Etiology and Prevention of Gastric Cancer

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Abstract
Background: Gastric cancer is a heterogeneous malignant disease associated with environmental and genetic predisposing factors. While gastric cancer incidence and mortality fell greatly globally over the past decades, it remains the fourth cause of cancer-related death worldwide. Thus, prevention of gastric cancer is still a major strategy for improvement of gastric cancer prognosis. Summary: Helicobacter pylori infection has been demonstrated to be a major risk factor for the development of gastric cancer. Unhealthy diet and lifestyle, including high-salt food, smoking and drinking, are able to induce genotypic and phenotypic transformation of gastric epithelial cells. Gene mutations (such as E-cadherin) in stomach epithelial cells are major genetic causes for gastric cancer. The eradication of H. pylori has been demonstrated to be an effective approach for primary prevention of gastric cancer. Increased intake of a diet rich in vegetables and fresh fruits as well as smoking cessation have been shown to reduce the incidence of gastric cancer. The secondary prevention strategy is to screen premalignant gastric lesions by endoscopy. Biomarker tests are also reliable methods to identify gastric precancerous lesions. Endoscopy screening is still the gold standard for diagnosis of gastric cancer. Key Message: H. pylori infection, a diet rich in salted and/or smoked food and red meat, as well as gene mutations are major risk factors for the development of gastric cancer. Practical Implications: The eradication of H. pylori is a major primary preventative strategy of gastric cancer. A healthy lifestyle, including increased intake of a diet rich in fruit and vegetables, reduced intake of salted and smoked food and red meat, a reduction of alcohol intake as well as smoking cessation will be effective approaches for the prevention of gastric cancer.
Introduction

Although the incidence of gastric cancer has greatly decreased in Western countries, it is still one of the most common cancers in Asia. In China, gastric cancer is the third most common cancer after lung cancer, liver cancer in men and lung cancer, breast cancer in women, and the third leading cause of cancer-related death [1]. To reduce gastric cancer mortality, prevention is the critical approach for improvement of gastric prognosis. This article will discuss the epidemiology, general risk factors and prevention of gastric cancer by reviewing the classic studies and also the new findings over the past few years.

There are several types of cancers arising from the stomach. The majority (about 90%) of stomach cancers belong to the group of adenocarcinomas, which originate from the glands of the gastric mucosa. Besides adenocarcinomas, other types of cancers may arise from lymphoid tissue and muscles of the stomach. For example, mucosa-associated lymphoid tissue lymphomas are derived from gastric lymphoid tissues, and leiomyosarcomas originate from the muscles below the mucosa. In this review, we will focus on gastric adenocarcinomas.

According to the Lauren classification [2], gastric adenocarcinomas can be classified into two major types: intestinal type and diffuse type. The intestinal type of gastric cancer is associated with *Helicobacter pylori* infection with gastric intestinal metaplasia and atrophy, whereas the diffuse type of gastric cancer originates from pangastritis without atrophy. According to the different anatomic sites, gastric adenocarcinomas are divided into cardia and non-cardia gastric cancers. The majority of gastric cancers are non-cardia cancers. The non-cardia gastric cancers have been increasing since the 1970s [3]. Non-cardia and cardia adenocarcinomas have very different biological characteristics.

Non-cardia gastric cancer is more common in males (twice as common as in women), blacks, older people, lower socioeconomic groups and developing countries [3, 4]. In China, the proportions of proximal gastric cancer were low, up to approximately one third [5]. In contrast, cardia gastric cancer has a male:female ratio of approximately 5:1.

Around one million new cases of gastric cancer were diagnosed worldwide according to Globocan 2012, making gastric cancer the fifth most common malignancy worldwide, after lung, breast, colorectal and prostate cancer. However, the incidence rate of gastric cancer has decreased worldwide [6]. In the USA, the incidence rate of gastric cancer decreased by 1.7% for men and 0.8% for women annually from 1992 to 2010 [7]. The highest incidence rate of gastric cancer occurs in Eastern Asia, Eastern Europe and South America, whereas the lowest rate of gastric cancer is found in North America and most parts of Africa [8]. While an overall decrease of gastric cancer incident rates has been observed in China, the decline was much less than in other countries. Moreover, gastric cancer incident rates are increased in the younger and older groups [9].

