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SYSTEMATIC REVIEWS AND META-ANALYSES

Siddharth Singh, Section Editor

An Approach to the Primary and Secondary Prevention of Gastric Cancer in the United States

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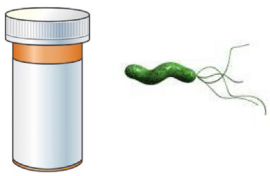
Primary Prevention

***Helicobacter pylori* testing and eradication**

Secondary Prevention

Endoscopic screening of at-risk populations



Gastric cancer remains a leading cause of cancer mortality among certain racial, ethnic, and immigrant groups in the United States. This *White Paper* offers a framework for how mechanisms of primary and secondary prevention can be used to improve outcomes and reduce disparities in the United States.

Clinical Gastroenterology and Hepatology

BACKGROUND & AIMS: **Gastric cancer (GC) remains a leading cause of mortality among certain racial, ethnic, and immigrant groups in the United States (US). The majority of GCs are diagnosed at advanced stages, and overall survival remains poor. There exist no structured national strategies for GC prevention in the US.**

METHODS: **On March 5–6, 2020 a summit of researchers, policy makers, public funders, and advocacy leaders was convened at Stanford University to address this critical healthcare disparity. After this summit, a writing group was formed to critically evaluate the effectiveness, potential benefits, and potential harms of methods of primary and secondary prevention through structured literature review. This article represents a consensus statement prepared by the writing group.**

RESULTS: **The burden of GC is highly inequitably distributed in the US and disproportionately falls on Asian, African American, Hispanic, and American Indian/Alaskan Native populations. In**

Abbreviations used in this paper: **ACG, American College of Gastroenterology; AGA, American Gastroenterological Association; CI, confidence interval; GC, gastric cancer; GIM, gastric intestinal metaplasia; Hp, *Helicobacter pylori*; HR, hazard ratio; OR, odds ratio; RCT, randomized controlled trial; RR, risk ratio; US, United States.**

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randomized controlled trials, strategies of *Helicobacter pylori* testing and treatment have been demonstrated to reduce GC-specific mortality. In well-conducted observational and ecologic studies, strategies of endoscopic screening have been associated with reduced GC-specific mortality. Notably however, all randomized controlled trial data (for primary prevention) and the majority of observational data (for secondary prevention) are derived from non-US sources.

CONCLUSIONS: **There exist substantial, high-quality data supporting GC prevention derived from international studies. There is an urgent need for cancer prevention trials focused on high-risk immigrant and minority populations in the US. The authors offer recommendations on how strategies of primary and secondary prevention can be applied to the heterogeneous US population.**

Keywords: Helicobacter pylori; Screening; Gastric Intestinal Metaplasia; Disparity.

Gastric cancer (GC) has been strongly associated with prior or current infection with the bacterium *Helicobacter pylori* (Hp).[1,2] GC is diagnosed in 1.2 million persons each year and results in more than 800,000 deaths.[3] In the United States (US), GC is diagnosed in more than 27,000 patients each year[4] and portends a poor prognosis (5-year survival of 32%).[5] These unfavorable outcomes reflect the generally late stage of diagnosis of this potentially preventable and curable cancer.

In the US, there exist both limited data and guidelines regarding the prevention of GC.[6,7] The lack of preventative strategies stands in contrast to certain Asian-Pacific countries that have witnessed improvements in mortality after initiation of national screening programs. Moreover, GC represents a major disparity in the US, disproportionately afflicting minority and immigrant groups.[8,9]

On March 5–6, 2020 a summit was convened on the campus of Stanford University (Stanford, CA) to propose a framework for GC prevention applicable to the US.[10] After the summit, a writing group was created to critically evaluate potential benefits and harms (both direct and indirect) of primary and secondary prevention. The writing group was charged to evaluate effectiveness, measured by the balance of benefits and harms, for specific groups on the basis of age, sex, and other risk factors.

In this article, the burden of GC in the US will be reviewed. The literature regarding the merits and risks of primary (Hp eradication) and secondary (GC screening) prevention will be critically analyzed, drawing evidence from interventional studies, observational studies, and ecologic observations. Finally, a framework for how the findings presented herein can be translated to actionable policies will be offered.

GC may be broadly inclusive of multiple cancer subtypes (eg, lymphomas, sarcomas, metastatic lesions). For the purposes of this article, GC refers specifically to primary gastric adenocarcinomas. Moreover, GC can be classified by anatomic location as cardia and non-cardia. Non-cardia GCs represent the majority of GCs both worldwide and in North America[11] and are more strongly associated with Hp infection. Although some preventative measures discussed herein (such as endoscopic screening) are effective in reducing both cardia and non-cardia mortality, prevention of non-cardia GCs will be the focus of this work.

