

Gastric Cancer Screening in the United States: A Review of Current Evidence, Challenges, and Future Perspectives

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Gastric cancer remains a leading cause of cancer-related mortality worldwide. In the United States, gastric cancer incidence and mortality are substantially higher among non-White racial and ethnic groups and new immigrants from high-incidence countries. This is in large part related to the higher prevalence of *Helicobacter pylori*-associated gastric premalignant changes in these populations. Apart from primary prevention, early detection of gastric cancer is the principal strategy to reduce gastric cancer mortality and improve survival. Extensive evidence in Asian countries has demonstrated the benefits of endoscopic screening in detecting early-stage gastric cancer and reducing gastric cancer-related mortality. By contrast, direct, high-quality US-based data, such as from large clinical trials or observational studies, on important outcomes of gastric cancer screening are still lacking. In this review, we evaluate and summarize the latest global evidence on the epidemiology and predisposing factors of gastric cancer as well as the efficacy, benefits vs. risks, and cost-effectiveness of gastric cancer screening. We further discuss the critical knowledge gaps and challenges in promoting gastric cancer screening in the United States. Dedicated research is urgently needed to enrich the US-based data on gastric cancer primary and secondary prevention to inform clinical practice and reduce gastric cancer-related morbidity and mortality in a cost and resource efficient manner.

KEYWORDS: gastric cancer; screening; prevention; disparity

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INTRODUCTION

Gastric cancer is the fifth most common cancer and the fifth leading cause of cancer-related mortality worldwide (1). In 2022, 968,350 new cases of gastric cancer were diagnosed globally with 659,853 cancer-related deaths. The annual burden is predicted to increase to 1.8 million new cases and 1.3 million deaths by 2040 (2). There is substantial global variation in gastric cancer incidence regarding geographic regions, race, and ethnicity, with the highest incidence rates reported in populations from East Asia, Central Asia, Eastern Europe, Mesoamerica, and Andean Latin America (1). In the United States, gastric cancer accounted for an estimated 26,890 new cases and 10,880 related deaths in 2024 (3,4). Although the United States is considered a “low-intermediate” incidence country for gastric cancer at 6.3 per 100,000 persons overall (4), incidence rates are significantly higher among Asian, non-Hispanic Black, and Hispanic populations compared with the non-Hispanic White population, and among first-generation immigrants from high gastric cancer

incidence regions (5). In the United States, gastric cancer continues to be among the top 8 causes of cancer-related deaths in Hispanic and Asian individuals (6,7). Importantly, estimates of gastric cancer incidence may underestimate the true burden of this disease because early-stage gastric cancer, which is typically asymptomatic, most often goes undiagnosed in the absence of endoscopic screening. In the United States, less than 20% of gastric cancer is diagnosed at early stage (i.e., before invasion past the submucosa) when resection is curative. This is in distinct contrast to Japan and South Korea in which early-stage gastric cancer makes up the bulk of diagnoses (50%–60%), thanks to their organized screening programs (8). Accordingly, the current 5-year survival of patients with gastric cancer in the United States is 36%, whereas gastric cancer survival in Japan and South Korea is >60% overall and 95%–99% for early-stage gastric cancer (3,8). In this review, we examine and summarize the latest global and US evidence on gastric cancer screening and discuss the knowledge gaps, challenges, and perspectives in gastric cancer screening

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in US populations. Data on endoscopic screening for gastric premalignant conditions (GPMC) such as atrophic gastritis or gastric intestinal metaplasia (GIM) alone outside the context of gastric cancer screening are scarce. Therefore, we will review available evidence for gastric cancer screening without a specific focus on screening for GPMC alone.

HETEROGENEITY OF GASTRIC CANCER

Gastric cancer comprises a group of morphologically and biologically heterogeneous malignancies including adenocarcinoma, lymphoma, neuroendocrine tumor, sarcoma, and stromal tumor, among others, with adenocarcinoma accounting for most cases (9). The main anatomic dichotomization is cardia vs. noncardia. Adenocarcinoma of the gastric cardia is closely associated with chronic acid reflux and shares biologic and epidemiologic characteristics with adenocarcinoma of the distal esophagus and gastroesophageal junction (2,10–13). By contrast, most noncardia gastric adenocarcinoma (NCGA) cases are attributable to chronic *H. pylori* infection. Gastric adenocarcinoma also has 2 main histologic subtypes by Lauren Classification: intestinal and diffuse subtypes (14,15). *H. pylori* is the single most important risk factor of intestinal type NCGA. Chronic *H. pylori* infection initiates and perpetuates the carcinogenesis cascade from chronic nonatrophic gastritis to mucosal atrophy, intestinal metaplasia, dysplasia, and eventually to adenocarcinoma—a multistep process known as the Correa cascade (16–19). The development of diffuse gastric adenocarcinoma is less well understood, but likely involves multiple factors involved in cell signaling pathways, cell-cell adhesion, and *H. pylori* infection (20). There are other classification systems of gastric cancer based on histopathology and molecular characteristics that are less commonly used in clinical practice (21–24). In this review, we restrict the terminology of gastric cancer to gastric adenocarcinoma, with the primary focus on NCGA.

