Published in final edited form as:

Cancer Epidemiol Biomarkers Prev. 2023 April 03; 32(4): 473–486.

doi:10.1158/1055-9965.EPI-22-0994.

Cancer Progress and Priorities: Gastric Cancer

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Abstract

Gastric cancer, the fifth leading cause of cancer worldwide, is estimated to be responsible for approximately 1.4% of all new cancers and 1.8% of all cancer-related deaths in the United States. Despite declining incidence rates and improved survival rates, however, gastric cancer continues to disproportionately affect racial and ethnic minorities and individuals of lower socioeconomic status at higher rates than the general population. To improve outcomes globally and address disparities within the United States, continued improvements are needed in risk factor modification and biomarker development and to improve access to existing preventative measures such as genetic testing and *H. pylori* eradication testing, in addition to expanding upon current clinical guidelines for premalignant disease to address gaps in endoscopic surveillance and early detection.

Keywords

gastric cancer; epidemiology; risk factors; genetic syndromes; prevention

Introduction

Gastric cancer is the fifth leading cause of cancer worldwide with 1,089,103 new cases diagnosed in 2020, and with marked geographic variability in incidence (Figure 1).[1] In 2022, gastric cancer is estimated to be responsible for approximately 1.4 percent of all new cancers in the United States (U.S.) and 1.8 percent of all cancer-related deaths.[2] Despite declining incidence rates and improved survival rates, gastric cancer continues to disproportionately affect racial and ethnic minorities and individuals of lower socioeconomic status at higher

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The authors declare no potential conflicts of interest

rates than the general population.[3,4] In order to improve outcomes globally and address disparities within the U.S., continued improvements are needed in risk factor modification, biomarker development, and early detection of gastric cancer lesions. This review will focus on recent advances in these areas over the past few years.

Background/Descriptive Epidemiology

In this review, we will focus on risk factors for gastric adenocarcinoma, the most common type of gastric cancer. Most gastric adenocarcinomas are thought to develop through a gradual progression from *Helicobacter pylori (H. pylori)*-induced chronic gastritis to atrophic gastritis, intestinal metaplasia, dysplasia, and ultimately adenocarcinoma.[5] Although over half of the world's population is infected with *H. pylori*, only a small subset of infected individuals progress to gastric cancer, and this process occurs over the course of around 15-20 years.[6]

In 2014, The Cancer Genome Atlas (TCGA) identified four molecular subtypes of gastric cancer: Epstein-Barr virus (EBV) subtype, microsatellite instability (MSI) subtype, chromosomal instability (CIN) subtype, and genomically stable subtype.[7] Gastric cancer is also classified into cardia and non-cardia subtypes depending on its location (proximal or distal, respectively) in the stomach. In 2018, gastric non-cardia cancer accounted for approximately 82 percent of gastric cancer cases worldwide compared to 18 percent for cardia cases.[8] Gastric cardia cancers are more likely to be associated with Epstein-Barr virus and their association with *H. pylori* is debated.[7,9,10] Within the U.S., gastric cardia cancer tends to affect predominantly non-Hispanic White individuals, similar to esophageal adenocarcinoma, while non-cardia cancer has a greater incidence among individuals from underrepresented racial and ethnic groups and residents of lower socioeconomic status.[11] Gastric cardia cancer is also more likely to be associated with diet and higher BMI.[12] Both cardia and non-cardia gastric cancers have been significantly associated with male sex and tobacco smoking.[13]

Risk Factors

H. pylori infection

Infection with *H. pylori* is the most important risk factor for gastric cancer, responsible for an estimated 89% of non-cardia gastric cancers.[5] *H. pylori* is a gram-negative bacterium that infects approximately 4.4 billion individuals worldwide, over half of the world's population.[6] In 1994, *H. pylori* was classified as a World Health Organization Class I carcinogen, the first bacteria to be directly associated with the development of cancer.[6] *H. pylori*-induced gastric cancer is thought to develop through chronic inflammation leading to atrophic gastritis, gastric intestinal metaplasia, dysplasia, and ultimately gastric adenocarcinoma.[14]

When *H. pylori* infects the gastric mucosa, it induces the production of several key players in the innate and adaptive immune response, including interferon gamma (IFN-y), tumor necrosis factor-alpha (TNF-a), and several cytokines, especially interleukin 8 (IL-8) and 10 (IL-10).[15] In recent years, differences in *H. pylori* strains have gained attention, as certain

virulence factors are more closely associated with gastric cancer. For example, cytotoxin associated gene A (*cagA*) and more virulent forms of vacuolating cytotoxin A (*vacA*), are most closely associated increased gastric inflammation, persistent infection, and gastric cancer risk.[16] *cagA* has been shown to upregulate proliferative and inflammatory pathways, interfere with tumor suppressors, and enable cells to evade the immune response, thereby promoting tumor development and growth.[17] The presence of serum antibodies to *H. pylori* antigens and virulence factors such as *cagA* may contribute to gastric cancer risk. For example, a case-control study of non-cardia gastric cancer cases in China, Japan, and Korea found that seropositivity to proteins *cagA*, *vacA*, OMP, HcpC, HP0305, GroEL, NapA, HyuA, and Cad was associated with a significantly increased odds of gastric cancer (OR range, 1.29-3.26).[18]

Although *H. pylori* infection has most consistently been associated with non-cardia gastric cancer rather than cardia gastric cancer, a recent study in China also identified a significant association of *H. pylori* infection with cardia cancer risk. A cohort study of gastric cancer cases in China found that 62.1% of cardia gastric cancer cases and 78.5% of non-cardia cases could be attributed to *H. pylori* infection, with a hazard ratio of 3.06 (95% CI, 1.54-6.10) for cardia cancer cases and 5.94 (95% CI, 3.25-10.86) for non-cardia cases.[9] *vacA* and *cagA* seropositivity were also associated with an increased risk of gastric cardia cancer.

Nonmodifiable Risk Factors

Race, ethnicity, age, and sex are all nonmodifiable risk factors that are associated with gastric cancer risk. Here, we consider their individual associations on gastric cancer risk in addition to their intersections.

Race and Ethnicity

Within the U.S., gastric cancer continues to disproportionately affect racial and ethnic minorities, and self-identified and electronic health record (EHR)-identified race and ethnicity have been recognized as independent risk factors associated with gastric cancer.[19] From 2015 to 2019, the age-adjusted rates of new gastric cancer cases among non-Hispanic White men and women were 7.6 per 100,000 and 3.7 per 100,000 respectively, compared with 13.7 and 7.6 among American Indian men and women, 12.3 and 8.4 among Hispanic men and women, 12.8 and 7.3 among Asian and Pacific Islander men and women, and 13.4 and 7.8 among non-Hispanic Black men and women (see trends by age and race/ethnicity: Figure 2, panels A and B, respectively).[2] When separated by subsite, non-Hispanic White individuals had the highest rates of cardia cancers (IR, 2.3; 95% CI, compared to Black, Hispanic, Asian and Pacific Islander, and American Indian and Alaska Native individuals (IR range 1.3-1.6) and the lowest rates of non-cardia gastric cancer (IR, 1.9; 95% CI, 1.8-1.9) compared to individuals from other racial groups (IR range 3.5-7.4).[4]

Of all cancers, gastric cancer is responsible for the greatest difference in rates of death from cancer between Black and White Americans, with Black men and women dying from gastric cancer at over twice the rate of non-Hispanic White men and women.[3] Notably, this disparity is restricted to non-cardia gastric tumors, which affect Black patients at higher rates

(55%) compared to White patients (33%), with both groups having comparable survival rates for cardia tumors.[3,4]

