Review Article

Gastric Cancer Screening by Combined Determination of Serum *Helicobacter pylori* Antibody and Pepsinogen Concentrations: ABC Method for Gastric Cancer Screening

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Abstract

Objective: Gastroscopy combined with gastric mucosa biopsies is currently regarded as a gold standard for diagnosis of gastric cancer. However, its application is restricted in clinical practice due to its invasive property. A new noninvasive population screening process combining the assay of anti-*Helicobacter pylori* antibody and serum pepsinogen (PG) (ABC method) is adopted to recognize the high-risk patients for further endoscopy examination, avoiding the unnecessary gastroscopy for most population and saving the cost consumption for mass screening annually. Nevertheless, controversies exist for the grouping of ABC method and the intervals of gastroscopy surveillance for each group. In this review, we summarized these popular concerned topics for providing useful references to the healthcare practitioner in clinical practice.

Data Sources: The PubMed databases were systematically searched from the inception dates to November 22, 2017, using the keywords "*Helicobacter pylori,*" "Pepsinogens," and "Stomach Neoplasms."

Study Selection: Original articles and reviews on the topics were selected.

Results: Anti-*H. pylori* antibody and serum PG concentration showed significant changes under the different status of *H. pylori* infection and the progression of atrophic gastritis, which can be used for risk stratification of gastric cancer in clinic. In addition, anti-*H. pylori* antibody titer can be used for further risk stratification of gastric cancer contributing to determine better endoscopy surveillance interval.

Conclusions: The early detection and diagnosis of gastric cancer benefit from the risk stratification, but the cutoff values for *H. pylori* antibody and serum PG concentration require further modification.

Key words: Gastroscopy Surveillance; *Helicobacter pylori* Antibody; Pepsinogens; Risk Stratification; Stomach Neoplasms

Introduction

Gastric cancer is still the leading cause of cancer-related deaths all over the world, especially in the countries of East Asia, such as Japan and China.[1-3] Correa[4] pointed out that the human gastric carcinogenesis is a slow progressive, multistep, and multifactorial pathology process. The multistep process is composed of chronic superficial gastritis, atrophy gastritis, intestinal metaplasia (IM), dysplasia, and adenocarcinoma.[5] Pathologically, gastric cancer is divided as intestinal type or diffuse type according to Lauren's classification.[6] Similarly, multifactorial process involves *Helicobacter pylori* infection and excessive ingestion of salt and nitrate.[7] Two significant risk factors of *H. pylori* infection and atrophic gastritis are considered to contribute to the development and deterioration of gastric cancer.[8,9] What's worse, the most patients with gastric cancer at early stage (EGC) are insidious and asymptomatic.[10] Due to

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lack of standardized screening system, many patients were advanced to the late stage of gastric carcinoma even at the time the endoscopy was first performed in clinical setting. At that time, the prognosis becomes very poor and the 5-year survival rate after surgery is only 20–30% compared with 90% in patient with EGC.[11] Therefore, it is important to establish an efficient and better cost-effective screening method for early detection of gastric cancer in regular mass survey.[12]

Compare to any other country in the world, as a high risk nation of gastric cancer, Japan has established a relatively better screening system and shown the obvious achievements.[13,14] In Japan, a gastric cancer screening program, named photofluorography, was launched in 1960.[15] Together with other traditional screening methods including double-contrast barium X-rays or panendoscopy, it has been wildly adopted throughout the country.[16] However, these traditional methods leave much more to be desired. They require further efforts in aspects of detection rate and economic cost improvement.[17]

Gastroscopy in combination with gastric mucosa biopsies is regarded as a gold standard model for diagnosis of gastric cancer.[18] However, it is hesitantly accepted by patients because it is an invasive procedure and may induce the discomfort. In addition, it is not suitable for large-scale survey as well due to the high cost consumption. On the contrary, it is advisable to make the risk stratification for gastric cancer first by other noninvasive tests. In recent years, a number of noninvasive diagnosis tests are developed, such as reevaluation of conventional serum markers, new biomarkers, circulating tumor cell and cell-free nucleic acids, tumor-associated autoantibodies, and exhaled breath analysis.[19] A new mass screening named ABC method which incorporates the assay of *H. pylori* antibody and serum pepsinogen (PG) has been implemented in Nishitokyo city from 2011 on the initiative of Nishitokyo Medical Association.[20] In comparison of the conventional mass screening, the ABC method not only increases the EGC detection rate but also reduces the screening cost.[21-23]