IDENTIFYING POPULATIONS AT INCREASED RISK OF GASTRIC CANCER IN THE UNITED STATES

Understanding the risk factors of gastric cancer is crucial to identifying populations that are at increased risk and may benefit from targeted screening (25). Currently identified risk factors include non-White race or Hispanic ethnicity, being an early-generation immigrant from a high gastric cancer incidence region, presence of GPMCs (including atrophic gastritis, GIM, and dysplasia), family history of gastric cancer, certain inherited cancer syndromes, chronic *H. pylori* infection, lower socioeconomic status and ethnic enclave, tobacco smoking, excessive alcohol use, dietary factors such as high salt diet, and possibly autoimmune gastritis (AIG) (5,26–29). In addition, there has been increasing evidence suggesting long-term acid suppression due to chronic proton-pump inhibitors or potassium-competitive acid blockers use may be associated with an increased risk of gastric cancer, although many studies had important limitations with conflicting results (30–35). Additional high-quality data are needed to further clarify the risk of gastric cancer associated with long-term proton-pump inhibitor or potassium-competitive acid blocker use.

Race, ethnicity, and immigration history

The United States is a melting pot of individuals from diverse racial and ethnic backgrounds. The incidence of gastric cancer is

significantly higher in Asian/Pacific Islander, Black, Hispanic, and American Indian/Alaska Native individuals and immigrants from countries of high gastric cancer incidence, compared with non-Hispanic White (nonimmigrant) individuals (1,26). Based on a population-based study using California Cancer Registry data, age-standardized and sex-standardized incidence of NCGA among individuals aged 50 years or older were 1.8-fold to 13.3-fold higher in the most populous non-White groups in the United States compared with non-Hispanic White persons (36). Specifically, the incidence rate ratio (95% confidence interval [CI]) for NCGA was 3.79 (3.50–4.09) for Hispanic individuals compared with non-Hispanic White individuals. Among Asians, NCGA risk varied substantially by subgroups, with incidence rate ratio of 4.77 (4.26–5.34) for Chinese Americans, 5.18 (4.33–4.75) for Japanese Americans, 13.3 (11.8–14.9) for Korean Americans, and 1.81 (5.16–5.41) for Filipino Americans, compared with non-Hispanic White Americans (36). These findings underscore the importance of collecting and reporting desegregated racial and ethnic data on gastric cancer incidence to identify the subracial/ethnic groups who are at high risk of gastric cancer. Of note, the incidence rates of NCGA in Japanese Americans (33.6 [27.0–41.4] per 100,000 person-years) and Korean Americans (70.0 [60.5–80.5] per 100,000 person-years) are similar to or higher than the incidence rates of colorectal cancer (35.9 per 100,000 person-years) among the general US population for which screening is recommended starting at the age of 45 years (36–38).

Based on data from the Pew Research Center, as of 2020, more than 40 million people living in the United States were born in another country, with the vast majority immigrating from countries that qualify as high-incidence countries for gastric cancer (Table 1). The region of origin is an important determinant of gastric cancer risk (39) because immigrants from high-to-low-incidence countries retain their elevated risk of gastric cancer incidence and mortality. Based on a recent systematic review and meta-analysis, first-generation immigrants from high-incidence geographic areas had markedly higher incidence and mortality of gastric cancer, with pooled standardized incidence ratio 1.66 (95% CI 1.52–1.80) for men and 1.83 (95% CI 1.69–1.98) for women for all gastric cancers, and 1.80 (1.65–1.95) for men and 1.62 (1.47–1.76) for women for NCGA (5). Of note, the risk of gastric cancer appears to decrease with subsequent generations of immigrants born to and acculturating in the host country (29). This observation highlights the impact of potentially modifiable environmental factors, such as diet and behavioral factors (discussed below), as adjuncts to gastric cancer screening to reduce gastric cancer incidence and mortality.

Chronic *Helicobacter pylori* infection

H. pylori has been classified by the World Health Organization's International Agency for Research on Cancer as a group 1 or definite carcinogen (45). Approximately 90% of noncardia gastric cancer cases are attributable to chronic *H. pylori* infection (16,17). In a recent meta-analysis of 10 randomized controlled trials, *H. pylori* eradication was associated with a 46% (relative risk [RR] 0.54, 95% CI 0.40–0.72; number needed to treat = 72) reduction in gastric cancer risk, with a 39% (RR 0.61, 95% CI 0.40–0.92, number needed to treat = 135) reduction in gastric cancer-related mortality (46). The mass eradication program of *H. pylori* in Matsu Island, Taiwan, led to a dramatic reduction in the *H. pylori* prevalence rate (from 64.2% to 15.0%) and a 53% (95% CI 30%–

Table 1. Age-standardized incidence rates of gastric cancer in high incidence regions and their corresponding immigrant populations in the United States

Region	Nation	Age-standardized incidence rate of gastric cancer (per 100,000 persons)	US foreign-born immigrant population
Total US foreign-born population			47.83 million
Mesoamerica	Honduras	19.9	943,617
	El Salvador	15.9	1,494,869
	Costa Rica	14.0	104,798
	Guatemala	12.2	1,250,053
	Nicaragua	10.4	377,152
	Southern Mexico	(>10)	(2,751,388)
Andean South America	Peru	14.3	529,682
	Chile	14.2	137,644
	Colombia	12.9	1,049,821
	Ecuador	12.8	539,546
East Asia	Japan	27.6	337,877
	S. Korea	27.0	680,747
	Bhutan	15.9	22,873
	China	13.7	2,827,634
	Vietnam	13.4	1,365,841
	Myanmar	11.8	159,647
	Laos	11.3	161,116
Central Asia	Kazakhstan	13.7	50,833
	Uzbekistan	10.3	74,967
Middle East	Iran	19.4	419,885
	Armenia	12.1	104,153
	Turkey	11.7	156,956
	Afghanistan	11.0	218,612
Eastern Europe	Bulgaria	18.2	70,801
	Belarus	15.3	75,035
	Russia	13.7	415,809
	Lithuania	11.7	36,743
	Ukraine	10.5	468,780
Other	Portugal	12.8	160,729
	Albania	12.6	106,957
	Zimbabwe	10.3	8,025