Disparities in non-cardia gastric cancer incidence and survival by Hispanic ethnicity have also been identified. The incidence of non-cardia gastric cancer among the Hispanic White population is more than two times that among the non-Hispanic White population (5.9 per 100,000 compared to 2.1 per 100,000).[20] In contrast, the incidence of cardia gastric cancer cases in the Hispanic White population (1.5 per 100,000) is lower than that in the non-Hispanic White population (2.3 per 100,000).[20] Although gastric cancer incidence has been declining in almost all ethnic and racial groups, incidence rates, particularly for stage IV gastric cancer, have been increasing in Hispanic men aged 20-49 years (APC, 1.55%; 95% CI, 0.26-2.86%).[21] A study of cancer-related deaths in Florida from 2008-2012 examined gastric cancer mortality rates according to major Hispanic groups (Cuban, Puerto Rican, Mexican, Central American, and South American).[22] Compared to non-Hispanic White individuals, Central American men and women (male RR, 3.22; 95% CI, 2.35-4.4; female RR, 2.52; 95% CI, 1.72-3.68) and South American men and women (male RR, 3.18; 95% CI, 2.59-3.9; female RR, 3.19; 95% CI, 2.53-4.03) had the highest stomach cancer mortality rates, while Cuban men and women had the lowest mortality rates of all Hispanic groups (male RR, 1.42; 95% CI, 1.21-1.68; female RR, 1.36; 95% CI,1.1-1.66).[22] These differences may reflect variation in the prevalence of *H. pylori* infection, socioeconomic status across different countries, and tumor classification.

More recent studies of gastric cancer incidence have also examined heterogeneity within growing Asian American subpopulations. This is particularly relevant given the rapid growth of these populations and that many of these individuals immigrate from countries with higher rates of gastric cancer than those found in the U.S. A recent study in California of adults aged 50 years and older from 2011 to 2015 found that all non-White groups were at anywhere from a 1.8 to 14.5-fold increased risk of developing non-cardia gastric cancer (IR, 3.70; 95% CI, 3.49-3.92), with Korean Americans being at greatest risk (IR, 49.0; 95% CI, 43.9-54.6).[23,24] Among Asian American subgroups, incidence rates of non-cardia gastric cancer were also high among Vietnamese (23.9), Southeast Asian (21.1), Japanese (19.2), and Chinese Americans (17.6), with Filipino and South Asian Americans having comparatively lower incidence rates (6.69 and 7.75, respectively), although still almost twice the incidence rate of gastric cancer in non-Hispanic Whites.[23] In contrast, the non-Hispanic White population had higher rates of cardia gastric cancer compared to non-cardia gastric cancer,[23] and the non-Hispanic White incidence rate of cardia gastric cancer was surpassed only by those of Korean Americans and Japanese Americans. Despite these observed disparities in incidence rates, Asian Americans had higher rates of surgical tumor resection and survival compared to non-Hispanic whites.[24]

Alaska Native and American Indian populations have also been shown to have higher rates of gastric cancer, especially non-cardia cancer, compared to the U.S. White population (adjusted-IRR, 1.72; 95% CI, 1.5-1.97).[4] Gastric cancer incidence rates, specifically for non-Hispanic American Indian and Alaska Native females living in urban areas, have increased by 76% from 1999-2017, compared to a decline in incidence by 22% among non-Hispanic White females.[25] A study of gastric cancer incidence among American Indian and Alaska

Native groups from 2005-2016 by region (Northern Plains, Alaska, Southern Plains, Pacific Coast, Eastern U.S., and Southwest U.S.) found significantly increased gastric cancer risk for all groups compared to White individuals, with populations in Alaska having the great risk (RR, 4.23; 95% CI, 3.47-5.17).[26] Specifically, the prevalence of non-cardia tumors and signet ring cell carcinomas was around threefold greater among the Alaska Native population than the non-Hispanic White population from 2006-2014.[27] Alaska Native individuals were also more likely to have a poorer prognosis with significantly more diagnoses of Stage IV gastric cancer (50% vs 37.6%)[27] and significantly more likely to be diagnosed with gastric cancer at a younger age (<40 years) compared to White individuals (11% vs. 3%).[28]

Differences in gastric cancer incidence and outcomes by race and ethnicity highlight underlying disparities in exposures to risk factors including *H. pylori* infection, as well as structural racism and inequitable access to resources – factors that are just now starting to be explored in relation to gastric cancer. Given that *H. pylori* infection is the greatest risk factor for non-cardia gastric cancer, trends in gastric cancer cases by race should be contextualized within trends in *H. pylori* infection by race. A study of gastric cancer incidence in Tennessee found that Black patients diagnosed with gastric cancer had a greater than three times higher rate of concurrent *H. pylori* infection than White patients at the time of diagnosis.[29] An analysis of participants in five large cohort studies in the U.S. found that Black individuals had an over twofold odds of having sero-prevalent *H. pylori*, and an over threefold higher odds for seropositivity to a virulent *cagA*-positive strain of *H. pylori*, as compared to White individuals, and moreover that while *cagA* and *H. pylori* seroprevalence is decreasing over time among White individuals, it is not decreasing among Black individuals .[30] Immigration from countries with a higher incidence of both *H. pylori* infection and non-cardia gastric cancer may also contribute to observed differences in individual of different racial and ethnic backgrounds. Self-identified race and ethnicity within the U.S. do not provide a translatable basis for identifying differences in genetic predisposition to gastric cancer between groups. Disparities in exposures to other risk factors by race, such as diet, smoking, and alcohol use may also contribute to observed differences in gastric cancer risk between racial and ethnic groups. While socioeconomic status can also vary with race and ethnicity, lower socioeconomic status is associated with an increased risk of gastric cancer even within racial groups and will be discussed further in a separate section.[4] Further research is needed to examine the specific interplay of these exposures with racial and ethnic identities directly in relation to gastric cancer risk.

Age

Gastric cancer risk increases with age, with most diagnoses taking place among individuals aged 65-74 (median age of diagnosis = 68) in the U.S.[2] However, in certain groups, gastric cancer is being diagnosed in an increasing number of younger adults. In a study of gastric cancer patients in the southeastern U.S., Black patients presented with gastric cancer at a significantly earlier age (median age of diagnosis = 64 years) compared to white patients (72.5 years).[29] Asian American patients and Alaska Native patients are also more likely to present with gastric cancer at an earlier age compared to White cancer patients.[24,28]

Sex

Over the past century, gastric cancer has tended to affect men at higher rates than women, with men also being more likely to die from gastric cancer than women. From 2010 to 2014, incidence rates of both cardia and non-cardia gastric cancer among men were higher than those of women across racial and ethnic groups.[31] This may be explained by differential exposure to other risk factors for gastric cancer, such as alcohol and smoking. However, some recent studies demonstrate changing trends in gastric cancer incidence, particularly among young women. For example, in a large cohort study of gastric cancer incidence in the U.S. from 1995 to 2013, non-Hispanic White women under age 50 saw an increase in the number of gastric adenocarcinoma cases by 2.6% each year (95% CI, 1.7%-3.4%).[32] This increased incidence rate among White women, specifically aged 25-39, was also observed from 1977 to 2006.[33] Another study similarly demonstrated that rates of non-cardia gastric cancer were increasing in women under 40 years by about 2% per year between 1997 and 2014.[31] These observed changes in trends have been suggested to be attributed to increasing rates of autoimmune causes of atrophic gastritis as opposed to *H. pylori*-induced gastritis. However, a recent study of young White women in Finland found that the majority of women with young-onset gastric cancer did have serologic evidence of *H. pylori* infection (68% of cases compared to 23% of controls), and that while serologic evidence of autoimmune gastritis was also associated with early-onset gastric cancer risk, it was much less common than *H. pylori* (8% of cases compared to 3% of controls).[34] Moreover, there is now increasing evidence that autoimmune gastritis without *H. pylori* infection does not significantly increase risk for gastric adenocarcinoma.[35] Despite possible increases the incidence of gastric cancer among younger White women, these incidence rates continue to remain lower than those for all other major racial and ethnic groups (Figure 2a).