While the incidence of gastric cancer has declined worldwide, the overall relative 5-year survival rate is only approximately 30% in most parts of the world [10]. In Japan, due to the effectiveness of its mass screening programs, the 5-year survival rates of stage I and II gastric cancer have been reported to be up to 70% [11, 12]. In China, the 5-year relative survival rate of gastric cancer has improved much over the last century, but it remains lower than 35% [13]. Gastric cancer is still the fourth leading cause of cancer-related death worldwide [6, 9]. Thus, prevention is a key strategy for reduction of gastric cancer-related mortality.
Risk Factors for Gastric Cancer

Gastric cancer is a genetically heterogeneous tumor with multifactorial etiologies, associated with environmental and genetic factors. Many factors play important roles in the development of gastric cancer. Among these, inherited genetic factors, *H. pylori* infection, dietary factors and lifestyle factors are strongly linked to gastric cancer [7, 14].

**Hereditary and Genetic Factors**

While hereditary gastric cancer is uncommon, genetic alterations in sporadic gastric cancer cases are frequently reported. Any family with two recognized causes of gastric cancer in the first- or second-degree relatives, with the tumor occurring in at least one member under the age of 50 years, or in three members in the first- or second-degree relatives at any age must be considered as genetically predisposed to gastric cancer. While genetic factors have been proposed to play important roles in gastric carcinogenesis by possibly affecting inflammatory and immune responses especially to *H. pylori* infection and thus altering susceptibility to gastric cancer, however, so far few high-penetrance genes have been identified for gastric cancer development.

Interleukin 1β gene (*IL-1β*) has been recognized as an important gene that contributes to initiation and amplification of inflammatory response. Polymorphisms of *IL-1β* and of the interleukin 1 receptor antagonist (*IL-1RN*) gene have been associated with gastric cancer risk [15]. Results from very large genome-wide association studies showed reproducible relationships between single nucleotide polymorphisms located at *Mucin 1*, cell surface-associated gene (*MUC1*), prostate stem cell antigen gene (*PSCA*) and *PLCE1* with different subtypes of gastric cancer risk. These results of genome-wide association studies are mainly from Chinese, Korean and Japanese populations, but the biological mechanisms involved in these polymorphisms are still not completely understood [7].

**H. pylori Infection**

*H. pylori*, a Gram-negative bacterium, has been characterized as a class I carcinogen of gastric cancer by the World Health Organization since 1994 [16]. *H. pylori* colonizes the gastric mucosa in 50% of the human population. Many epidemiological and classic studies have shown that *H. pylori* infection is the main risk factor of gastric cancer [17–21]. The oncogenic effects of *H. pylori* infection have been demonstrated through two major mechanisms: the direct epigenetic effects of *H. pylori* on gastric epithelial cells and the indirect inflammatory response of *H. pylori* on the gastric mucosa [16]. Certain *H. pylori* strains with the virulence factor (such as cytotoxin-associated gene A, CagA) are more likely to increase gastric cancer risk.

Many studies have shown that *cagA* virulence factors and vacuolating cytotoxin A in the cag pathogenicity island are linked to colonization and pathogenicity of *H. pylori*. *cagA* has been demonstrated to be associated with inhibition of p53 function, in a manner similar to human papillomavirus and other oncogenic DNA viruses [22]. The *vacA* encodes a secreted bacterial toxin (VacA) and induces multiple structural and functional alterations in gastric epithelial cells [23]. *H. pylori* strains with *cagA* and/or *vacA* are associated with increased risk for developing both intense tissue responses and premalignant and malignant lesions in the distal stomach through secreting a functional cytotoxin [24, 25].

**Dietary Factors**

The relationship between dietary factors and gastric cancer risk has been widely investigated. The World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) concluded that vegetables and fruits probably protect against gastric cancer, whereas
salt and salt-preserved foods as well as smoked foods, processed, grilled (broiled) and barbecued (charbroiled) animal meats are probably causes of gastric cancer [26].

Some large cohort studies in Korea have shown that people who prefer salty food have a higher risk for gastric cancer [27]. Intake of salted foods has been demonstrated to enhance the risk of *H. pylori* infection and, even worse, to increase the capability of *H. pylori* to promote gastric cancer development by enhancing *cagA* expression [28].

