



Gastric cancer: lessons learned from high-incidence geographic regions

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Abstract: Gastric cancer is a global health concern. There is a marked geographical variability in the incidence of gastric cancer, with higher incidence in East and Central Asia followed by Latin America and Eastern Europe. Survival rates in gastric cancer are low and strongly stage dependent. Due to the limited survival benefit achieved from currently available therapeutic options, prevention and early diagnosis are essential to minimize morbidity and mortality from this disease. Countries with high incidence of gastric cancer have pioneered the development and implementation of prevention and screening programs. *Helicobacter pylori* (*H. pylori*) eradication and dietary modifications are the main preventive strategies. Upper gastrointestinal (UGI) endoscopy is the mainstay screening strategy for early diagnosis. In this article, we review the lessons learned for gastric cancer diagnosis and treatment from high-incidence areas and discuss their applicability for treatment in the Western world to reduce morbidity and mortality from this disease.

Keywords: Stomach neoplasms; *Helicobacter pylori* (*H. pylori*); early detection of gastric cancer

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Introduction

Worldwide, gastric cancer is the fifth most commonly diagnosed cancer and is the third leading cause of oncological deaths (1,2). Adenocarcinomas comprise 95% of all gastric cancers and can be subdivided into cardia and non-cardia according to their anatomical location (1). Unless otherwise specified, gastric cancer refers to gastric adenocarcinomas throughout this article.

There is a marked geographical variability in the incidence of gastric cancer. Incidence is highest in East and Central Asia followed by Latin America and Eastern Europe (3). In contrast, the incidence is low in the United States and other Western countries, where gastric cancer is usually diagnosed at late stages due to non-specificity of symptoms and lack of population-based intervention programs (4). Though current treatment options have yielded modest benefits in terms of survival improvement,

patients with gastric cancer generally have low survival rates (3). Prevention and early diagnosis may be effective strategies to reduce morbidity and mortality (1,3). *H. pylori* eradication and dietary modification are the main prevention strategies in use. Endoscopic screening has become the mainstay screen for early diagnosis.

Incidence and prognosis

In 2018, there were over 1,000,000 new cases and approximately 783,000 deaths related to gastric cancer worldwide (2). Incidence of gastric cancer varies greatly with geographic location, race, gender and socioeconomic status (1).

Geographic location

East Asia carries most of the world's gastric cancer

Estimated age-standardized incidence rates (World) in 2018, stomach, both sexes, all ages