Socioeconomic Status

Lower socioeconomic status has been associated with both increased prevalence of *H. pylori* seropositivity, particularly the virulent *cagA*+ strains, and increased risk of developing gastric cancer, especially non-cardia gastric cancer.[36,37] A study of gastric cancer cases from 2000-2014 found a 1.3 times greater adjusted incidence rate ratio of gastric cancer among individuals from the lowest neighborhood socioeconomic quintile compared to those from the highest, although this variation was limited to non-cardia gastric cancer cases only.[4] These disparities in cancer incidence and outcomes may be accounted for by factors more directly linked to socioeconomic status such as *H. pylori* infection, comorbid conditions, and long-term access to health care. Another study found reduced rates of gastric cancer among both Hispanic individuals (OR, 0.79) and non-Hispanic White individuals (OR, 0.76) in zip codes with higher neighborhood incomes (≥$45,000) compared to neighborhoods with lower median household incomes (<$45,000).[19] Notably, higher (>50%) high school education rates were identified as protective among Hispanic populations (OR, 0.67; 95% CI, 0.48-0.93).[19] Education and literacy are closely linked to socioeconomic status and may also be independently associated with gastric cancer incidence. A meta-analysis of participant data within the Stomach Cancer Pooling (StoP) Project, which includes case-control studies across Europe, North America, and Asia, examined gastric cancer risk and education level grouped according to the 2011 UNESCO international standard

classification of education (ISCED).[38,39] After adjusting for age, sex, race/ethnicity, and factors including fruit/vegetable consumption, smoking, and alcohol use, they found that intermediate and high levels of education were associated with a significantly reduced risk of gastric cancer compared to low education levels (OR, 0.68; 95% CI, 0.55-0.84 and OR, 0.60; 95% CI, 0.44-0.84, respectively), and these associations were similarly observed for cardia and non-cardia cancers.[38]

Diet, Obesity, Smoking, and Alcohol

Diet, nutritional deficiencies and supplementation, smoking, and alcohol use, also contribute to gastric cancer risk.

Dietary Factors

Consumption of salt-preserved, smoked, and highly salted foods is associated with an increased risk of gastric cancer, likely through the induction of atrophic gastritis.[14,40] Some of the decline in gastric cancer incidence over the past century may be explained by the decline in reliance on salt-preserved foods.[41] A meta-analysis of 76 cohort studies found that gastric cancer risk increased by 55% with consumption of highly salted food, 15% with processed meat, and 25% with salted fish.[42] An updated meta-analysis published in 2019 found that high intakes of both red and processed meats, analyzed separately, were associated with an increased risk of gastric cancer (41% and 57%, respectively), while white meat consumption was associated with a decreased risk (20%).[43] Processed foods have also been recently linked to gastric cancer.[44] A case-control study of patients in Brazil from 2004 to 2015 found that, even after adjusting for smoking and alcohol use, consumption of processed and ultra-processed foods was associated with an increased risk of developing gastric cancer, specifically salted bread (OR, 2.03; 95% CI, 1.3-3.18), processed meats (OR, 2.96; 95% CI, 1.82-4.81), and fried meats and fish (OR, 2.21; 95% CI, 1.13-4.3).[44] There were no significant differences between associated risk ratios for cardia and non-cardia cancers.

Several different studies suggest that adherence to a diet rich in certain types of fresh fruits and vegetables is correlated with a decreased risk of gastric cancer. A pooled analysis of 15 case-controlled studies in Europe, Asia, and the Americas found that the highest and middle tertiles of citrus fruit intake, compared to the lowest, were associated with a 20% decrease in gastric cancer risk, and the protective effect of citrus fruit increased for up to three servings per week.[45] After stratifying by geographical location, there was no association in studies found in North and South America, where more citrus intake originated from consumption of fruit juices.[45] A prospective analysis of individuals in East Asia found that high fruit intake was associated with decreased non-cardia gastric cancer risk after adjusting for *H. pylori* seroprevalence, although this was more beneficial for individuals not infected with virulent, *cagA*-positive strains of *H. pylori*.[46]

Consumption of vegetables, especially green vegetables, has been shown to reduce the risk of developing gastric cancer by 62%.[47] Interestingly, the previously discussed meta-analysis of diet and gastric cancer risk also found that consumption of white vegetables and citrus fruits significantly decreased gastric cancer risk by 33% and 10%, respectively,

while consumption of tomatoes and pickled vegetables significantly increased risk by 11% and 18%.[42] Pickling vegetables can introduce toxins and carcinogenic molecules such as N-nitroso compounds (also present in salt-preserved foods), and their consumption has been even more strongly associated with gastric cancer risk in other studies. An analysis of studies in both the U.S. and East Asia found that consumption of pickled vegetables increased gastric cancer risk by 52% (RR, 1.52; 95% CI, 1.37-1.68).[48]

An analysis of studies in the StoP Project also identified an association between consumption of allium vegetables, such as onions, garlic, and leeks, and reduced risk of gastric cancer, specifically in Asian populations (OR, 0.71; 95% CI, 0.56-0.90).[49]

A prospective analysis of nut products and gastric cancer in individuals from the NIH AARP Diet and Health Study identified an inverse association between the highest nut consumption (including peanuts, walnuts, and seeds) and non-cardia gastric cancer (HR, 0.73; 95% CI, 0.57-0.94).[50] A similar inverse association was found for the highest peanut butter consumption (HR, 0.75; 95% CI, 0.60-0.94) with an additional decreased risk of non-cardia gastric cancer with every tablespoon.[50] Calcium intake among participants within this cohort was also examined with regard to gastric cancer risk. Median total calcium intake (>881.3 mg), including both diet and supplement intake, was associated with a 23% decreased risk for non-cardia adenocarcinoma, but there was no association for cardia adenocarcinoma.[51]

Given its abundance in fresh citrus fruits and vegetables and potential role in inhibiting *H. pylori* growth, vitamin C has been studied as a possible protective factor against gastric cancer.[52] Vitamin C intake was also shown to have an inverse relationship with *H. pylori* infection prevalence.[53]

A recent cross-sectional analysis of vitamin D serum levels and gastric cancer in a South Korean population found an inverse association between sufficient vitamin D concentrations (≥20 ng/mL) and gastric cancer compared to deficient vitamin D concentrations (<12 ng/mL) (OR, 0.57; 95% CI, 0.32-1.00), and a continued inverse association with a 5 ng/mL increment increase of vitamin D concentration (OR, 0.84; 95% CI, 0.72-0.98).[54]

Body Mass Index

Obesity, defined as body mass index (BMI) greater than 30, which is influenced by diet, lifestyle, environmental factors, and genetics, has been found to have a U-shaped association with risk of non-cardia gastric cancer. An analysis of BMI in patients with gastric cancer in the Asia Cohort Consortium found a significantly increased risk of gastric cancer, especially non-cardia, intestinal-type gastric cancer, in individuals with low BMI (<18.5 kg/m2; HR,1.15; 95% CI, 1.05-1.25) and high BMI (>27.5 kg/m2; HR, 1.12; 95% CI, 1.03-1.22).[55] A similar, smaller study of gastric cancer patients in Korea found similar, nonsignificant associations between gastric cancer and lower BMI (<23 kg/m2; HR, 10.82) or higher BMI (>25 kg/m2; HR, 11.33) but only in patients without serologic evidence of *H. pylori* infection.[56] Most recently, an analysis of over 500,000 East and Southeast Asian cohort participants replicated the U-shape finding for non-cardia gastric cancer, intestinal-type gastric cancer, and late-onset gastric cancer.[55]

For cardia gastric cancer, there have been more consistent findings of increasing risk with increasing BMI, particularly in American and European studies. [57] In fact, a recent analysis of the National Institutes of Health-the American Association of Retired Persons Diet and Health cohort estimated that obesity was associated with 19% of the cardia gastric cancer burden.[58] Interestingly, in the large East and Southeast Asian cohort analyses described above, no associations of obesity were found with cardia gastric cancer, [55] although it is not clear why there are geographical differences in this association.