Food carcinogens can also interact directly with the gastric epithelial cells and cause gene mutation of epithelial cells. A high level of sodium chloride has been shown to damage the gastric mucosa, cause cell death and induce regenerative cell proliferation in animal models [29, 30], finally resulting in inflammation and injury such as diffuse erosion and degeneration [31]. High-salt diet has been found to be associated with colonization of *H. pylori* [56] and to exacerbate *H. pylori*-induced inflammation [32], which is consequently responsible for gastric carcinogenesis promotion in a dose-dependent manner [33]. This result is confirmed in other studies showing that a high level of salt synergistically increases the expression of pro-inflammatory enzymes and cytokines in gastric mucosa with *H. pylori* infection [34]. High salt stimulation enhances expression of *H. pylori cagA* and enhanced ability of *H. pylori* to alter gastric epithelial cell function [35].

*N*-nitroso compounds are another dietary factor that might play a role in gastric carcinogenesis. Nitrates are endogenously produced in gastric acid and are likely to contribute to *N*-nitroso compound production and exposure; they are recognized as mutagens and carcinogens [26]. Dietary or endogenous exposure to *N*-nitroso compounds has been demonstrated to significantly increase gastrointestinal cancer risk, especially with non-cardia gastric cancer rather than cardia gastric cancer [36, 37]. Many processed meats contain high levels of salt and nitrite. Red meat has been shown to promote the formation of *N*-nitroso compounds through direct reaction between nitric oxide and hemoglobin and myoglobin [36]. Red meat also contains iron, which can lead to the production of free radicals.

### Roles of Smoking and Alcohol Habits

Among environmental factors, a variety of habits play important roles in gastric cancer development. The roles of smoking and alcohol intake have been paid most attention as important high-risk factors for gastric cancer. In a study of the role of *H. pylori* infection in gastric cancer development, current smoking showed a higher risk for gastric cancer (RR = 2.3, 95% CI 1.4–3.5, p < 0.001), with more diffuse-type than intestinal-type tumors (p < 0.05). In a prospective cohort of 18,244 middle-aged men in Shanghai over 20 years of follow-up, 391 gastric cancer cases were diagnosed. Smokers had an increased risk of gastric cancer (HR = 1.59, 95% CI 1.27–1.99) compared to non-smokers after adjustment for alcohol intake and other confounders. Smokers exhibited an 80% increase in the risk of gastric cancer (HR = 1.81, 95% CI 1.36–2.41) among non-drinkers. On the contrary, heavy drinkers showed a statistically significant increase in the risk of gastric cancer (HR = 1.46, 95% CI 1.05–2.04) among all subjects and a statistically non-significantly 80% increase in the risk among smokers [38]. In a cohort study of 7,150 men in Lithuania over 30 years, 185 cases of gastric cancer were found. A higher intake of wine >0.5 liter per occasion compared to less drinking was associated with a high risk of gastric cancer with a HR of 2.95 for men (95% CI 1.30–6.68) [39]. In an European prospective nutrition cohort study with the occurrence of 444 cases of gastric cancer, heavy alcohol consumption at baseline was positively associated with gastric cancer risk (HR = 1.65, 95% CI 1.06–2.58), whereas lower consumption (<60 g/day) was not [40]. Intestinal non-cardia carcinoma was associated with heavy alcohol intake.

Other risk factors, including positive family history, radiation exposure, older age, male sex, lack of physical activity and low socioeconomic status, have also been associated with increased risk of both non-cardia and cardia gastric cancer, whereas gastroesophageal reflux
disease and obesity have specifically been related to increased risk of cardia gastric cancer [7]. However, non-steroidal anti-inflammatory drugs (NSAIDs) and statin intake have inverse relations with gastric cancer risk [7].

**Epstein-Barr Virus Infection**

Besides *H. pylori*, another infectious agent is the Epstein-Barr virus (EBV), which has been associated with gastric cancer. EBV is a ubiquitous infectious agent with a prevalence of >90% in adults. EBV has been causally associated with the development of several malignancies, including nasopharyngeal carcinoma, Hodgkin’s lymphoma, Burkitt’s lymphoma and immunosuppression-related lymphoma [41]. Around 8% of gastric cancers have been estimated to harbor EBV, however there is insufficient epidemiological evidence to show a clear etiological role for EBV in gastric carcinogenesis [42]. The EBV genome exists in the tumor cells in a monoclonal form, and transforming EBV proteins are expressed in the tumor cells. A meta-analysis has shown that the percentage of EBV-positive gastric cancer varies according to age, sex and anatomic subsite. EBV positivity decreased with age among male cases [43]. EBV-positive gastric cancer with longer survival may have distinct clinical and genetic features, and therefore may be a separate clinical type.

