological type, intestinal and diffuse, a significant association between the serum pepsinogen level and gastric cancer held true for the intestinal type of cancer only. The proportion of patients with diffuse-type gastric cancer in Korean patients was higher than that in Japanese patients. The efficacy of pepsinogen testing might also be lower in regions or countries where diffuse type is the dominant gastric cancer type. When gastric cancer is divided into cardiac and non-cardiac cancer, pepsinogen testing is useful only in non-cardiac cancer. It has also been reported that smoking elevates pepsinogen levels and drinking reduces pepsinogen levels.

In this issue of *Gastric Cancer*, Kaise et al. [4] report that serum levels of trefoil factor 3 (TFF3) peptides are a better marker of gastric cancer than pepsinogen. TFF peptides are involved in mucosal maintenance and repair through motogenic and antiapoptotic activities. These peptides are overexpressed during inflammatory processes and cancer progression. The TFF family comprises the gastric peptides pS2/TFF1 and spasmolytic peptide (SP)/TFF2, and the intestinal trefoil factor (ITF)/TFF3. The authors found a significant difference in serum TFF3 levels between *H. pylori* antibody-positive and -negative healthy individuals. However, in gastric ulcer patients stratified by *H. pylori* eradication, they did not find significant differences in serum TFF3 levels or in positivity for high TFF3 levels until 5 years after the *H. pylori* eradication. The authors suggested that serum TFF3 could be a stable biomarker of gastric cancer risk even after *H. pylori* eradication, in contrast with pepsinogen testing. However, not much is known about this peptide. TFF3 is secreted from goblet cells in gastric intestinal metaplasia, and from cells in the intestine and colon. It is thought that TFF3 produced in the stomach would increase serum levels due to damage and inflammation from gastritis. However, because the area of the intestine and colon is far larger than that of gastric intestinal metaplasia, many questions concerning TFF3 have been raised. As the serum TFF3 level also reflects the potential presence of other cancers; for example, pancreatic cancer, an elevated level is not specific for gastric cancer.

In 1982, Samloff et al. [5] proposed that pepsinogen testing could be a useful, noninvasive "serological biopsy" for detecting gastric cancer. Thirty years have passed since this proposal, but the effectiveness of pepsinogen testing has not been proven in population screening for gastric cancer. We have found no satisfactory evidence of a decreased death rate due to gastric cancer linked to the use of this serological test. Since 1990, the first-line method of examination for gastric disease in Japanese medical facilities has been endoscopy rather than X-ray. The use of X-ray examinations has decreased because of the difficulties in educating practitioners about image interpretation and in making diagnoses without the assistance of pathologists. As a result, the cancer detection rate using direct X-ray examination has continued to decrease since 2000 in the Japanese population screening program. The future of X-ray screening is questionable. A changeover is necessary, but it is uncertain whether screening using serological tests, serum pepsinogen, and/or TFF3 before endoscopy can replace X-ray screening in the near future. Apart from the low positive predictive value of serological tests, the problem would be the low percentage of examinees that would undergo detailed examinations, because the discrepancy in numbers from those who would take the first step, blood tests, to those taking the second step, endoscopies, would be large.

References

1. Hamashima C, Shibuya D, Yamazaki H, Inoue K, Fukao A, Saito H, Sobue T. The Japanese guidelines for gastric cancer screening. Jpn J Clin Oncol. 2008;38:259–67.
2. Lee HY, Park EC, Jun JK, Choi KS, Hahm MI. Comparing upper gastrointestinal X-ray and endoscopy for gastric cancer diagnosis in Korea. World J Gastroenterol. 2010;16:245–50.
3. Hosokawa O, Shimbo T, Matsuda K, Miyanaga T. Effectiveness of opportunistic endoscopic screening for gastric cancer compared with organized X-ray screening. J Gastroenterol Cancer Screen. 2011;49:401–7.
4. Kaise M, Miwa J, Fujimoto A, Tashiro J, Tagami D, Sano H, Ohmoto Y. Influence of *Helicobacter pylori* status and eradication on the serum levels of trefoil factors and pepsinogen test–serum trefoil factor 3 is a stable biomarker. Gastric Cancer. 2012;. doi: 10.1007/s10120-012-0185-y.
5. Samloff IM, Varis K, Ihamaki T, Siurala M, Rotter JI. Relationships among serum pepsinogen I, serum pepsinogen II, and gastric mucosal histology. A study in relatives of patients with pernicious anemia. Gastroenterology. 1982;83:204–9.