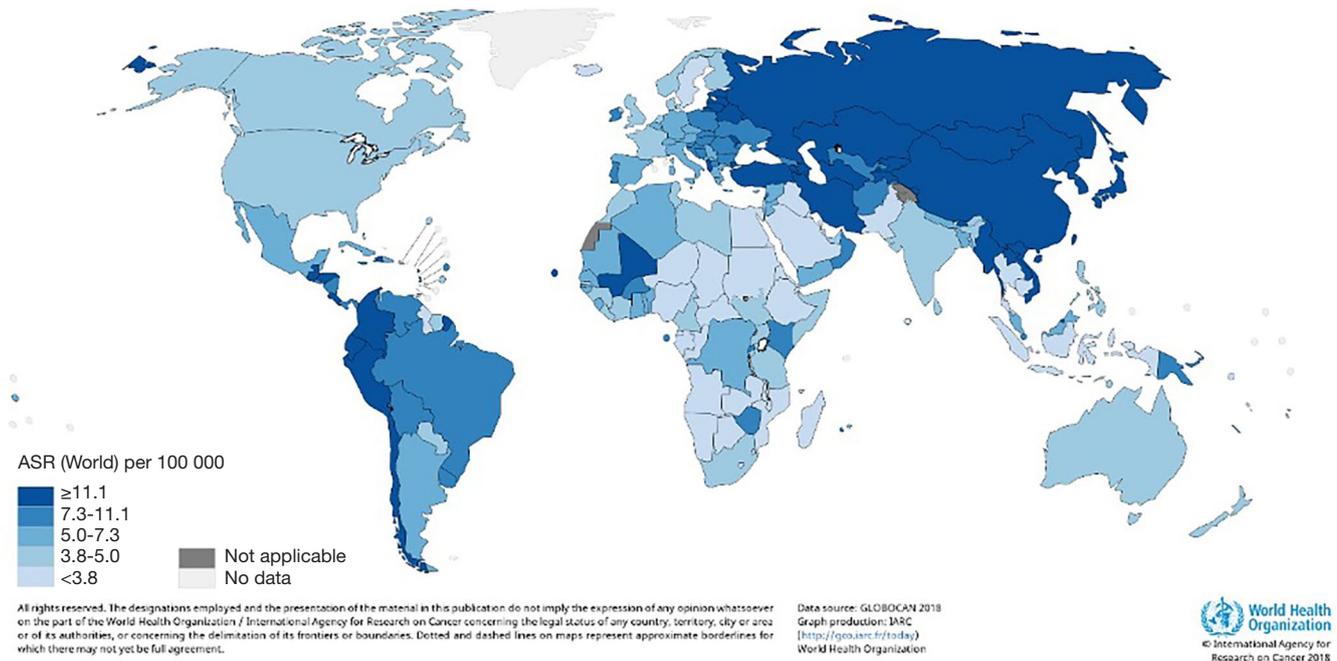


Figure 1 Worldwide estimated age-standardized (ASR) incidence rates of gastric cancer in 2018. Reproduced with permission from <http://gco.iarc.fr/survival/survmark> (6).

burden that accounts for approximately 75% of new cases worldwide (4). In 2012, the age-standardized incidence rates (ASIR) of gastric cancer in Korea, Japan and China were estimated at 41.8, 29.9 and 22.7 per 100,000, respectively (3). Other areas of high incidence are Central and Eastern Europe and Central and South America (3). Conversely, North America, Australia, New Zealand, South Asia, Northern Europe, and North and East Africa have a low incidence (3,5). Gastric cancer incidence in the United States is among the lowest in the world with an ASIR of 3.9 per 100,000 (3,4,6) (Figure 1).

The incidence of gastric cancer subtypes differs among geographic regions. Non-cardia gastric cancer is the predominant subtype globally and throughout East and Central Asia and Eastern Europe (3). Conversely, cardia gastric cancer is the most common subtype in Western countries. This is secondary to a decrease in the incidence of non-cardia gastric cancer, while rates of cardia cancer have remained unchanged (3).

Mortality rates from gastric cancer are higher in areas of high incidence such as East and Central Asia and Latin America (1,6) (Figure 2). Japan and South Korea exhibit the highest incidence of gastric cancer and the greatest number

of cumulative deaths, even though the mortality-incidence ratio is remarkably low due to increased survival rates (1,3,6,7) (Figure 3). Five-year gastric cancer survival rates of 67% and 69% have been reported in Korea and Japan, respectively (7-9). These survival rates are significantly better than the 5-year 20% relative survival rate seen in most parts of the world (8).

Race and ethnicity

There is marked variability in the incidence of gastric cancer between Eastern and Western nations. In the United States, Caucasian population have decreased risk of gastric cancer compared to Asian and Pacific Islanders, American Indian and Alaska Natives, African Americans, and Hispanics. Japanese and Korean Americans have an especially high rate of gastric cancer (1,8). However, Asian patients in the United States tend to have a better prognosis than Caucasians, with a 12% higher 5-year survival rate after adjusting for age, gender and stage (1).

Genetic polymorphisms among various ethnic groups are partly responsible for varying rates of gastric cancer (10). For example, polymorphisms in interleukin-10 and

Estimated age-standardized mortality rates (World) in 2018, stomach, both sexes, all ages