Gastric Cancer Burden in the United States

The epidemiology of GC demonstrates marked worldwide variability, with age-standardized incidence varying greater than 10-fold between nations of high and low incidence.[3,12] This geographic variability is mediated in part by differing prevalence of Hp infection.[13] Disease incidence and consequently mortality are highest in East Asia, Eastern Europe, and Andean Latin America.[3]

Within the US, the burden of GC is also unequally distributed. Asian Americans, Hispanic Americans, and African Americans are at significantly increased risk (Figure 1, top panel).[5,8,9] Among certain high-risk subgroups such as Korean Americans, the age-standardized relative risk for GC exceeds 5-fold that of non-Hispanic whites. Differences in GC burden are even more pronounced when stratified by cancer anatomic distribution. A study based on the California Cancer Registry analyzing non-cardia GC incidence found Korean Americans to demonstrate greater than 12-fold relative risk compared with non-Hispanic whites (Figure 1, bottom panel).[14]

Differences in GC incidence between racial/ethnic groups are mediated by differences in both the prevalence of Hp[15] and the prevalence of Hp-induced gastric precancerous lesions such as gastric intestinal metaplasia (GIM). GIM is a critical precursor to GC that develops in the gastric mucosa as a result of chronic inflammatory insult from Hp colonization through a histologic progression termed Correa's Cascade.[16] In the US, the prevalence of GIM has been estimated to be between 5% and 15% of the general population.[17,18] However, certain minority groups demonstrate higher GIM prevalence, which correlates closely with GC incidence (Supplementary Table 1).[19–23] The relative risk for progression to cancer among different racial groups once

GIM has been diagnosed has not been well-described in the US population and requires additional study.

Gastric Cancer Outcomes in the United States

Although GC survival has improved in the US since the 1970s, outcomes remain poor. Five-year observed survival from GC was 32% in 2016.[5] This figure is significantly lower than survival from breast cancer (the most common cancer in the US), lung cancer (the most common cause of cancer death), and colorectal cancer (the most common gastrointestinal cancer), whose 5-year survivals are 90%, 56%, and 64%, respectively.[5,24]

As with most cancers, GC survival is closely associated with stage of diagnosis. Outcomes after diagnosis of early GC (defined as tumor with invasion limited to the mucosa or submucosa) is excellent, with survival exceeding 95%.[5] Because GC is asymptomatic in the early stages of development, early detection is rare in the absence of effective screening programs. Unsurprisingly, the majority of GC patients in the US are diagnosed beyond an early stage when curative resection is no longer possible.

Outcomes from GC in the US are unfavorably compared with nations in East Asia that have adopted national screening programs. In Japan, a screening program was first introduced in 1983 and consisted of radiography-based screening of all adults ≥40 years old, with endoscopic examination performed on individuals with abnormal radiographic results.[25] The Japanese program was amended in 2016 to allow for either endoscopic or radiographic screening for adults ≥50 years old on a biennial basis.[25] South Korea initiated a biennial screening program consisting of either endoscopic or radiographic screening for adults ≥40 years old in 2002.[26] In practice, endoscopic screening has been the predominant modality practiced in South Korea because of patient preference.

Compared with Japan and South Korea, GC is diagnosed at more advanced stages and with reduced survival in the US (Supplementary Table 2). Moreover, both Japan and South Korea have increased the proportion of GCs diagnosed at an early stage over time.[10] In South Korea, the proportion of GCs diagnosed as early GC has increased from 39% in 2001 to 73% in 2016 (Figure 2).[10] Although these ecologic observations may have multifactorial etiologies, they do suggest a secular trend toward earlier diagnosis that coincides with governmental policy changes.

Strategies of Primary Prevention

Evidence Base

Hp was classified by the World Health Organization as a Class I human carcinogen in 1994 because of the strong evidence supporting its etiologic role in GC.[27] Identifying Hp-infected individuals at high risk for GC presents an opportunity for primary prevention. Specifically, a recent meta-analysis of 24 studies (inclusive of both randomized trials and observational studies) demonstrated that Hp eradication reduces GC incidence by 47% (pooled incidence rate ratio [RR], 0.53; 95% confidence interval [CI], 0.44–0.64).[28] Notably, none of these studies were conducted in North America. The benefit in reduction of GC incidence was significant even among asymptomatic individuals (pooled incidence RR, 0.62; 95% CI, 0.49–0.79) and did not differ by study design, sex, or follow-up period. A separate meta-analysis[29] analyzed 7 randomized controlled trials (RCTs) of Hp eradication in healthy individuals (Supplementary Table 3).[30–39] These RCTs were conducted in East Asia and Latin America (with no US studies identified). This meta-analysis demonstrated a 46% decrease in GC incidence (modified intent-to-treat analysis: RR, 0.54; 95% CI, 0.40–0.72), with no statistically significant heterogeneity found by study (I^2 = 0%, P = .61) (Figure 3). Among 4 studies analyzing metachronous GC incidence among patients who underwent endoscopic resection for early GC, an equally strong protective effect was seen favoring Hp eradication (RR, 0.49; 95% CI, 0.34–0.70). Among the 4 studies able to assess subsequent mortality, there was a significant decrease in cancer-specific mortality among those treated (modified intent-to-treat analysis: RR, 0.61; 95% CI, 0.40–0.92). There also exist RCT data favoring Hp treatment on the basis of family history. A recent single-center, double-blind, placebo-

What You Need to Know

Background

Gastric cancer remains a leading cause of cancer mortality among certain racial, ethnic, and immigrant groups in the United States. There exist few data and guidelines regarding gastric cancer prevention drawn from the multiethnic United States population.

Findings

In this article, the authors critically evaluate the effectiveness, potential benefits, and potential harms of methods of primary and secondary prevention. Mechanisms of primary (*Helicobacter pylori* test-and-treat) and secondary (endoscopic screening) prevention have been demonstrated to reduce gastric cancer mortality in international studies.

Implications for patient care

There is an urgent need for cancer prevention trials in the United States. The authors strongly believe that strategies of prevention applied to highly targeted populations within the United States can improve cancer outcomes and health equity.