Smoking

Tobacco use has been significantly associated with both gastric cardia and non-cardia cancers.[13] Across 23 studies within the StoP Project, gastric cancer was more likely to arise in smokers than nonsmokers with an odds ratio of 1.2 (95% CI, 1.09-1.32).[59] Risk of gastric cancer significantly increased with number of cigarettes smoked (especially greater than 20 cigarettes per day: OR, 1.32) and duration of smoking (OR, 1.33 for 40 or more years), suggesting a dose-response relationship between the number of cigarettes smoked and extent of gastric cancer risk.[59,60] Similarly, in the previously discussed follow-up study of participants in the Shandong Intervention Trial in China, smoking was associated with both an increased incidence of gastric cancer (OR, 1.72; 95% CI, 1.003-2.93) and gastric cancer-related mortality (HR, 2.01; 95% CI, 1.01-3.98).[61]

The interactions of smoking and *H. pylori* infection in increasing gastric cancer risk have also been studied in different contexts. A case-control study examining *cagA* status and smoking found that smokers who were seropositive for *cagA* had an odds ratio of 8.7 for non-cardia gastric cancer compared to an odds ratio of 3.5 for smokers who were seronegative.[62] A more recent prospective cohort study determined that patients with active, but not former tobacco use, had a 33% increased risk of gastric cancer, but only when they had serological evidence of *H. pylori* infection.[63] This suggests that smoking in combination with the presence other major risk factors such as *cagA*-positive *H. pylori* infection may synergistically increase one's risk of developing gastric cancer.

Alcohol Use

The role of alcohol in stomach carcinogenesis has been inconsistent across studies. Several earlier case-control studies and a few cohort studies have not found a strong association between alcohol use and gastric cancer risk.[60,64,65] However, in a meta-analysis of 24 studies of alcohol consumption and gastric cancer, alcohol consumption increased gastric cancer risk by 15%, with both beer and liquor consumption having significant associations with increased gastric cancer risk, but not wine, and no significant differences by subsite (cardia vs. non-cardia).[42] Recently, a study of adults living in the U.S. from 1999 to 2010 demonstrated that heavy alcohol use (five or more drinks per day for a prolonged period) was associated with gastric cancer development.[66] After adjusting for demographics and smoking history, individuals with heavy alcohol use were found to have an odds ratio of 3.13 (95% CI 1.15-8.64) for gastric cancer incidence (although the authors were not able to stratify by subsite).[66] Taken together, these findings suggest that high levels of alcohol consumption, as opposed to any lifetime alcohol use, are associated with increased gastric

cancer risk, and continued intake of certain types of alcohol (beer, liquor) may pose a greater risk than others.

Genetic Syndromes and Family History of Gastric Cancer:

Approximately 10% of gastric cancers demonstrate familial clustering, with about 1-3% of all cases arising from hereditary syndromes associated with gastric cancer.[67,68] Hereditary syndromes include hereditary diffuse gastric cancer (HDGC), gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS), familial adenomatous polyposis (FAP), Lynch syndrome, Peutz-Jeughers syndrome (PJS), juvenile polyposis syndrome (JPS), and Li-Fraumeni syndrome (Table 1).

HDGC presents with early onset diffuse gastric cancer with high penetrance (33-70% by age 80) and an increased risk of lobular breast cancer.[69] In about 25-40% of cases, HDGC is caused by germline mutations in CDH1, the gene encoding E-cadherin.[70,71] E-cadherin is a cell adhesion molecule that plays an important role in maintaining tissue structure, and reduced expression of E-cadherin is associated with poor prognosis in multiple cancer types.[72] While historically CDH1 variants have been estimated to be associated with a 40-83% lifetime risk, a recent study found that cumulative incidence of gastric cancer in CDH1 carriers is likely closer to 42% in men and 33% in women.[73] Additional mutations causing variable penetrance in CDH1-negative HDGC have been identified in CTNNA1, which codes for alpha-E-catenin, as well as PALB2, RAD51C, and BRCA1, all of which are involved with recombination repair.[74,75] Prophylactic gastrectomy is typically recommended for patients found to have a CDH1 mutation.[76] In recent years, newer guidelines recommend CDH1 variant genetic testing for selected patients to improve gastric cancer risk stratification and determine the need for prophylactic gastrectomy versus annual endoscopic gastric surveillance.[76,77] These criteria are outlined in further detail in our discussion on prevention.

GAPPS is a recently characterized autosomal dominant syndrome associated with gastric adenocarcinoma. First described in 2012, GAPPS is now understood to be caused by a mutation in the APC promoter gene with a penetrance of about 13% in carriers.[69,78,79] Diagnosed patients typically have greater than 100 polyps limited to the body and fundus of the stomach in the absence of duodenal and colorectal polyposis.[80] Endoscopic screening may begin at 15 years or earlier if symptomatic, with continued surveillance anywhere between six months and three years, although screening guidelines are not currently well established.[81] Notably, both GAPPS and CDH1 mutations are not associated with *H. pylori* infection, potentially representing an alternate pathway of gastric carcinogenesis.

FAP is an autosomal dominant syndrome caused by a germline mutation in the APC gene, which presents with numerous colonic and rectal polyps beginning in childhood or adolescence. FAP has classically been associated with a 100% risk of colorectal cancer and minimal risk of gastric cancer in the U.S. (~0.6%), similar to that of the general population.[82,83] However, recent studies suggest that this risk may be greater. For example, a study of 767 patients with FAP found that 1.3% of patients developed gastric cancer between 2012 and 2016, despite annual or more frequent esophagogastroduodenoscopy (EGD) surveillance.[84] These tumors may develop from gastric adenomatous or fundic gland

polyps, which are commonly found in patients with FAP, but the exact mechanism by which this occurs is poorly understood.[85] Recent studies have identified an increased incidence of high grade dysplasia in both fundic gland polyps and gastric adenomas, especially polyps that are large in size.[84,86] Upper gastrointestinal tumor screening typically begins at 20-25 years or at the onset of findings of colonic polyps. Repeat endoscopic surveillance ranges from every three to five years and frequency depends on the number, size, and histological findings of duodenal polyps.[87]

Of all the hereditary syndromes associated with gastric cancer, **Lynch** syndrome is the most common, affecting approximately 1 in 279 individuals in the general population.[88] Lynch syndrome is caused by a number of mutations in genes responsible for DNA mismatch repair including MLH1, MSH2, MSH6, and EPCAM.[81] Resultant mutations and/or hypermethylation of these genes generate microsatellite instability, which increases the risk of developing colorectal and intestinal-type gastric cancers in addition to extraintestinal cancers such as ovarian and endometrial cancers.[89] Affected individuals have a 5-9% lifetime risk of gastric cancer.[90] One study found that in individuals with Lynch syndrome, gastric cancer incidence was independently associated with male sex, older age, MLH1 or MSH2 mutations, and the number of first-degree relatives with gastric cancer.[91] Patients with several of these risk factors may benefit from more frequent endoscopic gastric cancer surveillance.