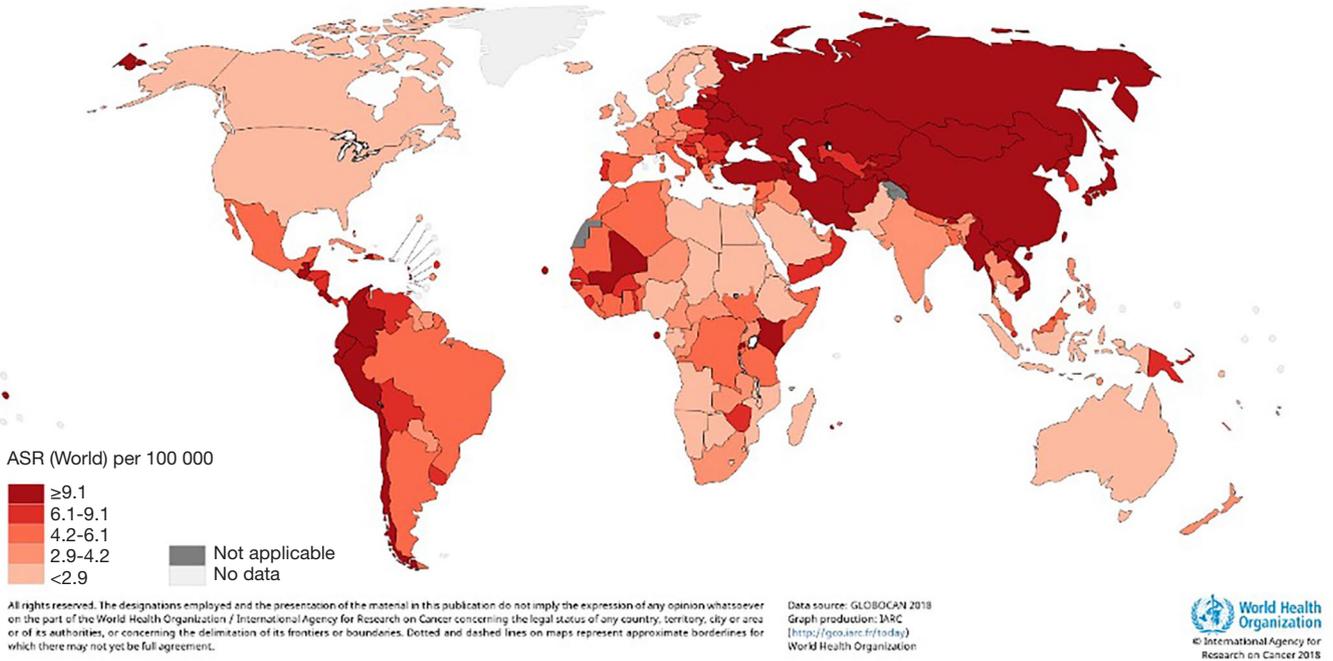


Figure 2 Worldwide estimated age-standardized (ASR) mortality rates of gastric cancer in 2018. Reproduced with permission from <http://gco.iarc.fr/survival/survmark> (6).

Estimated age-standardized incidence and mortality rates (World) in 2018, stomach, both sexes, all ages