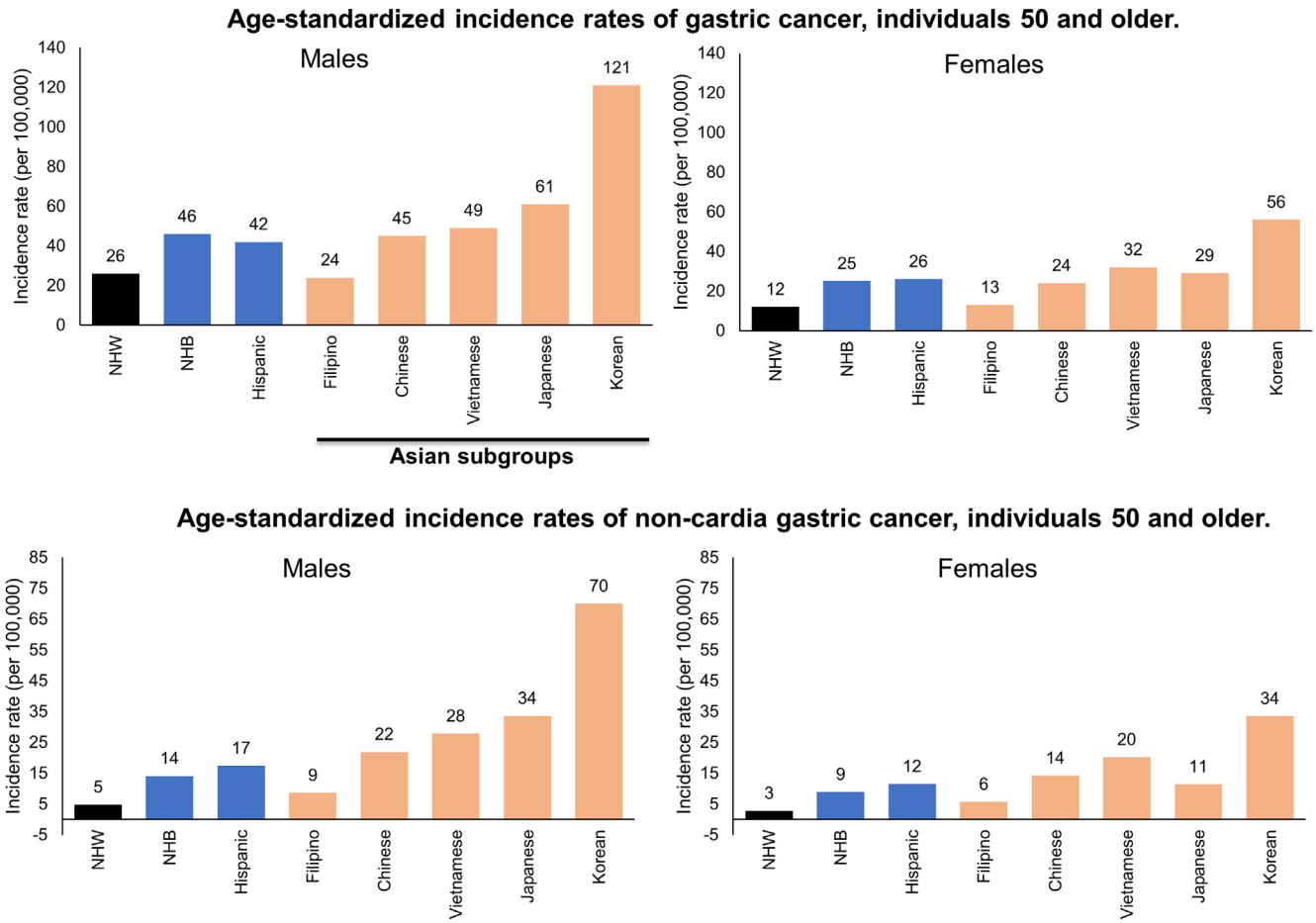

Figure 1. *Top panels,* age-standardized incidence rates of gastric cancer in the United States among individuals 50 years and older by race/ethnicity and sex in 2010–2017. Source: SEER Research Data. *Bottom panels*, incidence rates of non-cardia gastric cancer among individuals 50 years and older. Source: California Cancer Registry, 2011-2015. Data adapted from Shah et al, 2020.[14] NHB, non-Hispanic black; NHW, non-Hispanic white.

controlled trial in South Korea of 1838 first-degree relatives of patients with GC randomized to antimicrobial eradication vs placebo demonstrated 55% reduction in incidence of GC over a median of 9.2 years of follow-up (intent-to-treat analysis: hazard ratio [HR], 0.45; 95% CI, 0.21–0.94).[39]

