Published in final edited form as:
Dig Dis Sci. 2010 August ; 55(8): 2123–2125. doi:10.1007/s10620-010-1248-8.

Serum Pepsinogens in Gastric Cancer Screening

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Background and Significance

Approximately one million new cases of gastric cancer are expected in 2010 worldwide. This disease is the second most frequent cause of cancer deaths [1]. In most countries, the tumors are detected when the invasion of the muscularis propria has taken place and the prognosis is dismal, even after gastrectomy and chemotherapy, with 5-year survival rates around 20% [1]. If the tumors are diagnosed when limited to the mucosa and submucosa, so called “early” cancers, the 5-year survival rate is over 90% [2, 3]. In Japan, extensive screening programs taking advantage of abundant endoscopic resources and superb expertise, including the use of serum pepsinogen (PG) tests, have succeeded in diagnosing the majority of gastric cancers in their early stages [4]. Screening programs have led to an overall 5-year survival rate for gastric cancer in Japan of 40-60% [5]. Such resources are not available in most Western countries. In South Korea, with some of the highest incidence and mortality rates in the world, biannual endoscopy is recommended for every subject over 40 years of age. Such a program is very expensive and logistically problematic. The article by Kwak et al. [6] from Seoul University and Bundang Hospital published in this issue examined the association between serum pepsinogen (PG) levels and gastric cancer in a large series of cases and controls. The efficacy of gastric cancer screening utilizing PG tests can be measured with two types of studies: (1) case-control studies; (2) prospective longitudinal studies of cancer-free populations, generally as part of health screening programs, which are less susceptible to bias than case–control studies.

Gastric cancer of the intestinal type is usually preceded by a decades-long precancerous process driven by *Helicobacter pylori* infection with well-defined successive lesions. In the advanced stages, they are characterized by glandular atrophy and intestinal metaplasia [7]. These changes involve loss of the original glands and result in decrease of the mass of chief cells of the gastric corpus, where PGI is produced. Loss of chief cells leads to lower PGI levels and PGI/PGII ratio in the peripheral blood. Samloff et al. [8] proposed that such tests could be considered a noninvasive “serological biopsy,” reflecting the functional status of the gastric mucosa. The atrophic/metaplastic changes become more extensive with age. The extension of the atrophic changes is a good indicator of gastric cancer risk [9, 10]. Serum PG levels are therefore a key tool to be used in screening programs. The potential usefulness of serum PG tests has been documented in many countries such as Japan, China, Italy, Sweden, Finland, Portugal, Costa Rica, Mexico and others [4, 11–17]. However, such abundance of evidence in favor of its use has not resulted in generalized use of PG tests in identifying advanced gastric atrophy in gastric cancer screening and prevention [10, 18].

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The article by Kwak et al. [6] compares the results of the PG test with the histopathology index developed in a German population by Meining et al. [19]. This index was based on the comparison of lesions of the gastric mucosa in patients with gastric carcinoma as opposed to those seen in patients with duodenal ulcer. Gastric cancer patients display multifocal atrophic gastritis (MAG), a well-characterized nosological entity with foci of atrophy and metaplasia starting in the antrum-corpus junction and extending with time to the neighboring mucosa of the antrum and the corpus [20]. By contrast, duodenal ulcer patients display chronic active non-atrophic gastritis (NAG) limited to the antrum, without gland loss, atrophy or metaplasia. MAG and NAG are mutually exclusive entities [21]. Therefore, Meining et al. were documenting lesions of two separate nosologic entities. It would then appear that the reported association between PG levels and Meining's index is coincidental and does not address the issue of detecting patients at high risk in the general population.

PG tests are not perfect. They are useful as screening tests for the detection of subjects at high risk of gastric cancer with atrophic gastritis, rather than for screening for cancer itself. They reflect the degree of atrophy of the gastric corpus mucosa but will not be of much value to evaluate atrophy limited to the gastric antrum mucosa, a frequent component of the gastric precancerous process. That explains the findings of normal PGI values in some patients with overt gastric carcinoma [22]. In addition, the serum PG method seems to be of higher value in predicting gastric cancer of the intestinal type than the diffuse type [23]. Most patients with intestinal-type gastric adenocarcinoma display advanced MAG, including atrophic changes extending to the corpus mucosa, reflected in low PGI levels. Several cut-off points have been used for the PG tests to evaluate gastric cancer risk: (a) PGI ≤ 70 and PGI/II ratio ≤ 3.0, recommended by Miki et al. [3] and widely accepted in Japan, with a sensitivity of 77% and specificity of 73% [11]; (b) PGI ≤ 50 and PGI/II ratio ≤ 3.0; and (c) PGI ≤ 30 and PGI/II ratio ≤ 2.0. The last cut-off points reflect the most severe atrophy and therefore the greater cancer risk, with a sensitivity of 37% and a specificity of 96% [14].

Antral atrophy should be reflected in gastrin 17 (G17) serum levels because G17 is mainly secreted by antral glands. Published results are somewhat inconsistent and indicate that serum G17 as a marker of antral atrophy needs more evaluation [24]. G17 is unstable in serum, requires previous use of stabilizing solutions and previous protein food stimulation. If such technical difficulties are resolved, G17 could become a useful test of gastric antrum atrophy, a cancer precursor.

Summary and Future Directions

The study by Kwak et al. published in this issue shows the association between serum PG levels and gastric cancer in a Korean population. Prospective cohort studies including cancer-free populations with risk factors for gastric cancer are needed for evaluating the validity of PG tests in reducing the mortality by gastric cancer. PG testing of subjects suspected to be at high risk because of their age, family history, geographic origin or symptoms of epigastric discomfort could be useful. Detection of gastric cancer at an early stage is the only real hope of controlling this major health burden worldwide.