PJS, which presents with gastrointestinal hamartomatous polyps and mucocutaneous pigmented lesions, is caused by a mutation in the tumor suppressor gene LKB1 (STK11).[92] Patients have a significantly increased risk of breast, uterine, lung, and gastrointestinal cancers, especially gastric cancer.[93] PJS confers a 29% lifetime risk of gastric cancer (median age of diagnosis = 30) and routine EGD screening begins at age 8 and is repeated every 2-3 years.[94]

JPS is an autosomal dominant syndrome that presents in childhood with multiple hamartomatous gastrointestinal polyps and a 38% - 68% risk of colorectal cancer and 11% - 21% lifetime risk of upper gastrointestinal (duodenal and diffuse or intestinal gastric) cancers (median age of diagnosis, 58).[82,95] Mutations in BMPR1A and SMAD4 (MADH4, DPC4), both members of the TGF-beta signaling pathway, have been shown to be associated with JPS.[96] Specifically, carriers of SMAD4 mutations are more likely to develop severe gastric polyposis and progress to gastric cancer.[97]

Li-Fraumeni Syndrome is a rare condition caused by mutations in the TP53 tumor suppressor gene. Mutations may be inherited in an autosomal dominant fashion; however, between 7 and 20% of these germline mutations may be *de novo*.[98] It is associated with gastric cancer in addition to breast cancer, sarcomas, brain masses, skin cancer, lung cancer, and adrenal tumors.[99] Risk of gastric cancer in family members with inherited Li-Fraumeni syndrome has been variable across different studies, ranging from 1.3% to 22.6%.[81,100,101]

Familial intestinal gastric cancer (FIGC) is another type of autosomal dominant inherited gastric cancer risk syndrome. Currently, the genetic basis for this syndrome is unknown.

Candidate causative genes include those involved in DNA repair, including BRCA1 and BRCA2.

Mutations in BRCA1 and BRCA2, two genes encoding DNA repair enzymes in homologous recombination, demonstrate an autosomal dominant pattern of inheritance in familial hereditary breast and ovarian cancer (HBOC). Germline mutations in BRCA1 and BRCA2 have also been associated with gastric cancer, although the increased risk associated with these mutations has not yet been well-delineated.[102] In a study of families with inheritance patterns similar to FIGC and HDGC, in addition to BRCA1 and BRCA2, PALB2, a gene also involved in homologous recombination, and ATM, a gene involved in DNA repair, were also associated with these patterns.[69]

Although different modifiable and nonmodifiable risk factors are likely to increase gastric cancer risk in genetically predisposed individuals, further investigation is necessary to understand their contributions to this risk. Individuals with known mutations associated with gastric cancer and additional independent risk factors for gastric cancer will likely benefit from earlier and more frequent interventions such as endoscopic surveillance or surgical prophylaxis. More specific screening guidelines are needed to address these nuances.

In the absence of a defined genetic syndrome or known mutation, a family history of gastric cancer also confers an increased risk of an individual developing gastric cancer. An analysis of pathogenic variants in gastric cancer found that 19.8% of individuals with gastric cancer had a relevant germline mutation.[103] In a clinical trial in Korea of *H. pylori* eradication among individuals with a first-degree family history of gastric cancer, *H. pylori* treatment was associated with a 55% reduced risk of developing gastric cancer compared to placebo and 73% reduced risk of gastric cancer compared to those with persistent *H. pylori*.[104] This suggests that *H. pylori* eradication is even more critical to preventing gastric cancer in patients with a family history of gastric cancer.

Prevention

A study of healthcare cost in the U.S. found that total annual healthcare cost of gastric cancer per patient was greater than the cost of colorectal, liver, or lung cancer, per patient, at over 45,000 dollars.[105] Prevention of gastric cancer has the potential to be highly cost-effective and mitigate financial burdens to both patients and healthcare systems. Given the heterogeneity found in gastric cancer, prevention necessitates a multifaceted approach, including adherence to *H. pylori* treatment and eradication guidelines, improved understanding of the drivers of eradication failure and relevant next steps, and more specific guidelines to identify and effectively screen individuals at higher risk of progression across the spectrum of *H. pylori*-associated disease.

H. pylori Testing, Treatment, and Eradication

H. pylori infection is the greatest risk factor for developing gastric cancer; as a result, testing for and treating *H. pylori* are essential components of gastric cancer prevention. Common testing approaches include histopathological staining of endoscopic biopsies, as well as non-invasive methods such as stool antigen tests, urea breath tests, and antibody testing. A

Cochrane review of non-invasive *H. pylori* testing identified that urea breath tests had the greatest diagnostic accuracy of all of the non-invasive options, although false negatives can occur with all tests for active infection when patients are on antibiotics or taking proton pump inhibitors.[106]

Trials of *H. pylori* eradication therapy have found a significant reduction in gastric cancer incidence (RR, 0.54; 95% CI, 0.40-0.72) and gastric cancer-related deaths (RR, 0.61, 95% CI, 0.40-0.92).[107,108] Following diagnosis, *H. pylori* treatment reduces risk of gastric cancer but does not bring this risk to zero.[109] A retrospective cohort study of patients within the Veterans Affairs hospital system found that patients who were treated for *H. pylori* still had a non-significantly increased risk of gastric cancer (SHR, 1.16; 95% CI, 0.74-1.83), but those who additionally had eradication testing demonstrating successful treatment of their *H. pylori* infection had a significantly reduced risk of gastric cancer, compared to individuals who did not have successful eradication of their bacteria (SHR, 0.24; 95% CI, 0.15-0.41).[109] In a randomized controlled clinical trial of *H. pylori* eradication in first-degree relatives of patients with gastric cancer, 1.2% of participants in the *H. pylori* treatment group developed gastric cancer compared to 2.7% of the placebo group over the follow-up period of about 9 years.[110] Moreover, of the participants who developed gastric cancer in the treatment group, 50% had persistent *H. pylori* infection.[110] Taken together, these findings demonstrate that individuals with persistent *H. pylori* infection are at a particularly increased risk of developing gastric cancer.

The 2017 ACG guidelines recommend that all patients infected with *H. pylori* be treated with appropriate combination therapy and undergo eradication testing following treatment completion, reflecting the importance of reducing persistent *H. pylori* infection.[111] However, eradication testing and follow-up treatment in the event of repeat infection positivity do not always take place. In a retrospective cohort study of 152 patients with *H. pylori*-associated peptic ulcer disease, only 44% of patients received eradication testing.[112] In that cohort, predictors of eradication testing included outpatient status at the time of *H. pylori* diagnosis as well as follow-up care with a gastroenterologist.[112] These findings highlight inconsistent eradication testing practices between specialties and the potential for gaps in care after hospital discharge. These findings also illustrate the need for more consistent eradication testing and system-based approaches to ensure that *H. pylori* eradication testing is completed after treatment, such as implementing automated testing reminders in the electronic health record.

H. pylori antibiotic resistance also contributes to eradication failure and persistence of infection. A meta-analysis of 178 studies of the geographic distribution of *H. pylori* antibiotic resistance identified at least 10% overall prevalence of *H. pylori* resistance to clarithromycin, metronidazole, and levofloxacin across all World Health Organization regions.[113] Local antibiotic resistance rates should be closely monitored given these regional differences, especially when planning and implementing therapies for large-scale eradication programs in areas where populations are at increased risk of gastric cancer.[114]

Host factors may also contribute to treatment failures. For example, a meta-analysis of 57 studies examining *H. pylori* eradication found that individuals with CYP2C19

polymorphism enhanced metabolizer phenotypes were 82% more likely to experience *H. pylori* eradication failure than those with wild-type phenotypes (OR, 1.82; 95% CI, 1.52-2.19). CYP2C19 polymorphisms that enhance drug metabolism are prevalent among individuals across racial and ethnic groups within the U.S., and can be clinically tested.[115] In addition to genetic host factors, which can be costly to test for, incomplete understanding and education regarding treatment regimens, inconsistent healthcare follow-up, and treatment-related adverse effects may also contribute to antibiotic resistance. Active awareness and consideration of these contributors to antibiotic resistance and continued communication and follow-up between patients and healthcare professionals may improve *H. pylori* treatment-related preventative efforts. Taken together, ensuring completion of eradication testing in combination with improved assessments of antibiotic resistance on both individual and regional levels are essential to preventing future cases of gastric cancer.