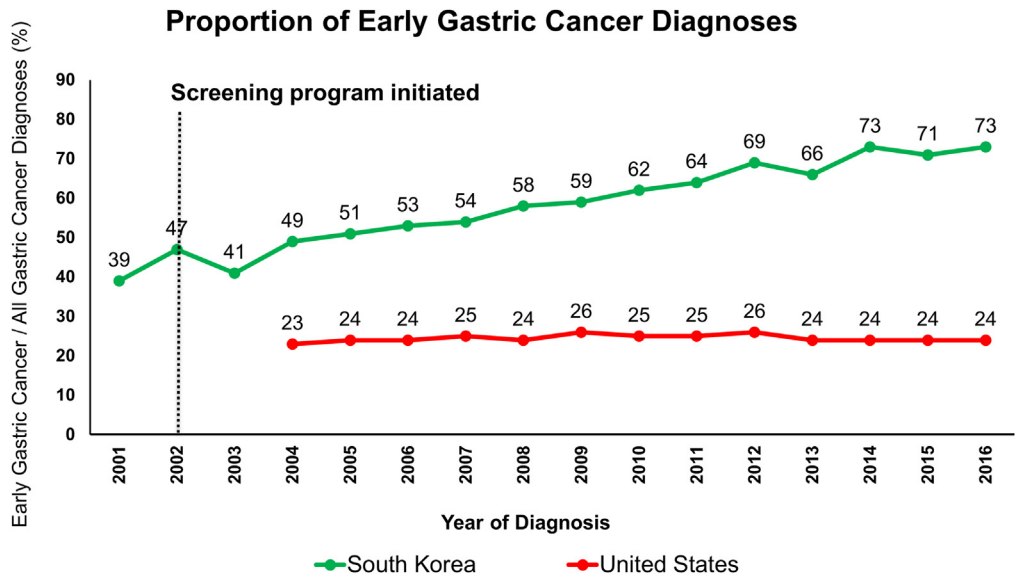

Figure 2. *Green line*: percentage of gastric cancers diagnosed at early stage in South Korea between 2001 and 2016. *Red line*: percentage of gastric cancers diagnosed at localized stage (using American Joint Committee on Cancer staging) in the United States from 2004 to 2016. Data adapted from Huang et al, 2020.[10]

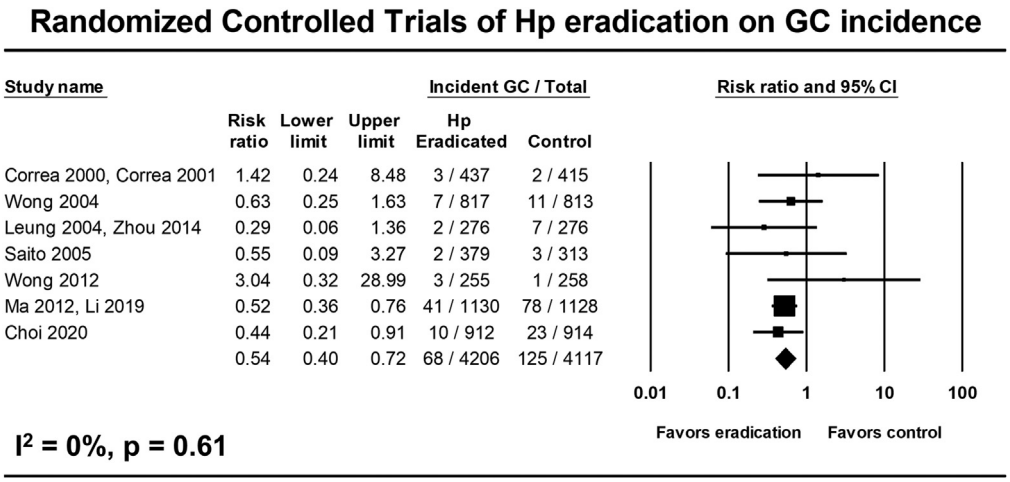

Figure 3. Forest plot of randomized controlled trials of *Helicobacter pylori* eradication therapy: effect on subsequent occurrence of gastric cancer (modified intention-to-treat analysis). CI, confidence interval; GC, gastric cancer; Hp, *Helicobacter pylori*. Data adapted from Ford et al, 2020.[29]

The experience of real-world population-level eradication programs also suggests the protective role of Hp treatment. A recent example is the mass Hp eradication campaign conducted from 2004 through 2018 on Taiwan's Matsu Islands, which resulted in significantly lower Hp prevalence, presence and severity of GIM, and GC incidence and mortality (compared with the historical control period of 1995–2003).[40] Although there have yet to be eradication trials conducted in the US, one recent cohort study from the Veterans Health Administration found that confirmed Hp eradication after treatment was associated with 76% reduced risk of GC, compared with those with unsuccessful Hp treatment (HR, 0.24; 95% CI, 0.15–0.41).[41]

Potential Harms

One potential concern of population Hp test-and-treat strategies includes the possibility of inducing acid reflux symptoms, thereby increasing risk of both Barrett's esophagus and esophageal adenocarcinoma.[42] Although some observational studies have found Hp infection associated with decreased likelihood of esophageal cancer incidence,[43] no study has yet shown an increase in esophageal cancer incidence after Hp eradication. The 2 trials that looked at this endpoint specifically did not find evidence of an increase in the subsequent development of esophageal cancer after Hp eradication.[29,38] Similarly, the real-world mass Hp eradication campaign on Matsu Islands (2004–2018) did not result in an increase in esophageal cancer incidence.[40]

Another concern is related to increasing antibitiotic resistance with broader application of Hp eradication therapy. On Matsu Island, no increase was found in Hp antimicrobial resistance over the 14 years of the mass eradication campaign (which included multiple treatments for some individuals).[40] Nonetheless, any population-based Hp test-and-treat strategy must incorporate patterns of resistance and previous antibiotic use to guide precision antimicrobial selection. For example, clarithromycin triple therapy is the most commonly used first-line therapy in the US.[44] Among individuals with a clarithromycin-susceptible Hp strain there is an 88% eradication rate, compared with 18% for those with clarithromycin-resistant strains.[45] Assessing previous macrolide exposure to determine whether to use clarithromycin triple therapy or an alternate can significantly improve eradication rates.[46] Another option is to universally move to quadruple therapy (metronidazole, tetracycline, omeprazole, and bismuth), which a multicenter trial in North America found was effective for both metronidazole-susceptible and –resistant strains (eradication rates of 92% and 80%, respectively), as compared with clarithromycin therapy (rates of 92% and 21% for clarithromycin-susceptible and -resistant strains, respectively).[47]

Finally, it is important to note tthat current practice in the US is focused on eradication of symptomatic individuals.[48] The long-term sequelae of population-level eradication has not been examined in a US population, and additional data may be needed before broad policy decisions can be made.