**Prevention Strategies for Gastric Cancer**

The prevention strategies for gastric cancer include the intervention of gastric cancer etiology (such as *H. pylori* eradication and changes in lifestyle) and early detection and treatment of gastric cancer.

**Eradication of *H. pylori***

Since *H. pylori* infection is the main cause of gastritis and precancerous conditions (atrophic gastritis, intestinal metaplasia and dysplasia), its eradication is a reasonable strategy for gastric cancer prevention. Many meta-analyses have demonstrated that *H. pylori* eradication can reverse intestinal metaplasia and reduce the risk for gastric cancer [44]. A meta-analysis of seven randomized clinical trials showed that eradication treatment of *H. pylori* can reduce gastric cancer risk by 35.3% [45]. Another meta-analysis of six reported randomized clinical studies in healthy asymptomatic adults showed that *H. pylori* can reduce gastric cancer risk by 30.4% [46]. A French clinical trial exhibited a statistically significant decrease in gastric cancer risk following 2-week antibiotic treatment for *H. pylori*. Short-term treatment with omeprazole and amoxicillin significantly reduced gastric cancer incidence by 39% after 14.7 years of follow-up [47]. The Asia-Pacific Gastric Cancer Consensus has recommended screening for and treatment of *H. pylori* infection in regions with high incidence of gastric cancer as an effective preventive strategy for gastric cancer [48]. A randomized controlled trial showed that *H. pylori* eradication prevented gastric cancer in a high-risk region of China [49]. In that study, among 1,630 healthy carriers of *H. pylori* infection, 18 new cases of gastric cancer were diagnosed. No overall reduction was observed in all participants who received *H. pylori* eradication treatment (n = 7) compared with those who did not (n = 11) (p = 0.33). However, in a subgroup of patients with no precancerous lesions on presentation, no patient developed gastric cancer during a follow-up of 7.5 years after *H. pylori* eradication treatment compared with those who received placebo (0 vs. 6, p = 0.02).

However, gastric cancer development cannot be easily prevented by the eradication of *H. pylori* when the gastritis has progressed to advanced precancerous conditions. As the development of gastric precancerous disease to gastric cancer usually takes a long time and occurs at an older age, *H. pylori* eradication must be conducted long before the atrophic
gastritis associated with intestinal metaplasia develops. It means that the eradication of *H. pylori* could have a preventive effect on gastric cancer only when eradication is performed at an earlier age. In a double-blind randomized prospective controlled study, successful eradication of *H. pylori* did not lead to regression, but ended the progression of intestinal metaplasia after 4.5 years compared to the non-eradicated group [50].

Since gastritis is a very common disease in most developing countries and few subjects develop gastric cancer, mass eradication of *H. pylori* in all members of these societies with a high prevalence of infection, even in areas with high risk for gastric cancer, seems to be unfeasible. Besides high costs, various side effects of eradication therapy and the occurrence of *H. pylori* drug resistance must be taken into consideration. Furthermore, recent studies have found that the development of esophageal and cardia cancer as well as esophagitis are associated with negative *H. pylori* infection [51, 52]. Thus, the advantage of *H. pylori* eradication must be evaluated against the probable hazard in any individual, which can occur many years or some decades later. *H. pylori* eradication should be conducted in the first-degree relatives of gastric cancer patients and in those having an individually high risk of developing gastric cancer, like patients with corpus-dominant gastritis. Therefore, the long-term consequences of interventional *H. pylori* eradication in the population for gastric cancer prevention remain to be further studied.