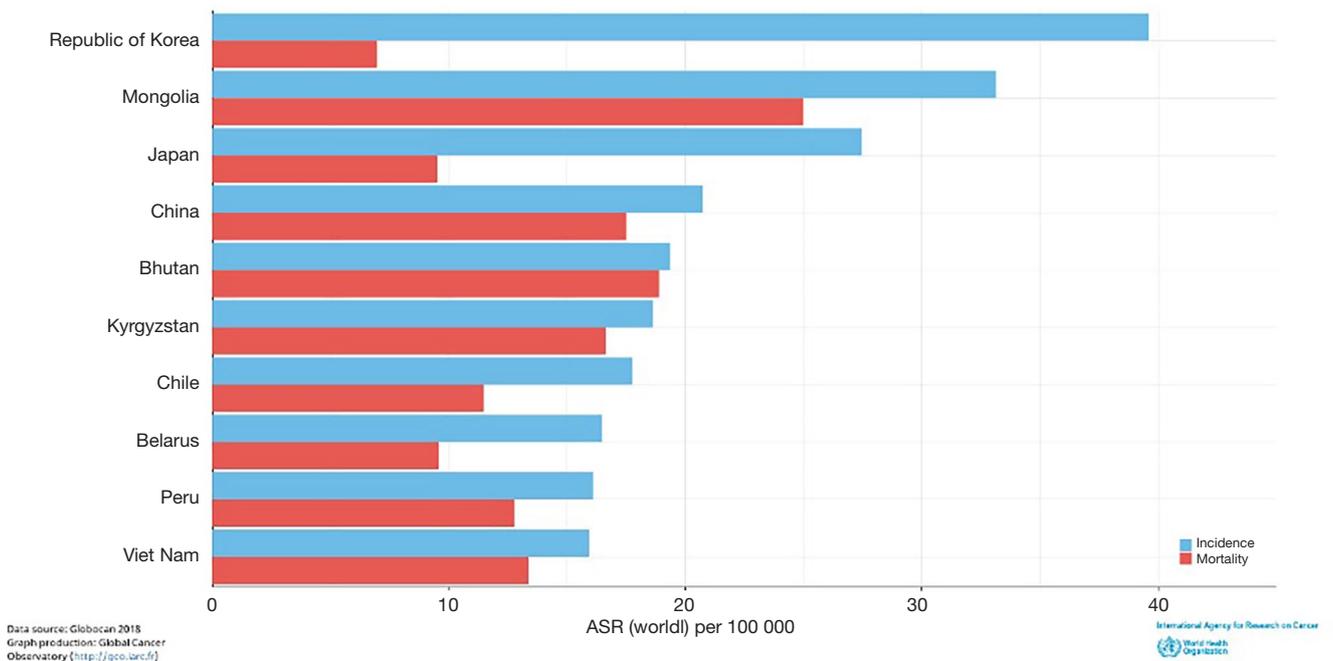


Figure 3 Estimated age-standardized incidence and mortality rates of gastric cancer in 2018. Reproduced with permission from <http://gco.iarc.fr/survival/survmark> (6).

-17 genes are common in Asian populations. These polymorphisms appear to impact *H. pylori* infection and are associated with an increased risk of gastric cancer (10). Nevertheless, a strong environmental component is considered the greatest factor for the geographic variability of gastric cancer incidence (1).

First-generation immigrants from areas with high incidence of gastric cancer exhibit a higher risk than the population native to the low-incidence countries where they relocate. The standardized incidence ratios are 1.08- to 5.05-fold higher than the destination native-born population. Second-generation immigrants from same countries remain at higher risk, although lower than first-generation immigrants. The level of acculturation, including dietary modification, influences the risk of gastric cancer. This explains the risk equalization in subsequent generations and the different rate at which this occurs in different groups. For instance, Japanese Americans experience an accelerated decrease in risk due to increased acculturation after immigrating, as compared to Korean Americans (11).

Gender

Incidence rates of gastric cancer clearly reflect a decreased risk of gastric cancer in females (1,2). Gastric cancer is the leading cause of death in males in several Western Asian countries, including Iran, Turkmenistan, and Kyrgyzstan (1). Estrogen seems to be the determinant factor due to its protective effect based on observations that delayed menopause and increased fertility are associated with a reduction in gastric cancer risk (12). This effect is blunted with the use of antiestrogen drugs such as tamoxifen (12). After menopause, the risk of gastric cancer in females equalizes to that of age matched males (1).

There are various mechanisms that can explain the protective effect of estrogen. Animal studies show that 17 β -estradiol mediates a protective effect in *H. pylori*-infected mice, presumably by increasing the expression of trefoil factor family (TFF) proteins, which protect the gastric epithelium from dysplastic changes and promote mucosal repair (13). High concentrations of estrogen inhibit the expression of estrogen receptor α 36 and halts the proliferation of gastric cancer cells, while low concentrations promotes its expression and stimulate gastric carcinogenesis (14).

Socioeconomic level

Low socioeconomic status is associated with increased risk of gastric cancer (1,3,15). The ASIR of gastric cancer in economically developed regions is 15.6 per 100,000 in males and 6.7 per 100,000 in females compared to 18.1 per 100,000 for males and 7.8 per 100,000 for females living in less developed areas of the world (3). These observations are likely secondary to higher rates of *H. pylori* infection or decreased access to fresh food, fruits, and vegetables in low socioeconomic strata (1).