Cost-Effectiveness Studies

The cost-effectiveness of population-level Hp screening has been evaluated in simulation studies. In one early study based on California incidence data (for white, Japanese, and African Americans), serologic Hp screening of all US persons aged 50–54 and treating those with a positive test demonstrated a net cost-effectiveness of $25,000 per life-year saved (1995 US dollars).[49] In this study, cost-effectiveness was greater among men, Japanese Americans, and African Americans. A later simulation study incorporating post-treatment confirmatory testing demonstrated that Hp treatment with and without confirmatory testing proved cost-effective.[50] A study incorporating the presence of precancerous lesions (such as GIM) demonstrated that Hp screening was cost-effective but only before the

development of precancerous lesions.[51] Notably, this study incorporated RCT data from an Hp eradication trial conducted in China in their model.[33] There currently exists no US prevention trial data for cost-effectiveness modeling.

Existing United States Practice and Guidelines

The American College of Gastroenterology (ACG) has published clinical guidelines regarding testing and treatment for Hp in adults.[48] The ACG guidelines strongly recommend Hp testing for patients with active peptic ulcer disease, past peptic ulcer disease, low-grade gastric mucosa associated lymphoid tissue lymphoma, history of endoscopic resection for early GC, and for patients <60 years old with uninvestigated dyspepsia and no alarm features. In the ACG guidelines, clarithromycin-based triple therapy remains a first-line option, but only in regions where clarithormycin resistance is <15% and in patients with no history of macrolide exposure. Confirmatory testing to prove eradication is recommended to be performed 4 weeks after completion of antibiotic therapy.

There exist clear knowledge gaps among US-based providers with regard to Hp testing, antibiotic treatment, and eradication confirmation. A national survey of US gastroenterology physicians revealed that only 58% of physicians routinely ordered eradication confirmatory testing.[44] Moreover, although standard clarithromycin-based triple therapy was the most commonly prescribed therapy, the overwhelming majority of surveyed providers were unaware of the resistance rates.[44]

Other groups believe these parameters should be expanded. Specifically, the Houston Consensus Conference was organized in 2018 to determine who should be tested and treated for Hp in the US. After recommendations were drafted by an 11-member expert panel, external validation was sought from 100 US-based gastroenterologists.[52] Indications to test for and treat Hp infection, as approved by both the expert panel and external group, included the conditions indicated by the ACG above, along with 3 other high-risk groups: patients with a family history of GC, patients who are first-generation immigrants from high Hp prevalence areas, and patients of Hispanic and African American racial or ethnic groups.

Author Recommendations

The authors agree with the expanded criteria for Hp testing and treatment proposed by the Houston Consensus Conference. In addition, the authors strongly believe that Asian Americans, Alaskan Natives, and American Indians should be offered testing for Hp on the basis of GC incidence in these racial groups.

The authors recommend testing for Hp in the following individuals, irrespective of presence of symptoms:

- Individuals with a family history of GC in a first-degree relative
- First-generation immigrants from high Hp prevalence regions
- Individuals belonging to racial/ethnic groups at increased risk for GC (African Americans, Alaskan Natives, American Indians, Asian Americans, and Hispanic Americans).

All individuals with a positive test of active infection should be offered treatment. Testing to confirm eradication should be performed following treatment.

Strategies of Secondary Prevention

Evidence Base

The following section summarizes published cohort and case-control studies evaluating the association between endoscopic screening and GC-specific mortality. These data are drawn partially from documents published by the national guidelines development committees of South Korea[53] and Japan.[54] Notably, the authors could not identify any prospective or observational data regarding GC screening derived from the US.

Six cohort studies,[55–60] all from East Asia, have reported on the association between endoscopic screening and GC mortality (Supplementary Table 4). In 4 studies, a significant reduction in GC-specific mortality was observed in the screened groups compared with the non-screened groups, ranging from 42% to 67%.[57–60] Of these studies, 2 from Japan also compared endoscopic screening with radiographic screening and found endoscopic screening to be superior in reducing GC-specific mortality.[58,59] In the 3 studies that reported proportion of early-stage cancers in the screened group, this ranged from 77% to 89%.[56,57,59] By comparison, early-stage GCs comprised 50%–53% of the group without organized endoscopic screening.[56,57]

Four nested case-control studies have been reported from China, Korea, and Japan.[61–64] In a study within the Korean National Cancer Screening program, the odds ratio (OR) of GC-specific mortality among screened subjects compared with never-screened individuals was 0.53 (95% CI, 0.51–0.56).[64] A Japanese study demonstrated that receipt of endoscopy within the prior 3 years was associated with 30% reduction in GC-specific mortality (OR, 0.70; 95% CI, 0.49–0.99).[61] A Chinese study evaluated the effects of a population-based endoscopic