Notes: (i) Data shown are based on GLOBOCAN 2022 (1), US Census data (40) and additional sources (41,42). (ii) Mexico is categorized as a low incidence and mortality nation by GLOBOCAN 2022. However, 7 states in southern Mexico, in proximity to Guatemala (Campeche, Chiapas, Mexico City [D.F.], Guerrero, Morelos, Oaxaca, Yucatan), are classified as high incidence and mortality regions (43). During the period of 2004–2015, these 7 states accounted for 25.2% of all US foreign-born immigrants from Mexico (5,44). (iii) The following high gastric cancer incidence countries (defined as age-standardized rate >10) were not listed as their corresponding US immigrant populations were limited or not reported: Mongolia, Tajikistan, Azerbaijan, Kyrgyzstan, Mali, Democratic Republic of Korea, Estonia, Guadalupe (France), Latvia, Turkmenistan, Samoa, Sao Tome and Principe, Martinique (France), and Brunei Darussalam.

69%) reduction in gastric cancer incidence (47). In a Colombian cohort study, *H. pylori* eradication therapy resulted in a 41% reduced risk of disease progression over the 20-year follow-up among individuals with GIM at baseline (48). Even in patients with a history of endoscopic resection of gastric dysplasia or early gastric cancer, *H. pylori* treatment substantially reduced the risk of metachronous gastric cancer and gastric neoplasms (49–51). Recent observational studies in the US populations also showed the benefits of *H. pylori* treatment on gastric cancer risk reduction in Western populations (52,53). In a large community-based population in California, *H. pylori* eradication therapy was associated with a 63% risk reduction in gastric cancer after 8 years (53).

In the United States, non-White racial and ethnic groups had substantially higher prevalence of *H. pylori* compared with non-Hispanic White population, which is the primary driver of

significantly increased risk of gastric cancer in these groups (25,54,55). In a recent large study of *H. pylori* burden among US veteran population, between 1999 and 2018, the overall *H. pylori* test positivity rate was highest in non-Hispanic Black (40.2%, 95% CI 40.0%–40.5%) and Hispanic (36.7%, 95% CI 36.4%–37.1%) individuals and lowest in non-Hispanic White individuals (20.1%, 95% CI 20.0%–20.2%) (56). In a large community-based population in California, nonserological *H. pylori* test positivity rate (95% CI) was significantly higher among Asian (23.2% [22.8%–23.6%]), Black (25.1% [24.4%–25.8%]), and Hispanic (28.1% [27.7%–28.5%]) individuals than non-Hispanic White individuals (10.0% [9.8%–10.2%]) (57). Patterns were similar for serological positivity, although with approximately 2-fold higher rates (57). Taken together, these results underscore the importance of optimizing *H. pylori* testing and eradication in high-risk populations as part of primary prevention of gastric cancer.

Gastric premalignant conditions

Main GPMCs include atrophic gastritis, GIM, and dysplasia. The overall prevalence of atrophic gastritis is estimated at 15% in the US population, while GIM is observed in approximately 5%–15% of patients undergoing upper endoscopy with gastric biopsies in Western populations (27,58). Limited data showed that the prevalence of dysplasia ranges from 0.5% to 3.75% in the general Western populations (59). However, the prevalence of GPMC is markedly higher in non-White groups and first-generation immigrants from high gastric cancer incidence countries (27,60,61). In a population-based study from Sweden, the hazard ratios (95% CI) for developing noncardia gastric cancer in individuals with atrophic gastritis, GIM, and dysplasia were 5.0 (3.8–6.7), 6.5 (4.8–8.9), and 12.1 (8.3–17.6), respectively, compared with normal gastric mucosa (62). A recent meta-analysis showed a 10-year cumulative risk of progression to gastric cancer among patients with GIM was 1.6% (1.5%–1.7%) (63). However, individuals with anatomically extensive atrophic gastritis or GIM (involving both antrum and corpus) or incomplete subtype of GIM have a significantly higher risk of progressing to NCGA. It is important to mention that once GIM is present, race, ethnicity, and country of origin in and of itself do not appear to be independently associated with a higher baseline risk of progression to gastric cancer (63).