Helicobacter pylori Infection

Discovered by Marshall and Warren in 1982, *H. pylori* is regarded as a strong cancerogen and a trigger of gastric cancer cascade.[24] Approximately 70% of gastric cancers are related to *H. pylori* infection which is called *H. pylori*-positive gastric cancer (HPPGC), while about 30% of gastric cancers are not correlated with *H. pylori*, called *H. pylori*-negative gastric cancer (HPNGC), but in association with the factors of demographic feature, life style, Epstein-Barr virus infection, and so on.[25,26] Actually, the proportion of HPNGC varied from 10% to 40% among GC in the literatures,[27-29] because of the prevalence and the differences in the definition of *H. pylori* status. For example, Tsai *et al*.[25] reported that the posteradicated patients may have negative tests for *H. pylori* and Yoon *et al*.[28] proposed that as progression of gastric atrophy and IM drives *H. pylori* out of the gastric mucosa, the possibility of false-negative *H. pylori* test results could significantly increase resulting in the different proportion of HPNGC. In other word, 70% of gastric cancer can be prevented potentially by removal of *H. pylori* infection.[30]

When infected by *H. pylori*, the bacteria can colonize the gastric mucosa and stimulate a series of inflammatory reactions.[31] The *H. pylori* antibody titers are related to the immune response intensity of each host and the density of *H. pylori* colonization.[32] The stronger immune response is, the higher antibody titers are. However, the controversy is raised whether immune suppression in advanced cancer impacts the titers of antibody.[33] The relationship between antibody titer and the density of *H. pylori* colonization is clear.[32] The titer of *H. pylori* antibody is significantly declined when the bacteria are successfully eradicated or spontaneously subsided.[34] Accordingly, *H. pylori* antibody titer can be used to evaluate the density of *H. pylori* colonization and the status of *H. pylori* infection. Patients with *H. pylori* antibody titer ≥10 U/ml (E-plate "Eiken" Hp antibody: enzyme immunoassay method) were categorized as the *H. pylori* infection-positive group based on manufacturer's recommended cutoff value, with 91.2% sensitivity and 97.4% specificity.[20]

Serum Pepsinogen

As an inactive precursor of pepsin, PG has two isoforms including PG I and PG II.[35] Both PG I and PG II are produced by the principal cells and mucous neck cells located at fundic glands, while PG II can be secreted by pyloric glands and Brunner's glands.[36,37] Approximately 99% PG secretes into the gastric cavity, only 1% enters into the bloodstream.[38,39] According to this concept, many previous studies advocated that the serum PG levels can represent the morphologic and functional status of gastric mucosa.[40,41] For example, in *H. pylori*-infected patients, with the progress of atrophic gastritis from the antrum to the corpus mucosa, the amount of PG I is considerably reduced or abolished owing to the damage of principal cells and parietal cells, while the level of serum PG II increases because the infiltration model of neutrophils and mononuclear cells is toward the upper stomach from the antrum.[38,39] One study concluded that PG II is independently associated with risk of gastric cancer.[42] This evidence indicated that the serum PG level was closely correlated with the progression of atrophic gastritis.[43] Meantime, it indirectly reflected the status of *H. pylori* infection as well.[44] It is widely accepted that patients with both serum PG I levels ≤70 ng/ml and PG I/II ratio ≤3.0 were classified as PG-seropositive type and all other situations were classified as PG-seronegative type, using a commercial RIA kit (PG I/II RIA bead kit; Dainabot Co., Tokyo, Japan) with 70.5% sensitivity and 97% specificity.[45-47]

Risk Stratification of Gastric Cancer with ABC Method

Several prospective studies have confirmed that the ABC method is an effective and convenient risk stratification pattern for gastric cancer through joint assay of *H. pylori* antibody and serum PG simultaneously.[45,48-51] By the aid of ABC method, patients are stratified into four categories: Group A [Hp(−)PG(−)], noninfected cases; Group B [Hp(+) PG(−)], free or mild chronic atrophic gastritis (CAG) with active or acute *H. pylori* infection; Group C [Hp(+) PG(+)], CAG with chronic inactive *H. pylori* infection; and Group D [Hp(−)PG(+)], severe CAG with extensive IM and spontaneous diminishment of *H. pylori* infection.[52] It is generally believed that the risk of gastric cancer is the highest in Group D, followed by Groups C, B, and A in order.[53] Thus, it is recommended that periodic endoscopic examination should be taken for patients in Group B, C, and D at the interval of 3, 2, and 1 year, respectively, except Group A.