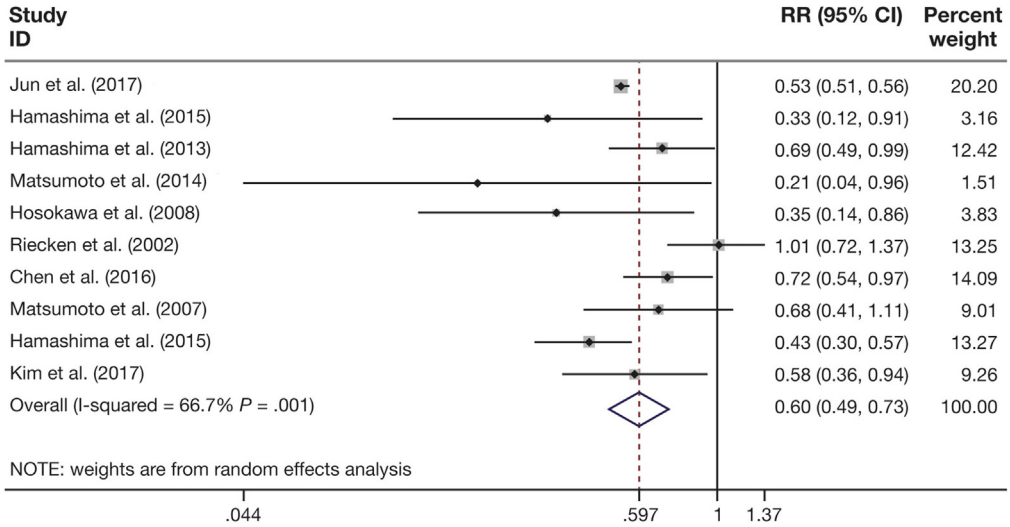

Figure 4. Pooled analysis of association between endoscopic screening and gastric cancer mortality from published cohort and case-control studies. CI, confidence interval; RR, risk ratio. Reproduced with permission from Gastroenterology, volume 155, 2018. Zhang X, et al. Endoscopic Screening in Asian Countries Is Associated With Reduced Gastric Cancer Mortality: A Meta-analysis and Systematic Review. Copyright (2018), with permission from the AGA Institute and Elsevier.[65]

screening program in a rural area of Linzhou, China.[63] A protective effect (OR, 0.72; CI, 0.54–0.97) was observed among those with documented endoscopic screening.

A meta-analysis pooling the results of 6 cohort and 4 case-control studies has been performed.[65] In the pooled analysis, exposure to endoscopic screening was associated with 40% reduction in GC-specific mortality (RR, 0.60; 95% CI, 0.49–0.73) (Figure 4). Endoscopic screening significantly associated with reduced mortality in subgroup analysis based on sex (male pooled RR, 0.62; CI, 0.48–0.81; female pooled RR, 0.58; CI, 0.44–0.78) and study design (cohort study RR, 0.57; CI, 0.39–0.83; nested case-control RR, 0.60; CI, 0.47–0.76).

Potential Harms of Endoscopic Screening

Potential harms of endoscopic screening include endoscopic-related adverse events, false-negative or false-positive results, and overdiagnosis. The balance between benefits and harms should be considered for endoscopic screening in the general population.

Upper endoscopy carries a low risk of adverse events and death. A large US-based single-center study reported adverse event rates of 0.02% (1 in 6000), with no fatalities.[66] International data also support a low rate of adverse events and death. A national survey study from Switzerland of 115,200 endoscopies revealed a sedation-related event rate of 0.1% and no recorded fatalities.[67] Similarly, a German registry reported a cardiopulmonary event rate of 0.005% (50 per million) and fatality rate of 0.0009% (9 per million).[68]

Overdiagnosis is defined as the detection of cancers that would not present symptomatically in the lifetime of an individual if screening were not performed. Although the magnitude of overdiagnosis by endoscopic screening has not been estimated, ecologic data from South Korea suggest this to be modest. As shown in Figure 5, although the number of screening examinations through the National Cancer Screening Program increased nearly 20-fold, the age-standardized incidence of GC has remained stable over the period 2002 to 2012.[69] These data, coupled with the stage shift data presented previously (Figure 2), suggest that endoscopic screening is leading to earlier stages of diagnosis rather than increasing the detection of indolent tumors. Additional ecologic or simulation data are needed to better estimate the degree of overdiagnosis from a comprehensive GC screening program.

Serologic Screening

Hp infection and precancerous lesions lead to perturbations in the serum concentrations of gastric hormones, notably pepsinogen I, pepsinogen II, and gastrin.[70,71] In East Asia and other regions with high Hp prevalence and GC incidence, these biomarkers have been used to screen for high-risk individuals with atrophy or GIM.[72] Their utility in low-incidence nations, and in particular the US, is less clear. A systematic review of 20 studies (18 from European populations) suggested a pooled sensitivity of 74%.[72] However, significant heterogeneity was observed, with some studies reporting sensitivity as low as 30%. One recent single-center study evaluated the sensitivity and discrimination of pepsinogens and gastrin in a multiethnic US population from California.[73] This study found inadequate sensitivity (15%–47%) and discrimination (area under curve <0.7) in this population, which was characterized by low Hp prevalence ($<10\%$) and high anti-secretory therapy use. Additional data are required before definitive conclusions can be drawn regarding use of serologic biomarkers in heterogeneous US populations.