**Chemoprevention of Gastric Cancer**

So far, no randomized controlled studies are present about the long-term effects of NSAIDs alone on gastric cancer development. In a meta-analysis of eight case-control studies and one cohort study with a total of 2,831 gastric cancer patients, NSAID users had a reduced risk of gastric cancer, with an OR of 0.78 (95% CI 0.69–0.87). Users of aspirin only (OR = 0.73, 95% CI 0.63–0.86) and non-aspirin NSAIDs (OR = 0.74, 95% CI 0.55–1.00) showed a similar reduction in gastric cancer risk [28]. The anti-angiogenesis and apoptosis-promoting effects of NSAIDs are likely to play roles in the inhibition of gastric carcinogenesis [53]. Some ongoing cohort and population studies for the prevention of gastric cancer, including low-dose aspirin, were administered to subjects in different countries [54]. The results of those large and long-term studies will clarify the effect of aspirin on the prevention of gastric cancer in the future.

One study [53] investigated the preventive effect of etodolac, a selective cyclooxygenase 2 inhibitor, on metachronous cancer development after endoscopic resection of early gastric cancer. Among 267 early gastric cancer patients who underwent endoscopic resection, 47 patients with extensive metaplastic gastritis were selected based on endoscopic examination. Non-randomized etodolac treatment (300 mg/day) was administered to 26 patients (group A), while the remaining 21 patients were left untreated (group B). Patients were followed for metachronous cancer development with endoscopy every 6–12 months for up to 5 years (4.2 ± 0.9 years). The results showed that five cancers developed in group B (incidence rate = 6,266/100,000 person-years), significantly more than the one cancer in group A (incidence rate = 898/100,000 person-years; p < 0.05). Long-term etodolac treatment did not influence the extent of metaplastic gastritis as revealed by endoscopic findings or by serum PG levels, but effectively reduced metachronous cancer development in patients with extensive metaplastic gastritis. These results strongly suggest that there is a potential for chemoprevention of cancer in the metaplastic stomach by using cyclooxygenase 2 inhibitor.

**Increased Intake of Vegetables and Fruits**

Sufficient fruit and vegetable intake has been demonstrated to reduce the prevalence of cancer in various organs, including gastrointestinal cancers. In a meta-analysis of clinical studies, a favorable effect on gastric cancer was found for a ‘healthy diet’ rich in vegetables and fruits.
Dietary intervention should increase fruit and vegetable intake and reduce the consumption of salt or salt-preserved foods. In Korea, gastric cancer-related mortality was negatively associated with use of refrigerators and intake of fruit but not vegetables [55]. From a meta-analysis of 29 case-control studies conducted in Latin America, fruit and total vegetable consumption were each associated with a moderately reduced risk of gastric cancer [56]. In a case-control study from Italy, among the four major diets, named ‘animal products’, ‘vitamins and fiber’, ‘vegetable unsaturated fatty acids’ and ‘starch-rich’, gastric cancer risk was positively associated with the ‘animal products’ (OR = 2.13, 95% CI 1.34–3.40, for the highest versus the lowest score quartile) and the ‘starch-rich’ dietary pattern (OR = 1.67, 95% CI 1.01–2.77), and negatively associated with ‘vitamins and fiber’ (OR = 0.60, 95% CI 1.01–2.77) [57]. These results demonstrate that an increased intake of vegetables and fruits (Mediterranean diet) can prevent the development of gastric cancer.

Studies have shown that vitamin C may protect against H. pylori-associated gastric carcinogenesis by enhancing mucosal immune response, neutralizing free radicals, decreasing the formation of gastric N-nitroso compounds and influencing H. pylori growth [37]. The level of gastric juice vitamin C was also shown to be lower with infection with cagA-positive H. pylori strains compared with cagA-negative H. pylori strains [51]. The WCRF/AICR assesses other dietary factors and suggests that pulses (legumes) and foods containing selenium can protect against gastric cancer [26].

Alteration of Lifestyle

Since smoking has been demonstrated to be an important environmental factor for gastric cancer risk, smoking cessation would be a critical preventive strategy for gastric cancer development. Other lifestyle modifications such as decreased alcohol intake, increased fruit and vegetable intake, reduced salt intake, increased physical activity and a Mediterranean diet may help reduce the risk of getting gastric cancer.