Family history

Multiple factors may contribute to the familial aggregation of gastric cancer, including shared genetic predisposition, environmental, lifestyle, diet and cultural factors, *H. pylori* infection, and a combination thereof. The risk of gastric cancer among individuals with a positive family history varies widely from approximately 2-fold to 10-fold based on observational studies (64). Approximately 10% of patients with gastric cancer have a positive family history, while only about 1%–3% are related to hereditary cancer syndromes (discussed below) (65). A recent systematic review and meta-analysis showed a significantly increased risk of gastric cancer among individuals with a first-degree relative with gastric cancer (odds ratio [OR] 2.92, 95% CI 2.40–3.55) (66). In addition, patients with GIM and a first-degree family history of gastric cancer had 4.5-fold higher odds (OR 4.53, 95% CI 1.33–15.46) of progressing to gastric cancer compared with patients with GIM and negative family history (63). The increased risk of gastric cancer among individuals with a positive family history provides the rationale to consider screening in this population. In a recent prospective pilot study of 61 individuals in California with a family history of gastric cancer in first-degree relatives, 27 (44%) were found to have GIM and 4 (7%) to have dysplasia on screening endoscopy with mapping biopsies (67).

Hereditary cancer syndromes

There are 2 main groups of hereditary cancer syndromes with increased gastric cancer risk: (i) principal hereditary gastric cancer syndromes: hereditary diffuse gastric cancer, familial intestinal gastric cancer, gastric adenocarcinoma and proximal polyposis of the stomach; and (ii) hereditary cancer syndromes with an increased gastric cancer risk: Lynch Syndrome, hereditary gastrointestinal polyposis syndromes, and other cancer syndromes with an increased gastric cancer risk (such as hereditary breast and ovarian cancer syndrome and Li-Fraumeni syndrome) (Table 2). A recent study from Japan reported enhanced gastric cancer risk related to

H. pylori infection in individuals who carried germline pathogenic variants of homologous-recombination genes (68). Patients with a strong family history suggestive of hereditary cancer should be referred to genetics for counseling (69,70). We suggest screening for gastric cancer in persons diagnosed with hereditary cancer syndromes with an increased risk of gastric cancer. The starting age and interval of screening should be individualized according to the risk associated with each condition.

Diet, lifestyle, and socioeconomic factors

The overall quality of evidence on the association between diet, behavioral and socioeconomic factors, and gastric cancer risk is low and insufficient to inform a clear threshold to consider gastric cancer screening based on these factors alone. However, these are relevant adjunctive modifiable measures for gastric cancer risk attenuation. Multiple studies reported that high salt diet, ingestion of red meat or processed meat, salted fish, and pickled vegetables were associated with increased risk of gastric cancer, while eating total fruit, citrus fruit, and white vegetable was associated with a lower risk (96–100). In a meta-analysis of 42 observational studies, current cigarette smokers had a 53% higher risk of gastric cancer compared with never smokers, and the risk was higher in men (RR 1.62, 95% CI 1.50–1.75) than in women (RR 1.20, 95% CI 1.01–1.43) (101). A meta-analysis of 68 case-control studies and 13 cohort studies found a significant association between alcohol use and gastric cancer risk (OR 1.20, 95% CI 1.12–1.27), with the risk being higher among heavy drinkers (OR 1.30, 95% CI 1.17–1.44) (102). Being overweight or obese is associated with an increased risk of cancer of gastric cardia but has not been consistently associated with noncardia gastric cancer (99). Last, a recent study revealed lower socioeconomic status and high ethnic enclave (indicating low acculturation) were associated with increased incidence of NCGA (29).

Autoimmune gastritis

AIG is a chronic inflammatory condition of the stomach caused by autoimmune destruction of parietal cells of the gastric corpus, resulting in progressive atrophy of the gastric oxytic mucosa with sparing of the gastric antrum. The estimated prevalence of AIG ranges from 0.5% to 2% in the general population, with female-to-male ratio of 2–3:1 (28,103,104). The parietal cell loss in AIG leads to chronic hypochlorhydria or achlorhydria with resultant enterochromaffin-like cell hyperplasia, a precursor of neuroendocrine tumor (105). Multiple studies showed that AIG and pernicious anemia (a late-stage complication of AIG) are associated with an increased risk of both gastric adenocarcinoma and type 1 neuroendocrine tumor (106,107). However, in a recent prospective cohort study of 211 patients with AIG but without current or prior *H. pylori* infection, no incident invasive gastric adenocarcinoma cases were detected after a mean follow-up time of 7.5 years (108). These findings need to be further validated in different populations and with a longer follow-up time to further inform the risk of gastric cancer in individuals with AIG with or without a history of *H. pylori* infection (109).

GLOBAL EVIDENCE ON GASTRIC CANCER SCREENING AND RELEVANCE TO US PRACTICE

Gastric cancer screening in principle

In 1968, the World Health Organization published guidelines on the principles of screening for disease (also known as the Wilson

Table 2. Hereditary cancer syndromes with an increased risk of gastric cancer

Syndrome	Gene	Lifetime risk of gastric cancer	References
Principal hereditary gastric cancer syndromes			
Hereditary diffuse gastric cancer	<i>CDH1, CTNNB1</i>	20.5%-42% for men and 13.6-33% for women by age 80	(71-73,87)
Familial intestinal gastric cancer	<i>IL12RB1, TP53</i>	Insufficient data	(74,75)
Gastric adenocarcinoma and proximal polyposis of the stomach	<i>APC</i> promoter 1B	Insufficient data	(76,77)
Hereditary cancer syndromes with increased risk of gastric cancer			
Lynch syndrome	<i>MLH1</i> <i>MSH2</i> <i>MSH6</i> <i>PMS2</i>	5%-7% 0.2%-9% <1%-7.9% Insufficient data	(78-80) (78-83) (79,81)
Familial adenomatous polyposis	<i>APC</i>	1%-2%	(69,84,85)
Peutz-Jeghers syndrome	<i>STK11</i>	29%	(86-89)
Juvenile polyposis syndrome	<i>SMAD4/BMPR1A</i>	Up to 21%	(87,88,90,91)
Li-Fraumeni	<i>TP53</i>	5%-10%	(92)
Hereditary breast and ovarian syndrome	<i>BRCA1/BRCA2</i>	Up to 21.3%	(93,94)
<i>MUTYH</i> -polyposis	<i>MUTYH</i>	1%	(95)
Homologous recombination genes (with <i>H. pylori</i> infection)	<i>ATM, BRCA1, BRCA2, and PALB2</i>	Vary	(68)