Many studies considered previously *H. pylori* serology was a categorical variable only, either positive or negative. However, Kishikawa *et al*. proposed that *H. pylori* serology was not a categorical variable, it is a consecutive variable, such as the antibody titer levels.[52]

Kishikawa *et al*.[52] pointed out that the risk stratification of all patients within each group is actually different. They suggested that the severity of *H. pylori* infection should be divided into four subgroups based on the titers of IgG anti-*H. pylori* antibody: low negative (<3 U/ml), high negative (3–10 U/ml), low positive (10–50 U/ml), and high positive (>50 U/ml), respectively.

Infected by *H. pylori*, the bacteria can colonize in the gastric mucosa and stimulate a series of inflammatory reactions, which result to the development of atrophic gastritis and impair the gastric secret function. It is generally believed that the eradication of *H. pylori* can reduce the risk of subsequent cancer development. However, it is unclear whether a critical irreversible point exists during the development of gastric cancer. CAG is considered as the first step in the process of gastric mucosal degeneration. When the disease progresses, the gastric intra-environment eventually becomes inhospitable for the bacteria survival, resulting in *H. pylori* diminished spontaneously. Nevertheless, it should be noticed that severe CAG and IM may be an irreversible gastric mucosal changes despite whether *H. pylori* is eradicated or not.[54,55] Therefore, it is quite important to eliminate *H. pylori* infection before the irreversible changes occur, in particular for the patients in Group C and D.[56,57]

Group A: [Hp(−)PG(−)]

Theoretically, patients in Group A (*H. pylori* antibody titer <10 U/ml, PG I >70 ng/ml or I/II ratio >3) have no history of *H. pylori* infection in fact. It is considered as the lowest risk group for gastric cancer development and is excluded from regular endoscopy requirement.[45] In *H. pylori*-noninfected cases, the function of the gastric mucosal remains intact, whereas the PG I secretion and PG II secretion increase because of inflammation of gastric mucosal.[58] The intragastric environment becomes hyperacidity, leading to the appearance of gastritis commonly seen under endoscopy, including chronic superficial gastritis and erosive gastritis. The endoscopic findings in this group include the exhibitions of regular configuration of collecting venules under gastric mucosa.[58] Chronic superficial gastritis may show several hyperemic strips at greater curvature side of antrum.[58] Erosive gastritis may present with multiple hyperemic erosions on the antrum.[58] These characteristics of gastric mucosa alterations are also observed in Group B.

However, some studies reported that about 2–10% cases of gastric cancer were classified into Group A. Although 30% cases of gastric cancer were not correlated with *H. pylori* infection (called HPNGC[25,29]), it was possible that patients had taken the eradicative treatment for *H. pylori* before, whether it was intentional or unintentional. The patients were then misclassified to Group A because of the negative *H. pylori* antibody. Actually, Group A can be subdivided into two subtypes. One is true *H. pylori* infection-negative cases and the other one is infection-positive case, but the bacteria were successfully eradicated. A study[29] once reported that in 345 patients classified to Group A by ABC method, 10 cases were found suffering from gastric neoplasia (gastric cancer and adenoma). This study suggested that patients who were classified as Group A by ABC method, with *H. pylori* antibody titer ≥3 U/ml and a PG I/II ratio ≤4.3, should take the endoscopic examination. As pointed out by Kishikawa *et al*.,[52] patients with high-negative antibody in a Subgroup A were considered as the posteradicated cases. These patients possess elevated risk for developing of intestinal-type gastric cancer.[59,60] Besides, some studies considered that the risk for gastric cancer in these patients is comparable to those in Group non-A.[61] Moreover, the patients with high-negative antibody in Group A are strongly recommended to have the reevaluation by other assays.[62] If the result is positive, the patients should receive the antibiotic therapy. Hence, a high-negative *H. pylori* antibody may be helpful to distinguish these patients from others in Group A. These patients need a careful follow-up at the interval of 3 years.[52,63]