Finally, *H. pylori* reinfection should also be considered when confirming eradication, especially in individuals more likely to be exposed to *H. pylori*. A meta-analysis of 132 studies of *H. pylori* reinfection found that the global annual rate of recurrence for *H. pylori* infection after confirmed eradication was 4.3% (95% CI, 4-5%) and that this rate was inversely related to the human development index (HDI), a statistical index combining life expectancy, education, and per capita income.[116]

Chemoprevention

As previously discussed, *H. pylori* eradication therapy can reduce the risk of developing gastric cancer. Aspirin use has also been associated with a reduction in risk of multiple gastrointestinal cancers, including gastric cancer, especially intestinal-type non-cardia gastric cancer.[117,118] A recent study of 316 individuals with gastric cancer within the Nurses' Health Study and Health Professionals Follow-up Study in the U.S. found that aspirin use at least twice per week was associated with a reduction in gastric cancer risk among women (HR, 0.52; 95% CI, 0.37-0.73), but not men.[119]

Some studies have also investigated the interaction of aspirin with *H. pylori*, finding that aspirin use is significantly associated with a reduction in gastric cancer risk in *H. pylori*-positive patients, but not among *H. pylori*-negative patients.[120,121] Additionally, a study of a cohort of over 63,000 patients in Hong Kong who had undergone successful eradication of *H. pylori* between 2003 and 2012 found that aspirin use following eradication was associated with a decreased risk of developing gastric cancer (HR, 0.3; 95% CI, 0.15-0.61).[122] A significantly greater reduction in risk of gastric cancer was also observed with increasing aspirin dosage, frequency, and regimen duration. However, this reduction in gastric cancer risk was not observed in a similar study of this cohort in association with non-aspirin nonsteroidal anti-inflammatory drugs.[123]

Vitamin and garlic supplementation have also been explored as potential chemoprevention in a large randomized controlled trial in a high-incidence area of China. During 22.3 years of follow-up, the Shandong Intervention Trial found that 7.3 years of vitamin (C, E, and selenium) supplementation was associated with a significant reduction in both gastric cancer incidence and mortality (OR, 0.64; 95% CI, 0.46-0.91; and HR, 0.48; 95% CI, 0.31-0.75).[124] In this same trial, 7.3 years of oral garlic extract and oil supplementation was

not significantly associated with a reduction in gastric cancer incidence (HR, 0.81; 95% CI, 0.57-1.13), but was associated with a significant reduction in gastric cancer mortality (HR, 0.66; 95% CI, 0.43-1.00), although these trends only became noticeable after 12 and 14.7 years of follow-up, respectively.[124] A further analysis of this trial exploring effect modification by lifestyle factors found that garlic supplementation was only associated with a reduction in gastric cancer mortality in participants with *H. pylori* infection who did not consume alcohol (*P* for interaction = 0.04).[61]

Endoscopic Surveillance—Endoscopic screening and surveillance in individuals at increased risk of developing gastric cancer is the primary screening method for gastric cancer prevention. In areas of the world such as East Asia, recent studies have shown mass gastric cancer endoscopic surveillance programs to be effective in reducing both gastric cancer incidence and mortality.[125,126] Currently, no endoscopic screening for individuals at average risk of gastric cancer is standard in the U.S. A modeling study found that upper EGD at the time of colorectal cancer screening colonoscopy in the U.S., with follow-up EGD every three years only in the presence of intestinal metaplasia or higher-grade pathologic lesions, was cost-effective for Asian American, Hispanic White, and non-Hispanic Blacks patients, but not for non-Hispanic White patients.[127]

Gastric intestinal metaplasia (GIM), characterized by the growth of intestinal-like epithelium in the gastric mucosa, is thought to be a precursor lesion to gastric dysplasia and cancer, with prevalence ranging from around five percent to greater than 20 percent in the U.S. and greater than 20 percent in regions with a greater incidence of *H. pylori* infection, such as China.[126,128,129] Since GIM is a histopathologic diagnosis requiring endoscopic biopsy for diagnosis, the prevalence of GIM may be difficult to estimate given the lack of universal endoscopic screening. Within the U.S., the prevalence of GIM varies among racial and ethnic groups, with Asian American, Black, and Hispanic White individuals having a twofold or greater prevalence compared to non-Hispanic White individuals.[128,130,131]

An analysis of over 25,000 patients with GIM across 10 studies found an incidence rate of approximately 12.4 cases of gastric cancer per 10,000 patient-years (95% CI, 10.7-14.3).[132,133] In a cohort of patients in California, the presence of extensive GIM on endoscopy was associated with a five-to-sevenfold greater risk of cancer progression compared to findings of focal GIM.[134] Furthermore, a recent study of GIM in a western European population with a generally low incidence of gastric cancer found that patients with GIM identified in both the antrum and body of stomach were more likely to exhibit disease progression (3.1% of cases) compared to patients with GIM found in one location of the stomach (0.4% of cases).[135] Additionally, incomplete GIM is associated with a higher risk of progression to gastric cancer compared to complete GIM.[136] A 10-year study of 81 patients with complete GIM and 11 patients with incomplete GIM found that while no patients with complete GIM experienced disease progression, 50% of patients with incomplete GIM progressed to dysplasia or cancer.[137] The Operative Link on Gastric Intestinal Metaplasia (OLGIM) assessment is a tool used to stratify patients at risk of progression to gastric cancer by staging the severity of histopathologic GIM findings from endoscopic biopsies.[138] A prospective study utilizing OLGIM for endoscopic surveillance of patients with GIM in Singapore found that both patients with intermediate (OLGIM II)

and high-risk GIM (OLGIM III-IV) were at an increased risk of developing high grade dysplasia and Stage I gastric adenocarcinoma (HR, 7.34; 95% CI, 1.60-33.7 and HR, 20.77; 95% CI, 5.04-85.6, respectively).[139] Furthermore, patients with both intermediate/high-risk GIM who had a smoking history of 20 or more pack years were at an even greater risk of developing gastric cancer (HR, 3.69; 95% CI, 1.03-13.2).[139] These findings support the utility of multifaceted risk stratification systems that incorporate multiple modifiable and nonmodifiable risk factors.

For patients found to have GIM on endoscopy, the most recent AGA clinical screening guidelines recommend *H. pylori* testing and eradication, but do not recommend routine endoscopic surveillance.[140] However, they do acknowledge that certain patient populations (racial and ethnic minorities, immigrants, patients with a family history of gastric cancer) may be at increased risk of developing gastric cancer and could elect for endoscopic surveillance, potentially after 3-5 years.[140] One study found that among patients with GIM in the U.S., Hispanic patients had the greatest risk of progressing to gastric adenocarcinoma compared to other racial and ethnic groups.[134] Although only an estimated 0.5% -2.7% of patients with GIM develop gastric adenocarcinoma annually, this is comparable to that of patients diagnosed with Barrett's esophagus who develop esophageal adenocarcinoma, estimated around 0.12-0.5% annually.[132,133,141–143] In contrast, the screening guidelines for Barrett's esophagus have been well-defined and recommend continued surveillance every 3-5 years, even in the absence of dysplasia.[144,145]

Improving gastric cancer surveillance guidelines for individuals with known hereditary cancer syndromes who are at increased risk of developing gastric cancer is another actionable component of gastric cancer prevention. For example, a retrospective analysis of 217 patients with Lynch syndrome found that five patients developed upper gastrointestinal (duodenal or gastric) cancers that were detected by surveillance, and four of these cancers were Stage 1 and occurred within two years of previous endoscopy.[146] Given these findings, for patients with Lynch syndrome, these researchers recommend *H. pylori* testing and treatment if needed at the time of Lynch syndrome diagnosis, in the form of non-invasive testing for individuals under 30 and endoscopic testing for those over 30.[147] They also suggest performing upper gastrointestinal endoscopic surveillance concurrently with colonoscopy beginning at age 30, or at least 2-5 years prior to the diagnosis of an upper gastrointestinal cancer in a family member if earlier.[147]

Circulating Biomarkers

Circulating biomarkers for gastric cancer prevention offer the potential of a noninvasive approach to identifying individuals at greatest risk of progressing to gastric cancer. Some of these biomarkers have already been employed in the clinical setting in areas with a higher regional incidence of gastric cancer.