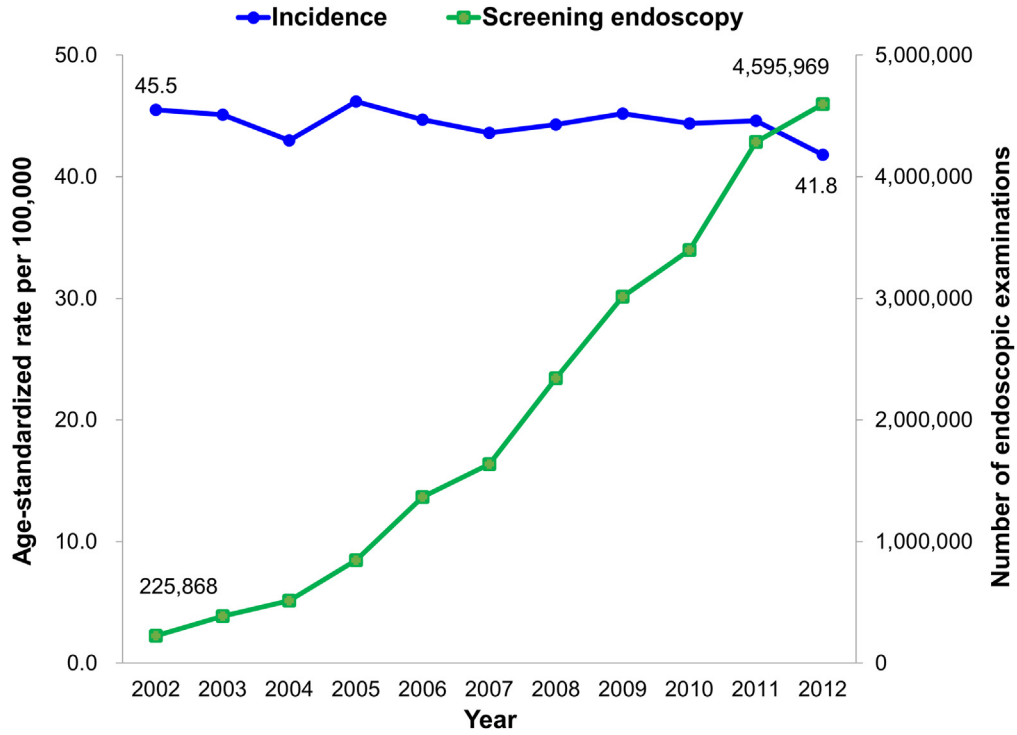

Figure 5. Secular trends in gastric cancer incidence and number of endoscopic screening exams in South Korea (2002–2012). Data from the Korean Statistical Information Service.[69]

Surveillance of Gastric Precancerous Lesions

The presence of GIM is an important marker of future GC risk. The risk for GC progression once GIM has been diagnosed was analyzed in a Technical Review accompanying the 2020 American Gastroenterological Association (AGA) guidelines.[74] Pooling studies from all geographies, an incidence rate of progression of 12.4 per 10,000 person-years was found. Of the 2 identified US studies, a pooled progression rate of 8.2 per 10,000 person-years was reported.[75,76] The relative risk for progression of GIM to either dysplasia or GC was higher among individuals with a family history of GC, individuals with incomplete GIM on histology, and individuals with topographically extensive (vs limited) GIM.[74]

Cost-Effectiveness Studies

The cost-effectiveness of endoscopic screening for GC and surveillance of precancerous lesions has been assessed in simulation studies. One study assessed the cost-effectiveness of screening upper endoscopy at time of screening colonoscopy (at age 50), compared with no screening upper endoscopy, with analysis stratified by race/ethnicity (non-Hispanic white, African American, Asian, and Hispanic).[77] A strategy of one-time screening at age 50 and continued surveillance only if GIM was identified was cost-effective at a quality-adjusted life-year threshold of $100,000/life-year (2018 US dollars) for Asian Americans, African Americans, and Hispanic Americans. Among patients diagnosed with GIM and dysplasia, another study suggested endoscopic resection with annual surveillance reduced lifetime cancer risk by 90% and cost $39,800 per quality-adjusted-life-year.[78]

Existing United States Practice and Guidelines

Currently the American Society of Gastrointestinal Endoscopy has issued guidance[6] that "endoscopic screening for GC in first-generation US immigrants from high-risk regions may be considered for those aged 50 years, particularly if there is a family history of GC in a first-degree relative." Notably, this guidance was published before recent evidence demonstrating cancer-specific mortality reduction associated with endoscopic screening. Moreover, it is unclear whether providers are aware of this guidance, because a recent US study suggested the vast majority of GCs are diagnosed because of symptoms (and not from screening/surveillance).[20]

Regarding surveillance of precancerous lesions, the 2020 AGA guidelines recommend against the routine use of endoscopic surveillance in patients with GIM but clarifies this is a conditional recommendation that is based on very low quality of evidence.[7] These guidelines further state that individuals with GIM "at higher risk for GC who put a high value on potential but uncertain reduction in GC mortality, and who put a low value on potential risks of surveillance endoscopies, may reasonably elect for surveillance." Higher-risk individuals include racial/ethnic minorities, immigrants from high-incidence regions, those with a family history of GC, and individuals with either extensive or incomplete GIM.

Author Recommendations

In the US, a precision-based strategy of screening should focus on groups at significantly heightened risk for GC. This group includes first-generation immigrants from high-incidence nations (East Asia, Eastern Europe, and Andean Latin America) and individuals with a family history of GC in a first-degree relative. Modeling studies have suggested that screening upper endoscopy with biopsy at age 50 and continued surveillance if GIM or more severe pathology is identified to be a cost-effective strategy among Asians, African Americans, and Hispanics.[77] Consistent with AGA guidelines, the authors strongly believe that individuals at heightened risk for GC who are diagnosed with GIM should be offered surveillance. The authors offer the following recommendation:

Endoscopic screening with biopsies should be offered beginning at the age of 50 to the following individuals:

- Individuals with a family history of GC in a first-degree relative
- First-generation immigrants from high GC-incidence regions
- Individuals belonging to racial/ethnic groups at increased risk for GC (African Americans, Alaskan Natives, American Indians, Asian Americans, and Hispanic Americans).