References

1. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin. 2005; 55:74–108. [PubMed: 15761078]
2. Saka M, Katai H, Fukagawa T, Nijjar R, Sano T. Recurrence in early gastric cancer with lymph node metastasis. Gastric Cancer. 2008; 11:214–218. [PubMed: 19132483]
3. Miki K. Gastric cancer screening using the serum pepsinogen test method. Gastric Cancer. 2006; 9:245–253. [PubMed: 17235625]

4. Miki K, Fujishiro M, Kodashima S, Yahagi N. Long-term results of gastric cancer screening using the serum pepsinogen test method among an asymptomatic middle-aged Japanese population. Dig Endosc. 2009; 21:78–81. [PubMed: 19691778]
5. Inoue M, Tsugane S. Epidemiology of gastric cancer in Japan. Postgrad Med J. 2005; 81:419–424. [PubMed: 15998815]
6. Kwak MS, Kim N, Lee HS, Lee HE, Jung HC, Song IS. Predictive power of serum pepsinogen tests for the development of gastric cancer in comparison to the histologic risk index. Dig Dis Sci. 201010.1007/s10620-010-1181-x
7. Correa P, Haenszel W, Cuello C, Tannenbaum S, Archer M. A model for gastric cancer epidemiology. Lancet. 1975; 2:58–60. [PubMed: 49653]
8. 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; 83:204–209. [PubMed: 7084603]
9. Ohata H, Kitauchi S, Yoshimura N, et al. Progression of chronic atrophic gastritis associated with *Helicobacter pylori* infection increases risk of gastric cancer. Int J Cancer. 2004; 109:138–143. [PubMed: 14735480]
10. Tava F, Luinetti O, Ghigna MR, et al. Type or extension of intestinal metaplasia and immature/atypical “indefinite-for-dysplasia” lesions as predictors of gastric neoplasia. Hum Pathol. 2006; 37:1489–1497. [PubMed: 16949645]
11. Dinis-Ribeiro M, Yamaki G, Miki K, Costa-Pereira A, Matsukawa M, Kurihara M. Meta-analysis on the validity of pepsinogen test for gastric carcinoma, dysplasia or chronic atrophic gastritis screening. J Med Screen. 2004; 11:141–147. [PubMed: 15333273]
12. Ren JS, Kamangar F, Qiao YL, et al. Serum pepsinogens and risk of gastric and oesophageal cancers in the general population nutrition intervention trial cohort. Gut. 2009; 58:636–642. [PubMed: 19136509]
13. Storskrubb T, Aro P, Ronkainen J, et al. Serum biomarkers provide an accurate method for diagnosis of atrophic gastritis in a general population: the Kalixanda study. Scand J Gastroenterol. 2008; 43:1448–1455. [PubMed: 18663663]
14. Mizuno S, Kobayashi M, Tomita S, et al. Validation of the pepsinogen test method for gastric cancer screening using a follow-up study. Gastric Cancer. 2009; 12:158–163. [PubMed: 19890696]
15. Mizuno S, Miki I, Ishida T, et al. Prescreening of a high-risk group for gastric cancer by serologically determined *Helicobacter pylori* infection and atrophic gastritis. Dig Dis Sci. 201010.1007/s10620-010-1154-0
16. di Mario F, Cavallaro LG. Non-invasive tests in gastric diseases. Dig Liver Dis. 2008; 40:523–530. [PubMed: 18439884]
17. Con SA, Con-Wong R, Con-Chin GR, et al. Serum pepsinogen levels, *Helicobacter pylori* CagA Status, and cytokine gene polymorphisms associated with gastric premalignant lesions in Costa Rica. Cancer Epidemiol Biomarkers Prev. 2007; 16:2631–2636. [PubMed: 18086767]
18. Correa P, Piazuelo MB, Wilson K. Pathology of gastric intestinal metaplasia: clinical implications. Am J Gastroenterol. 2010; 105:493–498. [PubMed: 20203636]
19. Meining A, Bayerdörffer E, Müller P, et al. Gastric carcinoma risk index in patients infected with *Helicobacter pylori*. Virchows Arch. 1998; 432:311–314. [PubMed: 9565339]
20. Correa P, Cuello C, Duque E. Carcinoma and intestinal metaplasia of the stomach in Colombian migrants. J Natl Cancer Inst. 1970; 44:297–306. [PubMed: 11515071]
21. Dixon MF, Genta RM, Yardley JH, Correa P. Classification and grading of gastritis. The updated Sydney system. International workshop on the histopathology of gastritis, Houston 1994. Am J Surg Pathol. 1996; 20:1161–1181. [PubMed: 8827022]
22. Varis K, Sipponen P, Laxen F, et al. Implications of serum pepsinogen I in early endoscopic diagnosis of gastric cancer and dysplasia. Helsinki gastritis study group. Scand J Gastroenterol. 2000; 35:950–956. [PubMed: 11063155]
23. Oishi Y, Kiyohara Y, Kubo M, et al. The serum pepsinogen test as a predictor of gastric cancer: the Hisayama study. Am J Epidemiol. 2006; 163:629–637. [PubMed: 16443800]

24. Leja M, Kupcinskas L, Funka K, et al. The validity of a biomarker method for indirect detection of gastric mucosal atrophy versus standard histopathology. Dig Dis Sci. 2009; 54:2377–2384. [PubMed: 19731026]