Group B: [Hp(+)PG(−)]

Patients with active or acute *H. pylori* infection in Group B (*H. pylori* antibody titer ≥10 U/ml, PG I >70 ng/ml or I/II ratio >3) usually show an increased risk of diffuse gastric cancer. It is recommended to take the regular endoscopy for these patients every 3 years. Typical endoscopic findings in this group include antrum nodules, hemorrhagic spots on the fundus, and thickened gastric folds.[58] The excretory function of gastric mucosa cells remains intact, no matter they were actively infected or not. The PG secretion increases, especially PG II, which was a good

marker for active *H. pylori* infection in stomach.[38,39] In addition, the intragastric environment becomes more acid due to inflammation. Therefore, at the stage with progressive deterioration of *H. pylori* infection, it is strongly recommended to eradicate the bacteria before the occurrence of irreversible lesions in stomach. In the study of Watanabe *et al*.,[64] no cancer development was observed in this group after *H. pylori* eradication. Although there is no significant progression of gastric mucosa damage in Group B, the high-positive antibody indicates the progressive mucosal inflammation, which has a higher risk for diffuse cancer in comparison to the patients with low-positive antibody titer.[52] Consequently, it is recommended that for the patients with high-positive antibody in Group B, endoscopic examination is required at the interval of each 2 years.[52]

Group C: [Hp(+)PG(+)]

Patients with chronic inactive *H. pylori* infection in Group C (*H. pylori* antibody titer ≥10 U/ml, and PG I ≤70 ng/ml, and I/II ratio ≤3) have an increased risk of intestinal-type gastric cancer. It is recommended to take a follow-up with regular endoscopy surveillance every 2 years. In patients with long-term *H. pylori* infection, the endoscopic findings show the appearance of atrophic gastritis, with or without IM extending from the gastric antrum toward the corpus and cardia. However, less atrophic and metaplastic damage were shown at the sites of greater curvature side of the upper corpus, where *H. pylori* can survive for the longest time before spontaneous regression.[58] According to the statistics, about 90% of new cases of noncardia gastric cancer worldwide are attributed to the infection of these bacteria.[65,66] With the evolution of atrophic lesion, the secretion of PG I and PG II decreases significantly and the intragastric environment becomes hypoacidic. Sung *et al*.[67] reported that the mean pH of gastric juice was higher in the *H. pylori*-positive group (n = 17) than that in the *H. pylori*-negative group (n = 29) (4.54 vs. 2.46, P = 0.002). Similarly, the amount of *H. pylori* was lower in the group at pH <3 (21.4%) than that in the group pH ≥3 (61.1%) (P = 0.007). Due to inhospitable survival environment, the amount and density of *H. pylori* are significantly reduced but still alive in the stomach, which result to the facts that although the titer of *H. pylori* antibody decreases, it remains at the level ≥10 U/ml. Thus, the low-positive antibody titer cases in Group C, representing advanced atrophy and/or metaplasia gastritis (MG), has a higher risk for intestinal-type cancer than the high-positive antibody titer ones. Thus, the patients in Group C require urgently the antibiotic treatment to eradicate *H. pylori* infection before reaching the irreversible stage.[68,69] After treatment, it is possible the test results both in histology and serology can return to normal ranges followed by the decrease of cancer risk correspondently.[70] Meanwhile, it has been reported that in some patients with severe corpus MG and low PG level, the damages were still reversible. At present, there is no consensus on the irreversible damage of stomach mucosa,[54,71] but regular endoscopic screening is necessary. The experts suggest that the annual endoscopy is required for the patients with low-positive antibody in Group C because the patients in Group D may originate from them who are with the spontaneous disappearance of *H. pylori* from the gastric mucosa.[52]

Group D: [Hp(−)PG(+)]