Stage at time of diagnosis

Survival rates in gastric cancer are highly dependent on the stage at time of diagnosis and surgical intervention (16). Screening programs result in diagnosis of gastric cancer in its early stages, which may account for some of the differences in survival among geographic regions, since over 50% of cancers are diagnosed at an early stage in Japan, as opposed to only 20% in the United States (8). In the United States, the 5-year survival rate for stage IA tumors treated with surgery is 94%, with rates dropping to 18% in the case of stage IIIC tumors (1).

Risk factors for gastric cancer

Helicobacter pylori

H. pylori infection induces inflammation of the gastric mucosa that results in the development of peptic ulcers, chronic and atrophic gastritis, intestinal metaplasia, gastric lymphoma, and adenocarcinoma (17). Approximately 85–90% of non-cardia gastric cancer are associated with this pathogen (18). As non-cardia gastric cancer constitutes the majority of gastric cancer, *H. pylori* infection is associated with 75–78% of all gastric cancers (1,19). *H. pylori* reportedly carries an odds ratio (OR) of 5.9 for the development of gastric cancer within 10 years of infection (1).

The association between *H. pylori* and gastric cancer is stronger in certain regions of the world, such as East Asia. Incidentally, other Asian areas like India and Taiwan have high frequency of *H. pylori* infection with a corresponding low incidence of gastric cancer (5,20,21). This is likely related to the geographical distribution of different strains of the bacterium in addition to interactions between *H. pylori* and different environmental factors (5,21). The

vacuolating cytotoxin A (*VacA*) and cytotoxin-associated gene A (*CagA*) are virulence factors that mediate cellular damage and oncogenesis in *H. pylori* infections. Patients infected with strains with an intact *cag* pathogenicity island develop a greater inflammatory response and are more susceptible to gastric cancer development. Most *H. pylori* isolates in Japan and South Korea possess both *CagA* and *VacA* with genetic variants associated with progression of gastric preneoplastic lesions and increased cancer risk (21). In contrast, Indian *H. pylori* strains have European origin and are less pathogenic than the strains that are predominant in Far East Asia (20,21).

Diet and environmental factors

Consumption of certain foods is associated with increased risk of gastric cancer. Ingestion of pickled vegetables, salted, smoked, cured or chemically preserved foods, together with a diet low in fresh fruits and vegetables, increase the risk of gastric cancer (5,21). Additionally, diets high in salt are implicated in the development of gastritis and potentiates the noxious effects of known gastric carcinogens such as *N*-methyl-*N*-nitro-*N*-nitrosoguanidine (MNNG) (22). Red meat, especially when preserved or cooked to high temperatures, is rich in *N*-nitroso compounds, heterocyclic amines (HCA) and polycyclic aromatic hydrocarbons (PAH), which have carcinogenic and pro-inflammatory effects (1,23,24). This effect is not seen with lamb or white meat, while consumption of fresh fish was found to be protective due to high content of polyunsaturated fatty acids (5,24). Furthermore, *H. pylori* inhibits the activity of ascorbic acid and favors the synthesis of *N*-nitroso compounds, increasing inflammation and the risk for gastric cancer (5).

Conversely, fruits and vegetables are rich in antioxidants like carotenoids, folate, phytochemicals and vitamin C that prevent metabolic damage (24,25). Higher intake of fruits and vegetables is associated with a 30–40% lower risk of gastric cancer (25). However, evaluation of the protective effect of non-dietary antioxidant sources, such as green tea and vitamin supplements have produced mixed results in preventing gastric cancer (1). Epidemiologic studies of Japanese immigrants to the United States who assimilated a Western diet exhibited a substantially lower rate of gastric cancer relative to those who did not (1,26).

Volcanic and high land regions are characterized by nitrous soils that lead to high concentrations of nitrate and nitrite in water and agricultural products. This is associated with a higher risk of gastric cancer in certain regions of

Costa Rica, Chile, Japan and Iran (24). Soil containing low concentration of molybdenum may contribute to a higher risk of gastric cancer due to its inhibitory effect in the formation of nitrosamine compounds (24).