and Jungner criteria) (Table 3) (110). Targeted gastric cancer screening among high-risk individuals in the United States fulfills most of the criteria, although some critical evidence gaps remain to be addressed. Multiple studies from East Asia demonstrated unequivocal benefits of gastric screening in early gastric cancer detection and reducing gastric cancer-related mortality. By contrast, no direct, high-quality data exist in the United States, such as randomized controlled trials or large observational studies, regarding the impact of gastric cancer screening on important health outcomes, such as gastric cancer mortality (Table 4). This critical evidence gap creates a major barrier to soliciting endorsement from professional societies, policy changes, and insurance coverage. In this section, we summarize the experience in Japan and South Korea—2 prototype nations that have established systematic gastric cancer screening programs, and discuss gaps and challenges we are facing in implementing gastric cancer screening in the United States.

Methods of gastric cancer screening

Fluoroscopy (or upper gastrointestinal series). Fluoroscopy/upper gastrointestinal series (UGIS) has been used as a primary screening method for gastric cancer in Japan since the 1960s (111-113). However, the performance of fluoroscopy is inferior to endoscopy for gastric cancer screening based on multiple studies and is now less often used in East Asia, particularly in the current era of easy access to endoscopy and advances in endoscopic diagnostic and therapeutic techniques (114,115).

Endoscopy. Upper endoscopy allows for direct visualization of the gastric mucosa and possible endoscopic resection of visible neoplasia. Data from South Korea showed the sensitivity of screening endoscopy and UGIS for gastric cancer detection was

69.0% and 36.7%, respectively, and specificity was 96.0% and 96.1%, respectively (116). Endoscopy has a distinct advantage of detecting GPMCs, which is critical for appropriate risk stratification and formulating surveillance strategies (105,117). The newer generation high-definition white light endoscopy and image enhancing technologies further improve the ability of endoscopy to identify early gastric cancer and GPMCs (118,119). On high-definition white light endoscopy, atrophic mucosa appears pale with a loss of rugal folds and increased visibility of submucosal vessels while typical intestinal metaplasia presents as tubulovillous mucosal patterns, with light blue crests or white opaque substance on image-enhancing techniques, such as narrow-banding imaging (105). Areas with dysplasia may manifest with irregular mucosal vessels with loss of architecture. Visible areas of dysplasia can be resected endoscopically or surgically, which eliminates the risk of malignant transformation.

Serum biomarkers. Screening for *H. pylori* is not considered a screening test for gastric cancer per se, but has been shown to be effective in reducing gastric cancer incidence and mortality through *H. pylori* eradication, as discussed above (120). Serum pepsinogen (PG) I and II levels have been extensively studied in East Asia as a tool for risk stratification (121-123). A decreased PG I level (<70 µg/L) or decreased PG I/II ratio (<3.0) indicates extensive mucosal atrophy involving the gastric corpus, a well-established change associated with increased risk of gastric cancer (121,123-127). However, PG testing is not routinely available in the United States, with limited data on its efficacy as a screening tool (128). Other blood tests such as gastrin 17, microRNA, and serum trefoil factor 3 are not routinely available in the United States (121,129,130). Liquid biopsy based on detection of

Table 3. World Health Organization principles for screening of disease and relevance to gastric cancer as a potential target for screening

Wilson and Jungner principles of screening for disease (110)		Eligibility of gastric cancer as a target for screening in the United States
1	The condition sought should be an important health problem	Increased disease burden in non-White racial and ethnic groups, persons with a strong family history of gastric cancer, and new immigrants from high-incidence countries
2	There should be an accepted treatment for patients with recognized disease	Early diagnosis and resection are associated with superior 5-yr survival
3	Facilities for diagnosis and treatment should be available	Endoscopic and surgical resection techniques are available in the United States
4	There should be a recognizable latent or early symptomatic phase	Long sojourn time from premalignant conditions to cancer allows for early endoscopic detection through screening and surveillance
5	There should be a suitable test or examination	Endoscopic detection of gastric premalignant conditions and gastric cancer is feasible, although the expertise is not widely established in US practices
6	The test should be acceptable to the population	Upper endoscopy for gastric cancer screening is generally safe, although invasive and costly. Screening for asymptomatic individuals is generally not covered by insurance
7	The natural history of the condition, including the development from latent to declared disease, should be adequately understood	The natural history of noncardia gastric adenocarcinoma is a well-understood multistep pathogenesis process including chronic gastritis, atrophic gastritis, intestinal metaplasia, dysplasia, and adenocarcinoma
8	There should be an agreed policy on whom to treat as patients	Screening for asymptomatic individuals is not agreed on by the US professional guidelines due to lack of direct, high-quality evidence on important outcomes such as mortality benefits from screening
9	The cost of case finding (including a diagnosis and treatment of patients diagnosed) should be economically balanced in relation with possible expenditure on medical care as a whole	Targeted endoscopic screening of gastric cancer in high-risk individuals such as non-White racial and ethnic groups and new immigrants from high-incidence countries has been shown to be cost-effective in the United States, if combined with colonoscopy
10	Case finding should be a continuous process and not a "once and for all" project	Screening for gastric cancer and surveillance for premalignant conditions should be performed periodically in high-risk individuals