Patients with spontaneous regression of *H. pylori* in Group D (*H. pylori* antibody titer <10 U/ml, PG I ≤70 ng/ml and I/II ratio ≤3) are considered with the highest risk for intestinal-type gastric cancer.[72] It is recommended to take the careful follow-up and regular endoscopy surveillance annually. The endoscopic findings in this group are similar to those in Group C with low-positive antibody titer; however, it is more severe in patients with spontaneous diminishment of *H. pylori*.[58] In such advanced cases, most damage of gastric mucosa is irreversible, which will further develop into carcinoma in accordance with Correa's hypothesis. It is rare to diagnose the patients with extremely atrophy of gastric mucosa and spontaneously *H. pylori* vanishment. About 99% of *H. pylori*-infected patients are classified into Groups A, B, and C; only 1% patients are defined to Group D.[52] The separate reports by Miki[45] and Yoshida *et al*.[73] revealed that the individuals enrolled to Group D were merely 0.66% (33 of 5209 individuals) and 0.71% (33 of 4655 individuals), respectively. With spontaneous diminishment of *H. pylori*, gastric cancer in Group D also may be misclassified as HPNGC. According to the hypothesis of Correa's cancer progressive cascade, it indicates that no matter HPNGC or HPPGC, its development of gastric cancer must go through atrophic gastritis. In other words, according to the risk stratification of ABC method, before gastric cancer occurrence in these HPNGC patients, they may be allocated to Group A before gastric atrophy appearance or to Group D with gastric atrophy appearance. In addition, there is no particular prevention and treatment for HPNGC. But, no matter being allocated to Group A or to Group D according to the ABC method, all these patients are suggested to receive corresponding periodic endoscopy examination with different surveillance interval. Accordingly, HPNGC can be detected at the early stage and even receive corresponding intervention treatments during precancerosis. In Group D, the efficiency of antibiotic therapies is very limited.[74] However, effective therapy and regular endoscopy are vital to prevent the patients in other groups evolving to Group D before the disease reaches irreversible stage.

No matter HPPGC or HPNGC, the early detection rate and the prognosis can be improved using the risk stratification of ABC method, but in order to increase the risk stratification precision, it is suggested that combination with the histological change information of gastric mucosa is required to modify the cutoff values of *H. pylori* antibody and serum PG concentration in the future. Meanwhile, the level of anti-*H. pylori* antibody titer should be applied for further risk stratification of gastric cancer to determine

better endoscopy surveillance interval for different risk stratified groups.

Discussion

According to the hypothesis of Correa's cancer progressive cascade,[4] atrophic gastritis and IM are considered as preneoplastic gastric lesions, which will develop to dysplasia and adenocarcinoma spontaneously. With *H. pylori* infection, the bacteria can colonize in gastric mucosa and stimulate a series of inflammatory reactions, leading to the deterioration of atrophic gastritis and the impairment of gastric secretory function. CAG is considered as the first step of a sequence of mucosal changes in the stomach, which finally results to the changes of intragastric environment inhospitable for *H. pylori* survival. Therefore, *H. pylori* infection has an indirect association with gastric carcinogenesis via atrophic gastritis.[75] During this process, *H. pylori* antibody and serum PG concentration showed significant changes, which can be used for risk stratification of gastric cancer in clinic.[76-78]

Since gastric cancer is a potentially curable disease if diagnosed early, it is advisable to make risk stratification first for patients before taking invasive examinations such as gastroscopy, regardless in the disease high-incidence or low-incidence areas. A new mass screening named ABC method was developed for risk stratification of gastric cancer in Japan. However, the optimal PG cutoff value for atrophic gastritis remains controversial. The criteria of PG-seropositive levels (PG I ≤70 ng/ml, and PG I/II ratio of ≤3.0) proposed by Miki are widely accepted at present time. Nonetheless, Park *et al*.[48] disagreed because this criteria were only based on the data from endoscopy diagnosis for atrophic gastritis rather than histological information. In fact, the cytological changes of minor gastric atrophy appear before the morphological changes of stomach mucosa endoscopically. Therefore, the criteria proposed by Miki *et al*. seem hysteretic. In other word, the best PG cutoff value for gastric atrophy may be higher based on histological examination.

Furthermore, certain previous studies supported that *H. pylori* infection would impact on PG level.[79,80] The reliable PG cutoff values may differ from the differences of various bacteria infection status.[81,82] Park *et al*.[48] concluded that the optimal cutoff values of the PG I/PG II ratio for predicting gastric neoplasms were 3.1 for *H. pylori* antibody negative patients and 4.1 for *H. pylori* antibody positive patients.