Atrophic gastritis and intestinal metaplasia

Atrophic gastritis and intestinal metaplasia are considered precursors of gastric cancer, and both are strongly associated with *H. pylori*. A Dutch cohort study found a direct association between the severity of premalignant lesions and risk for gastric cancer (8). Within 5 years of diagnosis, the annual incidence of gastric cancer is 0.1% in patients with atrophic gastritis, 0.25% for intestinal metaplasia, 0.6% in mild-moderate dysplasia, and increases to 6% in the case of severe dysplasia (8).

Family history of gastric cancer and familial syndromes

Approximately 1–3% of gastric cancers are believed to be related to familial syndromes (27). Having a first-degree family member with gastric cancer is associated with an OR of 2–10 for developing the disease (8).

Familial adenomatous polyposis, the most common form of familial intestinal gastric cancer, is an autosomal-dominantly inherited condition that predisposes individuals to adenomatous polyps caused by germline mutations in the *APC* gene (28). Nevertheless, the lifetime risk of developing gastric cancer among these patients is less than 1%, indicating that an environmental component is also necessary for oncogenesis (1).

Other familiar syndromes associated with increased risk of gastric cancer are Lynch syndrome, gastric adenocarcinoma and proximal polyposis of the stomach, and hereditary diffuse gastric cancer (1).

Trends

The incidence of gastric cancer has been steadily decreasing over the last 50 years (1). This phenomenon can be partially explained by reduction in rates of *H. pylori* infection and improved food preservation and produce availability (1,26). However, a decrease in *H. pylori* infection rates cannot be the sole driver of this trend, which preceded the inception of any eradication program (1).

Decreases in incidence rates vary by geographic region. East Asia is experiencing a decrease in non-cardia cancer in relationship with a reduction in *H. pylori* infection rates (1).

Table 1 Recommendations for *H. pylori* eradication from the Second Asia–Pacific Consensus Guidelines

Indication for <i>H. pylori</i> eradication	Recommendation
Gastric cancer screening and eradication in communities with high incidence of gastric cancer	A
Patient's request	A
After gastric cancer resection	B
Patients with first-degree relatives with gastric cancer	B
Atrophic gastritis	B

Classification of recommendations: A (at least one randomized controlled trial in addition to consistent good quality literature), B (good quality clinical studies but no randomized clinical trials), C (absence of clinical studies of good quality, evidence obtained from expert committee reports and/or respected authorities).

This phenomenon is not seen in Central and South America, where *H. pylori* infection rates have remained stable (1). Prevalence rates of *H. pylori* infection have notably decreased in younger populations in most areas of the world. For instance, in Japan, cross sectional studies reported a prevalence of *H. pylori* infection of 80% in people born before 1950 compared to 5% among people born after 1980, while the prevalence rate in Central and South America was estimated to be 70–85% in all age groups (3). This may be due to the lack of an effective campaign for infection prevention and treatment (1). In general, the survival rates of gastric cancer have also improved over the last 40 years due to earlier detection of disease and better treatment options (1).

Gastric cancer prevention

Helicobacter pylori testing and eradication

The eradication of *H. pylori* in the developing world remains a primary goal in the prevention of gastric cancer due to its strong association with non-cardia gastric cancer. *H. pylori* eradication effectively reduces gastric cancer rates, with a greater protective effect seen in patients with higher baseline gastric cancer risk and in high incidence areas (19).