circulating tumor cells or tumor DNA, circulating free DNA, in blood, saliva, and urine has shown great promise as a novel tool for early detection, monitoring, and prognostication of gastric cancer (131). A recent study from China using extracellular vesicle-derived long noncoding RNA (GC1nc1) identified early-stage gastric cancer (stage I/II) with an area under the curve of 0.94 (95% CI 0.91–0.97). This marker also distinguished early-stage gastric cancer from GPMC, such as atrophic gastritis and GIM (132). The utility of liquid biopsy as a population-based screening tool still needs to be further investigated before it can be adopted in clinical practice.

Organized screening in Asia with high gastric cancer incidence
 Population-based screening programs in Japan and South Korea have resulted higher rates of curable-stage gastric cancer detection and substantially better 5-year survival rates compared with Western countries (3,133,134). Japan was the first country in the world to initiate a national gastric cancer screening program, which was established in 1983 (112). Current guidelines recommend screening for gastric cancer among individuals aged 50 years or older using either upper endoscopy or UGIS (111). In South Korea, a gastric cancer screening program was initiated in 1999 and formally integrated into the National Cancer Screening Program (NCSP) in 2002 (135). The program recommended either biennial upper endoscopy or UGIS to screen individuals aged 40 years or older (135).

The efficacy of gastric cancer screening in detecting early-stage gastric cancer

Early gastric cancer, defined as gastric cancer that has not invaded past the submucosa irrespective of lymph node involvement, is curable with complete resection, either surgically or endoscopically (136–138). A prospective study by the Japan Clinical Oncology Group examining curative endoscopic submucosal dissection for early gastric cancer revealed a 5-year survival rate of 97.0% (136). In South Korea, the proportion of gastric cancers diagnosed at an early stage increased from 39% in 2001 to 73% in 2016 based on NCSP data (8). Compared with the United States where only 28% of gastric cancers were localized at the time of diagnosis, the percentages of localized cancers at diagnosis were 51% in South Korea and 48% in Japan; 37% gastric cancers diagnosed in the United States already had distant metastasis in contrast to 12% and 16% in South Korea and Japan, respectively (8). These data provide convincing evidence that supports the benefit of organized gastric cancer screening using upper endoscopy in detecting early-stage cancer and reducing mortality in Asia where the population risk of gastric cancer is high. However, direct US-based data on the efficacy of gastric cancer screening in detecting early-stage gastric cancer are not available (Table 4).

The impact of gastric cancer screening on reducing mortality

Multiple observational studies from East Asia have also shown clear benefits of gastric cancer screening in reducing cancer

Table 4. Comparison of available evidence related to gastric cancer screening in East Asia and United States^a

	East Asia	United States
Population risk of gastric cancer	High	High among first-generation immigrants from high-incidence countries; intermediate-to-high among individuals of non-White races or Hispanic ethnicity; low in non-Hispanic White individuals
Organized population screening program	Yes	No
Randomized controlled trials on gastric cancer screening	No	No
Large observational studies on gastric cancer screening	Yes	No
Gastric cancer screening outcomes		
Improved detection of early-stage gastric cancer	Yes	No data
Improve gastric cancer-related mortality	Yes	No data
Is gastric cancer screening cost-effective?	Yes	Yes, if endoscopy is bundled with colonoscopy, starting at age 45–50 for high-risk individuals

^aEast Asia here refers to Japan and South Korea, which have organized screening programs for gastric cancer.

mortality (114,139–143). Retrospective cohort studies and case-control studies from Japan reported an overall 31%–79% reduction in gastric cancer mortality through endoscopic screening (139,141–144). The NCSP in South Korea using either endoscopy or UGIS resulted in a 21% reduction in overall mortality among individuals aged 40 years or older compared with no screening (114). Gastric cancer-related mortality decreased by 47% using upper endoscopy, primarily in individuals aged 40–74 years. In addition, the mortality benefits seemed to be dose dependent with the number of endoscopies performed, with gastric cancer-related death decreased by 40%, 68%, and 81% after 1, 2, and 3 or more endoscopies, respectively (114). In a recent meta-analysis that included 6 cohort studies and 4 nested case-control studies comprising 342,013 individuals, all from Asia, endoscopic screening was associated with an overall 40% risk reduction in gastric cancer mortality (145). Importantly, endoscopy screening was not associated with a reduction in gastric cancer incidence (RR 1.14, 95% CI 0.93–1.40), indicating that it was the early

detection of gastric cancer in organized screening programs that drove the mortality benefits (145). At this time, no studies have evaluated the impact of screening on gastric cancer mortality in US populations.