Numerous studies have explored the association of serum antibodies to *H. pylori* proteins and risk of gastric cancer, and a recent meta-analysis of nine studies found that five *H. pylori* virulence factors were significantly associated with non-cardia gastric cancer risk: *cagA* (OR, 3.22; 95% CI, 2.10-4.94); HP 0305 (OR, 1.72; 95% CI, 1.32-2.25); HyuA (OR, 1.42; 95% CI 1.13-1.79); Omp (OR, 1.83, 1.30-2.58); and *vacA* (OR, 2.05; 95% CI, 1.67-2.52).[148]

Notably, the meta-analysis found no significant associations between any of the antigens and risk of cardia gastric cancer.

The ABC method, which combines serum *H. pylori* antibodies with pepsinogen-defined chronic atrophic gastritis, was first developed by Miki et al. in Japan and has been used to risk stratify patients for further gastric cancer screening in East Asia. [149,150] A recent study sought to utilize antibody responses to specific *H. pylori* antibodies to create a new predictive model in three East Asian cohorts, and found that in addition to pepsinogen-defined chronic atrophic gastritis, adding antibody responses to the *H. pylori* proteins HP 0305, HP 1564, and UreA, along with gender and age, resulted in a model with a greater area under the curve (AUC) than that of the ABC method alone (AUC, 73.79%; 95% CI, 75.37%-82.35%; vs. AUC, 68.75%; 95% CI, 65.91-71.58; p for difference <0.001).[151]

Using an untargeted global profiling platform to assess 1,000 metabolites in pre-diagnostic plasma, a recent case-control study in Shanghai of 250 incident gastric cancer cases and one-to-one matched controls identified eighteen metabolites that were significantly associated with gastric cancer.[152] One of these metabolites, methylmalonic acid, is elevated in B12 deficiency. Vitamin B12 deficiency is linked with both gastric cancer and atrophic gastritis, a potential precursor lesion to gastric cancer.[153]

Personalized Medicine

Employing a more personalized approach to assessing risk that includes tailored genetic testing poses another opportunity for improved risk stratification of patients more likely to develop gastric cancer. Genetic testing for gastric cancer has focused on the diffuse histopathologic type. As discussed earlier, CDH1 may be used as a marker for HDGC. The Blair criteria for HDGC recommend CDH1 testing, followed by CTNNA1 testing if CDH1 testing is negative, for patients who meet any of the following family (first or second-degree blood relatives) criteria: ≥2 cases of gastric cancer in the family regardless of age, with at least one diffuse gastric cancer (DGC), ≥1 case of DGC at any age, and ≥1 case of lobular breast cancer at age <70 years, in different family members, ≥2 cases of lobular breast cancer in family members <50 years of age.[76] Individual criteria include a diagnosis of DGC at age <50 years, at any age in individuals of Māori ethnicity or personal or family history of cleft lip or palate, or history of DGC and lobular breast cancer or bilateral lobular breast cancer diagnosed at age <70 years.[76] For patients who carry a germline CDH1 mutation, the National Comprehensive Cancer Network (NCCN) guidelines recommend prophylactic total gastrectomy between 18 and 40 years of age, with opportunities for endoscopic surveillance every 6-12 months for patients who do not wish to undergo surgery.[154] However, endoscopic surveillance may not always identify precursor gastric lesions.[155] In the future, we anticipate that genetic testing and related preventive strategies will be broadened to include other known genetic contributors to gastric cancer risk for both diffuse and intestinal types. Mixed models of susceptibility incorporating multiple hereditary and non-hereditary risk factors, such as those that have been developed in breast cancer, will further advance risk stratification in gastric cancer.[156]

While genetic testing is a promising clinical tool for cancer prevention, we must also acknowledge the disparities that exist both in the accessibility of this testing to all patients

and in the clinical decision making of who gets tested. Significant racial and ethnic disparities have been identified regarding referrals made for breast cancer-related genetic counseling for non-Hispanic Black patients compared to non-Hispanic White patients.[157] Barriers to genetic counseling and hereditary cancer testing include patient and provider awareness of testing options, stress surrounding testing, disparate insurance coverage of testing, reduced availability of family medical history, and lower levels of trust in the health system among racial and ethnic minorities.[158] Increased awareness of these disparities in addition to interventions can improve access to these screening tools for individuals at increased risk of developing gastric cancer, which can in turn reduce risk of disease progression.

Future Directions

Most people living with *H. pylori* infection do not develop gastric cancer. More detailed, research-driven guidelines are necessary to identify those individuals who, within this population, are at an increased risk of cancer, and develop personalized testing, treatment, and surveillance strategies while ensuring equitable resource allocation and access to these options. This includes the development of multifactorial algorithms incorporating serum biomarkers, exposures, family history, and demographic information to predict gastric cancer risk to create a more personalized approach to screening and surveillance. These algorithms could help focus resources such as endoscopy on patients most likely to benefit from invasive testing. Infection with *H. pylori* may also contribute to dysbiosis within the gastrointestinal tract, which can promote progression of *H. pylori*-associated disease (gastritis, metaplasia, dysplasia, and cancer).[159]

It is currently unclear exactly why *H. pylori* persistence occurs in some patients, although it may be attributed to infection with more virulent strains of *H. pylori*, such as *cagA*-positive strains, and/or increased antibiotic resistance. Persistent *H. pylori* infection can be identified and addressed through eradication testing; however, as discussed earlier, eradication testing is often not performed. This could be due to several reasons, such as a lack of reminders for healthcare practitioners to set up eradication testing, losing patients to follow-up due to logistical and/or financial reasons, and variable applications of existing guidelines. Designing systems level interventions can address this discrepancy, and potentially reduce the risk of developing gastric cancer that accompanies persistent infection.

Conclusions

While the incidence of gastric cancer has been declining within the U.S. and worldwide, the overall high mortality rates and existing disparities in both incidence and mortality suggest the need for delineating and implementing risk-stratified prevention strategies, which would be highly cost-effective. Future research should include developing multifactorial mixed models of nonmodifiable and modifiable risk factors for gastric cancer to identify patients at greatest risk of progressing to gastric cancer. Finally, future interventions should improve access to existing preventative measures such as genetic testing and *H. pylori* eradication testing in addition to expanding upon current clinical guidelines for premalignant disease to address gaps in endoscopic surveillance.

Acknowledgements

This work was supported in part by the National Institutes of Health (NIH) grants P20 CA251657 (to M. Epplein and K.S. Garman) and Duke Cancer Institute P30 CA014236 (to M. Epplein and K.S. Garman), as well as the Eugene A. Stead Scholarship through the Stead Fellowship Endowment Fund (to P. Alagesan).