For patients with *H. pylori* infection, it is urgent to take proper antibiotic treatment before the disease reaching the irreversible "critical point," particularly at the stage of chronic inactive *H. pylori* infection.[83-85] There is no standard available for the severity of CAG at the irreversible stage. Serum PG assay may be a good selection as PG level can indicate the severity of CAG and the efficancy of *H. pylori* eradication.[86-88] Osumi *et al*.[88] proposed that a significant increase of PG I/II ratio is a reliable biomarker for evaluation of successful *H. pylori* eradication, with 93.1% sensitivity and 93.8% specificity. Thus, further studies are required to define the optimal PG cutoff values of gastric atrophy on the basis of histology and a PG serum level on the irreversible stage of gastric mucosa impairment.

Based on the original ABC method, the risk of gastric cancer is the highest in Group D, followed by Groups C, B, and A consecutively.[89] Accordingly, it is recommended that patients in Groups B, C, and D requiring gastroscopy at the interval of each 3 years, 2 years and 1 year, respectively. Group A is excluded from endoscopic surveillance requirement because of unnecessary. However, further risk stratification by anti-*H. pylori* antibody titer was introduced for the early detection of gastric cancer. Kishikawa *et al*.[52] believed that the interval of endoscopic surveillance should be shorten, for instances, to every 3 years for patients with a high-negative antibody titer in Group A, to every 2 years for patients with a high-positive antibody titer in Group B and to every 1 year for patients with a low-positive antibody titer in Group C.

They proposed to set up the cutoff value for *H. pylori*-seropositive patients at the point where *H. pylori* positive patients are averagely distributed into each subgroup. Whilie in *H. pylori*-seronegative patients, antibody titer 3–10 U/ml is considered as the high-negative titer. Patients with titer less than 3 U/ml is considered as a low-negative titer case. However, there is no consensus currently on the cutoff value of antibody titer. It is generally believed that lowering the cutoff value of *H. pylori* antibody titer is helpful to precisely recognize the high-risk patients for further endoscopic surveillance periodically and administrate the antibiotic therapy. Specifically, it is important to recognize the patients with positive *H. pylori* infection but was successfully eradicated in Group A because these patients still have a chance to develop the intestinal-type gastric cancer.[90,91] In this aspect, it is always ignored. Haneda *et al*.[92] suggested that the optimal cutoff value of PG I/II in posteradication is 4.5, including more gastric cancer cases compared with the traditional PG method. All in all, the prognosis improvement of gastric cancer depends on the early detection and diagnosis. In order to receive accurate risk stratification, further studies are required in the recent future.

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Conflicts of interest

There are no conflicts of interest.

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联合血清幽门螺杆菌抗体和胃蛋白酶原浓度的胃癌筛查：胃癌筛查的ABC方法

摘要

目的： 胃镜联合胃黏膜活检被认为是目前胃癌诊断的金标准，但作为侵入性检查，其临床应用受到了限制。一种新的非侵入性的大规模筛查，被称为“ABC方法”，结合了抗幽门螺杆菌抗体和血清胃蛋白酶原(PG)，用于识别高危人群，以作进一步的胃镜检查，避免了每年对大多数人群进行不必要的侵入性检查，节省了每年人群胃癌筛查成本。然而，对于ABC方法的分组标准及每组的胃镜随访间隔均存在争议。在此综述中，我们总结了上述大家普遍关心的问题，为临床实践中的医疗从业者提供有用的参考。

数据来源：使用关键词“幽门螺杆菌”、“胃蛋白酶原”和“胃癌”，对PubMed数据库进行系统检索，检索时间截止在2017年11月22日。

资料选择：与本次研究主题相关的原创文章和综述均被纳入。

结果：当处于不同严重程度的幽门螺杆菌感染及萎缩性胃炎，抗幽门螺杆菌抗体和血清胃蛋白酶原浓度确实展示出显著变化，而这种显著的改变可应用于临床胃癌的风险分层.此外，抗幽门螺杆菌抗体滴度可用于胃癌的进一步风险分层，有助于确定更适宜的胃镜复查时间间隔。

结论：胃癌的早发现和早诊断得益于风险分层，但幽门螺杆菌抗体和血清胃蛋白酶原浓度的界值则需要进一步的完善。