COST-EFFECTIVENESS OF ENDOSCOPIC SCREENING FOR GASTRIC CANCER

The increased detection of early-stage cancer and mortality benefit associated with endoscopic screening needs to be economically balanced with the costs of case finding and treatment (110). Indeed, multiple studies supported the cost-effectiveness of gastric cancer screening in high-incidence countries, such as in East Asia (146–151). A cost-utility study in Portugal, an intermediate-incidence Western country with ASR 13.1/100,000, showed endoscopy every 5–10 years at the time of colonoscopy for a positive FOBT was cost-effective, while stand-alone endoscopy was not. The author concluded that endoscopic screening for gastric cancer in Europe could be cost-effective if

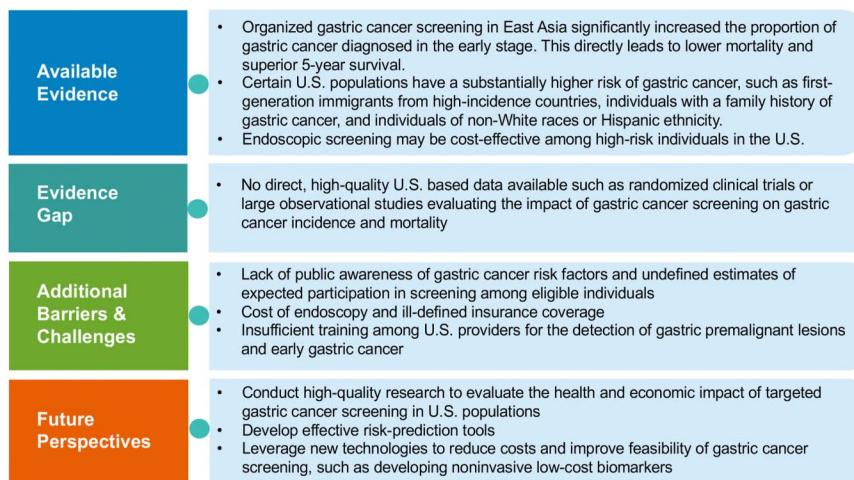


Figure 1. Gastric cancer screening in the United States: available evidence, knowledge gaps, barriers and challenges, and future perspectives.

combined with a screening colonoscopy in countries with a gastric cancer risk ≥ 10 per 100,000 (152).

Regarding US populations, Gupta and colleagues found that one time endoscopic screening for esophageal adenocarcinoma and squamous cell cancer in addition to gastric adenocarcinoma in the general US population at the time of screening colonoscopy at the age of 50 years required \$115,664 per quality-adjusted life year (QALY) compared with no screening or surveillance (153), although this study did not stratify the risk based on race and ethnicity. Saumoy and colleagues assessed the cost-effectiveness of endoscopy screening for NCGA bundled with screening colonoscopy for a person aged 45 years to 50 years, stratified by race and ethnicity, with a willingness-to-pay threshold of \$100,000/QALY (154). The study found that endoscopy with continued surveillance when GIM or more advanced pathology was identified was cost-effective for Asian Americans (\$71,451/QALY), Hispanic Americans (\$76,070/QALY), and non-Hispanic Black Americans (\$80,278/QALY), but not for non-Hispanic White Americans (\$122,428/QALY). This group further demonstrated that the same screening strategy was cost-effective for Asian Americans across many countries of origin, with the lowest incremental cost-effectiveness ratio observed for Chinese, Japanese, and Korean Americans (all $< \$75,000$ /QALY) (155). These US-based studies required bundling endoscopy with screening colonoscopy, and thus, the findings cannot be applied to those who undergo colorectal cancer screening through non-endoscopic methods, such as testing fecal occult blood or fecal DNA, or opt out of colorectal cancer screening. In a recent microsimulation modeling study, surveillance of GIM independent of colonoscopy was cost-effective, particularly among high-risk individuals, and associated with lower mortality and increased life-years gained (156).

GASTRIC CANCER SCREENING IN THE UNITED STATES: THE EVIDENCE GAPS, CHALLENGES, AND FUTURE PERSPECTIVES

Paucity of direct, US-based data on gastric cancer screening

In 2015, the American Society of Gastrointestinal Endoscopy suggested endoscopic gastric cancer screening may be considered in US immigrants from high-risk regions including Korea, Japan, China, Russia, and South America, especially if there is a family history of gastric cancer in a first-degree relative, based on low-quality evidence (157). However, despite robust evidence demonstrating the benefits of endoscopic screening in improving the detection of early gastric cancer and reducing gastric cancer mortality in Asian countries, direct, high-quality US-based data on important outcomes of gastric cancer screening, such as randomized trials or large observational studies, are nonexistent. The inaugural guidelines from the American College of Gastroenterology could not make a recommendation for or against screening for gastric cancer and GPMC among high-risk US populations due to insufficient evidence, as determined by the Grading of Recommendations, Assessment, Development, and Evaluations methodology (158). This represents a critical knowledge gap that awaits to be addressed with further research before more definitive guideline recommendations can be made. At this point, consideration of screening endoscopy for individuals deemed at high risk for gastric cancer based on aforementioned demographic factors and/or family history should be individualized and based on a shared decision-making process between the providers and patients. Adding endoscopy at the

time of colonoscopy to reduce the cost of separate endoscopy can be considered at the discretion of the provider, balancing the estimated yield of detection of premalignant lesions or gastric cancer and the risks and cost associated with endoscopy.