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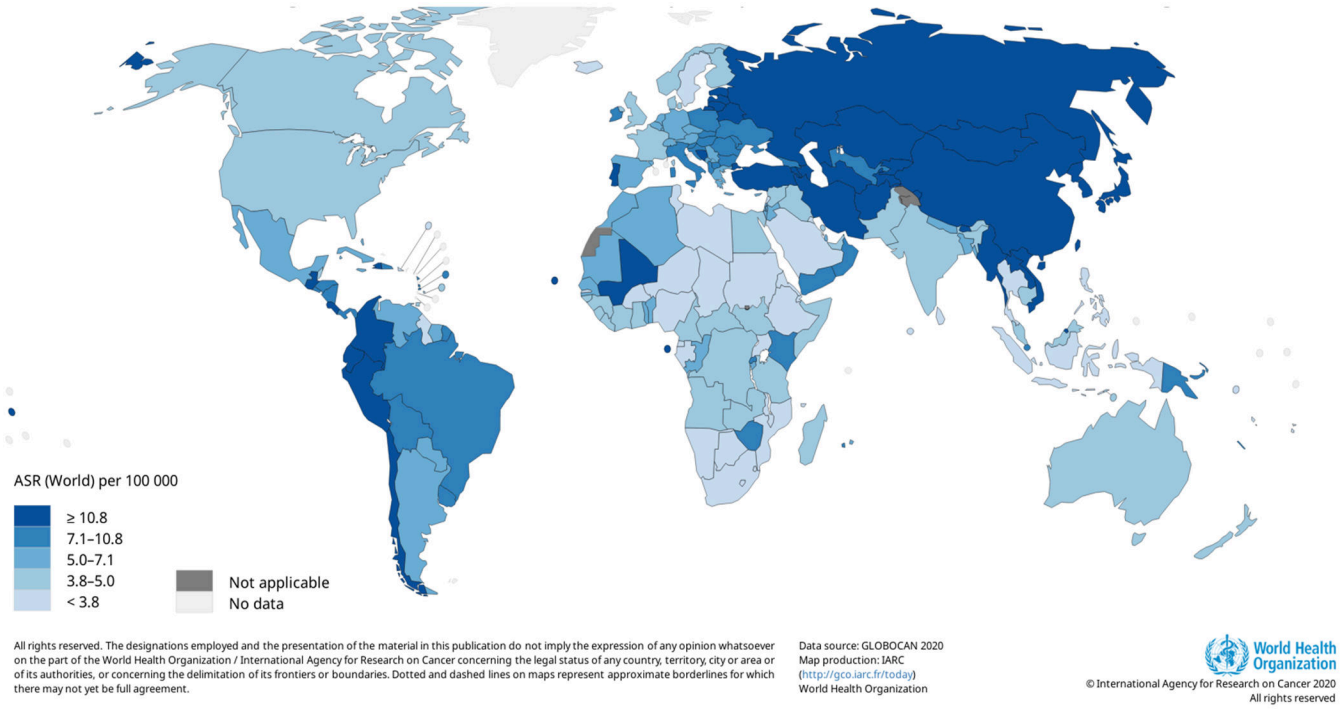

Figure 1:
Estimated age-standardized incidence rates (World) in 2020, stomach, both sexes, all ages.

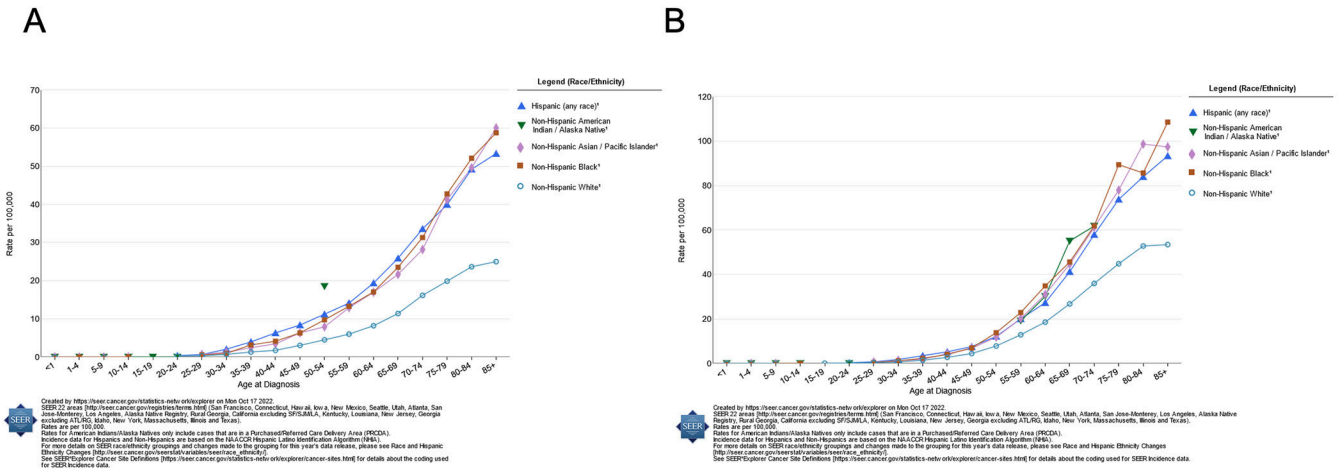

Figure 2:

Delay-adjusted SEER stomach cancer incidence rates by age at diagnosis, 2015-2019, by race/ethnicity; panel A displays rates among women; panel B displays rates among men.

Table 1:

Genetic syndromes associated with gastric cancer

Syndrome	Clinical features	Associated gene alterations	Lifetime risk of gastric cancer	Gastric cancer screening and prevention
Hereditary diffuse gastric cancer (HDGC)	Increased risk of early-onset diffuse subtype gastric cancer and lobular breast cancer	CDH1, CTNNA1, RAD51C, BRCA1, PALB2	33-70%[69,73]	CDH1 and CTTNA genetic testing[76] Prophylactic gastrectomy recommended between 18 and 40 years, endoscopic surveillance every 6-12 months if declined[154]
Gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS)	>100 polyps in the body and fundus of the stomach without duodenal and colorectal polyposis	APC promoter B1	13%[79,160]	No current guidelines, but consider upper endoscopic surveillance at symptom onset or 15 years.[161] Gastrectomy if dysplasia, or at 30-35 years or 5 years prior to youngest family member diagnosis of gastric cancer[160,161]
Familial adenomatous polyposis (FAP)	Adenomatous and/or fundic gland polyps in stomach in addition to colon and rectal polyps	APC	0.6-2%[154]	Upper endoscopic surveillance at symptom onset or 25-30 years with specialized surveillance if dysplasia[154,161]
Lynch Syndrome	Increased risk of intestinal subtype gastric cancer, other gastrointestinal cancers, endometrial and ovarian cancers	MLH1, MSH2, MSH6, EPCAM	5-9%[90]	Test for *H. pylori* and treat if present. Upper endoscopic surveillance at 30-35 years every 2-4 years, or earlier and more frequently based on family history or presence of high-risk endoscopic findings.[82,161]
Peutz-Jeughers Syndrome (PJS)	Gastrointestinal hamartomatous polyps and mucocutaneous pigmentation	LKB1(STK11)	29%[94]	Upper endoscopic surveillance beginning at age 8-10 years, repeated every 2-3 years if polyps or resuming at 18 years if no polyps[161]
Juvenile Polyposis Syndrome (JPS)	Gastrointestinal hamartomatous polyps	BMPR1A SMAD4	11-21%[82,95]	Upper endoscopic surveillance beginning at age 15 every 1-3 years[154] Gastrectomy in severe cases[82]
Li-Fraumeni Syndrome	Increased risk of multiple cancer types	TP53	1.3-22.6%[81,100,101]	No current centralized guidelines
Familial intestinal gastric cancer (FIGC)	Increased risk of intestinal subtype gastric cancer	Currently unknown	Currently unknown	No current centralized guidelines