Despite these results, there are currently no worldwide guidelines for screening and eradication of *H. pylori* in asymptomatic individuals (29). On a smaller scale, the Asia-Pacific Consensus Guideline recommends *H. pylori* screening and treatment in high-risk populations (grade A recommendation) (30) (Table 1). Additional studies conducted in Japan advocate for *H. pylori* eradication in patients who have undergone endoscopic resection of a gastric adenocarcinoma (31). These studies show a decrease

in the incidence of metachronous lesions in patients who underwent *H. pylori* eradication when compared to the control groups (32). The Japanese Society for Helicobacter Research recommended *H. pylori* eradication as a measure for gastric cancer prevention (grade A recommendation) (33) (Table 2). The Europe Maastricht IV/Florence report recommends eradication of *H. pylori* in the following scenarios (grade A recommendation): populations at high-risk, first degree relatives of family members with gastric cancer, patients with previous gastric cancer treated with endoscopic or subtotal gastric resection, chronic gastric acid inhibition over 1 year, strong environmental risk factors (such as heavy smoking, occupational exposure), and per patient's request (34) (Table 3).

H. pylori screening and eradication appears to be a viable and effective preventive strategy against gastric cancer. Reducing *H. pylori* infection rates would be a more cost-effective method for preventing gastric cancer in developing regions and low socioeconomic stratus compared to endoscopic screening due to high cost and increased need for resources (35–37). Mass screening and eradication would be especially beneficial in areas with high incidence of gastric cancer, but it could also be implemented in low-risk areas (19).

Lifestyle modifications

Dietary and lifestyle interventions represent a practical strategy to prevent gastric cancer, which can be implemented in the general population (26). A wholesome diet rich in fruits, vegetables, whole grains, and low in alcohol, salt, pickled foods, and processed, smoked, or cured meats lowers the risk of stomach inflammation and gastric

Table 2 Recommendations for *H. pylori* eradication from the Japanese Society for Helicobacter Research

Indication for <i>H. pylori</i> eradication	Recommendation
Helicobacter pylori infection	A
Atrophic gastritis	A
Gastric hyperplastic polyps	A
Patients after endoscopic treatment of early gastric cancer	A

Classification of recommendations: A (at least one randomized controlled trial in addition to consistent good quality literature), B (good quality clinical studies but no randomized clinical trials), C (absence of clinical studies of good quality, evidence obtained from expert committee reports and/or respected authorities).

Table 3 Recommendations for *H. pylori* eradication from the Maastricht IV/Florence Consensus Report

Indication for <i>H. pylori</i> eradication	Recommendation
Populations at high-risk	A
First degree relatives of family members with gastric cancer	A
Chronic gastric acid inhibition over 1 year	A
Patients with previous gastric cancer treated with endoscopic or subtotal gastric resection	A
Strong environmental risk factors (heavy smoking, high exposure to dust, coal, quartz, cement and/or work in quarries)	A
Per patient's request	A

Classification of recommendations: A (at least one randomized controlled trial in addition to consistent good quality literature), B (good quality clinical studies but no randomized clinical trials), C (absence of clinical studies of good quality, evidence obtained from expert committee reports and/or respected authorities).

cancer (1,5). As mentioned previously, there are mixed results regarding the benefits of vitamin supplementation and green tea consumption (1).

Other behaviors, such as regular exercise, may also have a protective effect against gastric cancer, especially non-cardia gastric cancer (38,39). Since tobacco use has been shown to increase the risk of gastric cancer and numerous other cancers, tobacco cessation programs would also benefit individuals by decreasing their risk of gastric cancer (1).

Prophylactic therapeutics

Non-steroidal anti-inflammatory drugs (NSAIDs) have been shown to lower the risk of stomach cancer, especially non-cardia gastric cancer (28). However, NSAIDs also increase the risk of bleeding, and therefore are not recommended as a prophylactic measure for gastric cancer in the general population. Use of NSAIDs for gastric cancer prevention

should be determined on a case-by-case basis (1).

Diagnosis

Screening for gastric cancer generally involves contrast radiography and endoscopy. Endoscopy is currently considered the gold standard for gastric cancer screening because it allows direct visual examination of the gastric mucosa, as well as biopsy for histologic evaluation (1). Conventional white light endoscopy is not sufficient for accurate diagnosis and surveillance of preneoplastic lesions. Newer technologies such as magnification chromoendoscopy and narrow band imaging increased the diagnostic yield of endoscopic screening. However, this technique is operator dependent and limited by the absence of standardized interpretation (29). Though less invasive, contrast radiography has low sensitivity for early gastric cancer diagnosis (40).