Additional barriers to early diagnosis of gastric cancer in the US populations

As discussed above, a substantially higher proportion of patients with gastric cancer diagnosed in the United States already had distant metastasis, with significantly worse 5-year survival, which is in stark contrast with the outcomes in Japan and South Korea. Factors contributing to this difference in outcomes include limited awareness of high-risk populations among both providers and patients, lack of insurance coverage for upper endoscopy performed for asymptomatic patients, lack of consistent implementation of and adherence to endoscopy quality benchmarks to ensure a high-quality examination, and insufficient training for endoscopists of all levels to improve the detection of GPMC and early gastric cancer.

Lack of awareness of eligible high-risk populations. Gastric cancer has long been underappreciated as a leading GI cancer in the United States and the leading GI cancer among certain immigrant groups, with significantly higher incidence than esophageal cancer and, in some groups, colon cancer, both of which have well-established screening and surveillance guidelines (159). Despite this rank order regarding incidence, gastric cancer ranks the *lowest* in funding by the National Cancer Institute on the list of 19 most common cancers in the United States (160). To move the needle, there needs to be increased awareness through education and campaign among patients, clinical providers, stakeholders, and funding organizations regarding the substantial racial and ethnic disparities in gastric cancer risk and mortality (161).

Cost of endoscopy and lack of insurance coverage for asymptomatic patients. Without coverage, the cost of endoscopy (along with pathology costs) can be prohibitive for most individuals deemed at high risk for gastric cancer. The US Preventive Services Task Force has endorsed screening coverage for breast, cervical, colorectal, and lung cancer as preventive care (162). High-quality US-based evidence on the benefits and efficacy of gastric cancer screening in high-risk populations is needed to inform policy changes to cover the cost of screening, hand in hand with efforts on engaging stakeholders and policy makers.

Lack of endoscopic quality metrics and insufficient training for US endoscopists. Available data suggest that approximately 10% of gastric cancers are missed by endoscopy (163,164). High patient volume and fast-paced gastroenterology practice make it particularly challenging to perform a high-quality examination. The new guidelines by the American College of Gastroenterology and recent American Gastroenterological Association Clinical Practice Update both recommend using high-definition endoscopy with sufficient gastric inspection time and photo-documentation of the entire gastric mucosa to improve the detection of both gastric cancer and GPMC, such as GIM or dysplasia (158,165). In contrast to the focuses on endoscopic detection of Barrett esophagus or colorectal adenomas, little training is included in the current US Gastroenterology fellowship curriculum on following standardized biopsy protocols and on endoscopic detection of GPMC or early gastric cancer. This insufficiency has contributed to high variation in the quality of endoscopy with poor patient risk stratification (166–169).

Systematic training programs for US endoscopists are urgently needed to address this gap.

FUTURE PERSPECTIVES

In addition to generating high-quality US-based data on important outcomes of gastric cancer screening, future research aimed at improving the precision, reducing the cost, and improving the uptake and adherence of cancer screening may also lead to paradigm shifts that make targeted gastric cancer screening more feasible and cost-effective.

Improve the precision of gastric cancer screening

The heterogeneity of gastric cancer and varying incidence among different populations make it impossible to design a one-size-fits-all screening strategy. Development of effective risk prediction tools that incorporate both available data on gastric cancer risk factors and the rapidly expanding evidence on genetic predisposition will greatly improve the precision for identifying individuals who would benefit most from gastric cancer screening.

Develop noninvasive markers and new screening methods

Noninvasive markers have the advantages of being convenient, safe, and with potentially superior adherence as a screening tool. The feasibility of using 1 or more of known noninvasive markers as a screening tool, such as *H. pylori*, serum pepsinogen I and II, gastrin 17, microRNA, and serum trefoil factor 3, in US population should be further investigated (120–130). Recent progress in understanding the molecular landscape of gastric cancer offers great potential for new screening modalities (22). In particular, liquid biopsy methods based on detection of circulating tumor cells or tumor DNA, circulating free DNA, in blood, saliva, and urine may become a highly effective tool for screening, monitoring, and prognostication of gastric cancer (131,132).

CONCLUSIONS

Gastric cancer remains a leading gastrointestinal cancer in incidence and mortality in the United States. Apart from primary prevention of gastric cancer, early detection is the principal strategy to reduce cancer-related mortality and improve survival. Accumulating epidemiological evidence has indicated substantial higher burden of gastric cancer in certain US populations, particularly first-generation immigrants from the high gastric cancer incidence geographic regions, those with a strong family history of gastric cancer, and people of non-White races or Hispanic ethnicity. Although targeted screening in these populations may be reasonable and is supported by cost-effective data, direct, high-quality US-based data such as large clinical trials or observational studies demonstrating the benefits of gastric cancer screening on important outcomes such as early cancer detection or improved cancer mortality are not available (Figure 1). Further research is urgently needed to address this critical evidence gap to inform clinical practice. In addition, efforts are needed to raise awareness among both providers and patients regarding the risk factors of gastric cancer, improve the precision of risk prediction, and leverage new technologies, with the ultimate goal of reducing gastric cancer-associated morbidity and mortality.

CONFLICT OF INTEREST

Guarantor of the article: Dan Li, MD.

Specific author contributions: D.L., D.R.M., and S.C.S.: study concept and design. D.L., D.R.M., and S.C.S.: drafting of the

manuscript. All authors: analysis and interpretation of evidence and manuscript editing.

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