Endoscopy Screening

While a critical strategy for gastric cancer prevention is to target prevention of risk factors, early diagnosis and treatment of precancerous diseases is also an important approach for gastric cancer prevention. Individuals with premalignant gastric lesions, including atrophic gastritis and intestinal metaplasia, have been defined as high-risk populations for gastric cancer [58]. These populations with high risk of cancer need special endoscopic surveillance at appropriate time intervals. Endoscopy is the best approach for detecting either precancerous lesions or gastric cancer and is widely used for gastric cancer screening in China, Japan, Korea and Venezuela. A population-based pilot study was conducted in Linqu County of China for detection of early gastric cancers to evaluate the prevalence of precancerous gastric lesions from 1989 to 1990. A total of 3,400 residents (1,792 males, 1,608 females) aged 35–64 years were selected randomly and enrolled, representing 77.6% of the eligible population in 14 villages [59]. A nationwide study showed that the annual incidence of gastric cancer increased gradually within 5 years after the diagnosis of premalignant conditions. The incidence of gastric cancer was 0.1% for patients with atrophic gastritis, 0.25% for patients with intestinal metaplasia, 0.6% for patients with mild to moderate dysplasia and 6% for patients with severe dysplasia [60]. Consensus guidelines developed by gastroenterology societies recommend that high-risk patients with extensive atrophy or intestinal metaplasia should be surveilled with endoscopy every 3 years [61].

Many methods can be used for screening and detecting early-stage gastric cancer. One of those is the use of photofluoroscopy, which has been conducted for gastric cancer screening in Japan since the 1960s [12]. Photofluoroscopy has been developed into a double-contrast method by combining a barium meal and air. The double-contrast method can provide better
contrast shadow of early cancer lesions [12]. The data from five case-control studies and two cohort studies in Japan demonstrated that photofluoroscopy for gastric cancer screening can decrease gastric cancer mortality by 40–60% [12]. By now, many new advanced approaches providing better visualization of gastric mucosa lesions have been developed, such as chromoendoscopy [62], confocal laser endomicroscopy [63], narrow-band imaging endoscopy [64], magnifying endoscopy [65] and narrow-band imaging with magnifying endoscopy [66]. A large number of studies showed that these new advanced endoscopic imaging technologies have better accuracy for diagnosing premalignant gastric lesions than standard ‘white light’ endoscopy [67–69].

Biomarker Screening of Individuals with High Risk for Gastric Cancer

While endoscopic screening can diagnose early gastric cancer and reduce mortality of gastric cancer, it is an invasive examination and has possible side effects [70], including hemorrhage and perforation. Blood-based biomarker detection, as a non-invasive method, has been used for the detection of gastric precancerous lesions [71].

Serum pepsinogen testing is a widely used non-invasive method to screen for precancerous gastric lesions. The level of serum pepsinogen I (Pgi) gradually declines during the development of atrophic gastritis, while the concentration of pepsinogen II (PgiI) remains constant [72]. A low Pgi level and a decreased Pgi/PgiI ratio mean gastric mucosal atrophy [73, 74]. In addition, the combination of serum pepsinogen levels with anti-H. pylori IgG testing may better predict the risk of gastric cancer development. Low Pgi (or Pgi/PgiI ratio) and negative H. pylori antibodies suggest the highest risk [75]. Recent studies showed that low serum ghrelin predicts high risk of gastric cancer [76, 77]. Gastrin-17 has been also considered as a biomarker for antral atrophy [78, 79]. Trefoil factor 3, a small and stable molecule secreted by the gastrointestinal tract, has been shown to be a better biomarker for both atrophy and gastric cancer than pepsinogens [80, 81]. In addition, anti-gastric parietal cell antibodies have been considered as independent biomarkers for gastric atrophy [82]. The combination detection of these biomarkers may increase the sensitivity and specify of prediction of gastric cancer development in high-risk populations.

Conclusions

Although the incidence of gastric cancer has decreased in developed countries, it remains a major disease with high mortality in developing countries [83]. In China, most gastric cancers are detected in their advanced stage [84]. Such a situation needs a more effective prevention strategy. Currently, the eradication of H. pylori remains a major approach for primary gastric cancer prevention, especially for the high-risk group with H. pylori infection. In addition, changes in lifestyle and dietary habits could further help prevent gastric cancer incidence. The secondary prevention strategy needs more reliable screening approaches to find premalignant gastric lesions and early gastric cancer and conduct a personalized therapy for these lesions by endoscopy. Endoscopy screening is still the gold standard for diagnosis of gastric cancer and biomarker tests are also a reliable method to identify gastric precancerous lesions.

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References

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