If GIM or more severe pathology is identified, endoscopic surveillance should be offered.

Summary

The burden of GC remains high among certain groups in the US, especially racial and ethnic minorities. There exist substantial data demonstrating GC-specific mortality reduction associated with both primary and secondary prevention, which are derived from high-incidence regions of the world. Immigrants from high-incidence regions and minority groups in the US may benefit from these proven methods of cancer prevention, although US-specific cancer prevention trials are urgently needed. The authors strongly believe that strategies of prevention applied to highly targeted populations can maximize the benefit of mortality reduction while minimizing harms, increase value to the healthcare system, and improve health equity.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2021.09.039.

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Supplementary Table 1. Estimated Prevalence of Gastric Intestinal Metaplasia Among Patients Undergoing Upper Endoscopy, Stratified by Race and Ethnicity[19–23]

Racial/ethnic group	Prevalence of GIM (%)
Non-Hispanic white	9–14
Non-Hispanic black	21–27
Hispanic	13–34
East Asian	18–40
Japanese	18
Vietnamese	21
Chinese	26
Korean	40

GIM, gastric intestinal metaplasia.

Supplementary Table 2. Comparison of Gastric Cancer Stage of Diagnosis and Survival by Nation

	South Korea (2006–2010)		Japan (2006–2008)		United States (2010–2014)	
Stage at diagnosis	Proportion, %	Survival, %	Proportion, %	Survival, %	Proportion, %	Survival, %
Localized	51	92.4	48	95.9	28	70.3
Regional	26	55.7	22	50.0	26	32.0
Distant	12	5.5	16	5.7	37	5.8
Unknown	11	49.2	14	—	9	21.8
All stages	100	67.0	100	64.6	100	32.1

NOTE. South Korean data adapted from the Korea National Cancer Incidence Database. Japanese data derived from the Center from the National Cancer Center of Japan. United States data derived from Surveillance, Epidemiology, and End Results Program (SEER) of the National Cancer Institute. Five-year relative survival rates are presented. Summary stages defined by SEER. Data adapted from Huang et al, 2020.[10]

Supplementary Table 3. Characteristics of Randomized Controlled Trials of *Helicobacter pylori* Eradication Therapy Versus Placebo or No Treatment in the Prevention of Gastric Cancer in Healthy Individuals

Study (reference)	Location	Sample size (no. receiving Hp eradication)	Population characteristics	Eradication rate (%)	Last point of follow-up
Correa, 2000 [30] Correa, 2001 [31]	Colombia	852 (437)	Age 51.1 (29–69), 46% male	58.0	6 y
Wong, 2004 [33]	China	1630 (817)	Age 42.2 (35–65), 54% male	83.7	7.5 y
Leung, 2004[32] Zhou, 2014 [37]	China	587 (295) and 552 (276)	Age 52.0 (35–75), 47.8% male	55.6	5 y in Leung and 10 y in Zhou
Saito, 2005 [34]	Japan	692 (379)	Age 20–59	74.4	≥4 y
Wong, 2012 [36]	China	513 (255)	Age 53.0 (35–64), 46.4% male	63.5	5 y
Ma, 2012 [35] Li, 2019 [38]	China	2258 (1130)	Age 46.8 (35–64), 50.0% male	73.2	22.3 y
Choi, 2020 [39]	South Korea	1838 (917)	Age 48.8 (40–65), 49.5% male	60.4	9.2 y

Hp, *Helicobacter pylori*.
NOTE. Data adapted from Ford et al (2020).[29]

Supplementary Table 4. Cohort and Case-Control Studies of Endoscopic Screening

Study (reference)	Design	Country	Study period	Sample size	Age, *y*	Men, %	Follow-up, *mo*	Adjustments or match
Jun, 2017 [64]	NCC	Korea	2004–2012	272,090	≥40	69.4	≥36	Year of entry, age, sex, socioeconomic status
Hamashima, 2015 [59]	RC	Japan	2007–2013	14,274	40–79	35.3	66.6	Age, sex, resident city
Hamashima, 2013 [61]	NCC	Japan	2003–2010	2702	40–79	70	NR	Age, sex, resident city
Matsumoto, 2014 [62]	NCC	Japan	1996–2008	143	54–91	61.5	NR	Age, sex, resident city
Hosokawa, 2008 [57]	RC	Japan	1990–1992	11,763	40–75	50.3	<120	Age, sex
Riecken, 2002 [55]	PC	China	1989–2000	4392	35–64	NR	138	Age, sex, resident city
Chen, 2016 [63]	NCC	China	2005–2015	2189	40–69	69.3	NR	Age, sex, resident city
Matsumoto, 2007 [56]	RC	Japan	1996–2006	7178	≥40	33.9	120	Age, sex
Hamashima, 2015 [58]	RC	Japan	2005–2010	16,373	40–79	39.6	60	Age, sex
Kim, 2017 [60]	PC	Korea	1993–2014	10,909	58.0 ± 10.3	40	≥120	Age, sex, Hp infection, cigarette smoking, alcohol consumption

NOTE. Table adapted from data from Zhang X, et al (2018).[65]
Hp, *Helicobacter pylori*; NCC, nested case control; NR, not reported; PC, prospective cohort; RC, retrospective cohort.