Implementation of national screening programs in high incidence regions

Japan and South Korea are countries with the highest incidence of gastric cancer (41). In 1983, Japan initiated an annual gastric cancer screening program for all residents 40 years and older that consisted of an upper gastrointestinal (UGI) series. In 2016, the Japanese guidelines were updated to allow screening with either endoscopy or UGI series (41). More recent guidelines recommend screening every 2–3 years in patients that are 50 years and older (8). South Korea also initiated a national gastric cancer screening program in 1999. Similar to Japan, endoscopy or UGI series is recommended every 2 years for individuals aged 40 years and older (1). As a result of these screening programs, early gastric cancer represents over 50% of the gastric cancer diagnoses in Japan and 46–67% in South Korea (42). The high rates of early gastric cancer improved patient outcomes and multiple studies have demonstrated a reduction in gastric cancer mortality (7,8).

Possible application of screening programs in low incidence regions

Gastric cancer screening could be implemented as mass screening or selectively for individuals at increased risk. Despite the success of gastric cancer screening programs in high-incidence countries, mass screening might not be cost-effective in low incidence areas such as the United States. Therefore, screening may be considered only in individuals at high risk for gastric cancer, such as immigrants from countries with high incidence of gastric cancer, individuals with family history of gastric cancer, and patients with *H. pylori* infection (7,29). Nevertheless, a 2011 study by Gupta, Bansal, and Wani found that the cost-effectiveness of performing an upper endoscopy for screening of upper GI tract cancers at the time of screening colonoscopy was comparable to other screening interventions routinely performed in the United States (43). The cost-effectiveness relationship would be expected to improve if this intervention is performed in a predefined high-risk population.

Regarding age for screening initiation, there is data to support screening initiation both at age 40 and 50 (8). Due to a trend of decreasing gastric cancer incidence between ages 40 to 49, the new national Japanese guidelines recommend screening in individuals that are 50 years or older (8).

However, the optimal interval for endoscopic screening has not been established (1,8). In a Japanese study, the 5-year survival rate was significantly higher in those patients that had undergone endoscopic screening within the previous two years when compared to patients that had not, suggesting that a 2-year interval for screening would be appropriate (44). Furthermore, a Korean study indicated that there was an increased rate of endoscopic resections in patients that had endoscopic screening every 2 years (45). Evidence is even more limited with regards to interval screening in Western countries. Two studies from England and Italy showed that almost two-thirds of newly diagnosed gastric cancers were in advanced stages despite a surveillance interval of 1 to 2 years (46,47). Annual endoscopic surveillance has been proposed in patients with intestinal metaplasia who present additional risk factors such as smokers, patients with a family history of gastric cancer, incomplete type intestinal metaplasia, or involvement of more than 20% of the gastric mucosa (48). In the United States, an interval screening ranging between 1–3 years has been proposed in patients with atrophic gastritis or intestinal metaplasia (7,49). The same recommendations may be considered for other high-risk gastric conditions.

Although gastric cancer incidence rates are low in the United States, due to lack of screening programs, cases of gastric cancer are generally diagnosed at a later stage when treatment options are limited. Therefore, there is a need for development of clear screening guidelines in western countries.

Conclusions

- Gastric cancer is an important cause of morbidity and mortality worldwide;
- High-incidence countries have laid the foundation for disease prevention and early diagnosis strategies;
- Gastric cancer survival is low in Western countries due to diagnosis at late stages;
- Prevention mainly involves dietary changes and *H. pylori* eradication. There are no current global guidelines, but some national or continental guidelines recommend *H. pylori* screening and eradication;
- Endoscopy is the preferred gastric cancer screening modality. Chromoendoscopy and narrow band imaging are favored. Japan and South Korea have well-established endoscopic screening programs that translate into early diagnosis and increased survival;
- There is a need for the development of comprehensive

guidelines for gastric cancer screening and surveillance tailored to Western countries. Screening programs should be tailored to high-risk individuals to ensure cost-efficiency in the context of low incidence of the disease.

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