Gastric Cancer Epidemiology

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KEYWORDS

• Incidence • Survival • Risk factors • Genetics • Environment

KEY POINTS

- Globally, gastric cancer remains the fifth most common cancer and the third leading cause of cancer-related mortality.
- In the United States, despite overall decreasing rates over the past five decades, incidence of noncardia gastric cancer is increasing among adults less than 50 years.
- *Helicobacter pylori* is the main cause of gastric cancer, accounting for approximately 89% of distal gastric cancer cases worldwide.
- Population-based programs of screening and surveillance and *H pylori* screening and eradication hold greatest promise for reducing the burden of gastric cancer.

INTRODUCTION

Gastric cancer is the fifth most common cancer worldwide and the third leading cause of cancer-related mortality.[1] There are two main topographic types of gastric cancer: cardia gastric cancer (arising in the area of the stomach adjoining the esophagogastric junction) and noncardia gastric cancer (arising from more distal regions of the stomach). The epidemiology of the two topographic types is distinct. Furthermore, according to the Lauren classification, there are two histologic types of gastric cancer: intestinal and diffuse. Both histologic subtypes are associated with *Helicobacter pylori* infection. The diffuse type contains diffuse carcinoma cells that lack cohesion and invade tissues independently or in small clusters. The intestinal type of adenocarcinoma forms glands or tubules lined by epithelium with cohesion among tumor cells that resemble the intestinal mucosa. The intestinal type is the most frequent type found in high gastric cancer incidence populations. A prolonged precancerous process occurs before the development of the intestinal type of adenocarcinoma, known as the Correa cascade, with well-defined, consecutive stages.[2] The process is initiated with *H pylori* infection causing chronic active gastritis. With sustained infection for decades, gastric mucosal inflammation may lead to glandular loss, known as chronic atrophic gastritis. Atrophy typically first occurs in the incisura angularis and

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then extends over time to the anterior and posterior gastric walls. Atrophy is then replaced with intestinal metaplastic cells, initially with small intestinal complete phenotype, then eventually to large intestinal (incomplete or colonic) phenotype. Following incomplete intestinal metaplasia, dysplasia then develops (first low grade, then high grade), after which invasive carcinoma is the final stage. This article describes the descriptive epidemiology of gastric cancer, its main risk factors, and opportunities and challenges for primary and secondary prevention.

INCIDENCE AND MORTALITY

Worldwide Trends

According to GLOBOCAN estimates, there were 1,033,701 new cases of gastric cancer worldwide and 782,685 deaths related to gastric cancer in 2018.[3] Gastric cancer was the fifth-most commonly diagnosed cancer type in 2018 (representing 5.7% of all cancer cases diagnosed) and was responsible for 8.2% of all deaths from cancer in 2018, making it the third-most common cause of cancer-related death after lung (18.4% of deaths) and colorectal (9.2% of deaths) cancers.[3] In 2018, the global age-standardized incidence and mortality rates for gastric cancer were 11.1 and 8.2 per 100,000, respectively. Gastric cancer incidence rates increase with increasing age and are two-fold to three-fold higher for men than women. Gastric cancer was the fourth most commonly diagnosed cancer type in men (incidence rate, 15.7 per 100,000) and the seventh most commonly diagnosed cancer type in women (incidence rate, 7.0 per 100,000) in 2018.[3] Recent studies examining global trends in incidence and mortality rates for gastric cancer have confirmed a continued decline worldwide[4–6]; however, these studies also highlight the global variability in incidence and mortality rates and differences in secular trends. Approximately 86% (885,119 of 1,033,701) of new gastric cancer cases in 2018 occurred in regions with high and very high Human Development Index. Environmental factors likely explain this, particularly *H pylori* infection because highly virulent strains of *H pylori* are found in Eastern and South Eastern Asia, regions with high Human Development Index level and where 64% (657,254 cases) of new gastric cancer cases were diagnosed in 2018 (**Fig. 1**).[1,7] The highest incidence rates for gastric cancer are observed in Eastern Asia (32.1 per 100,000 men; 13.2 per

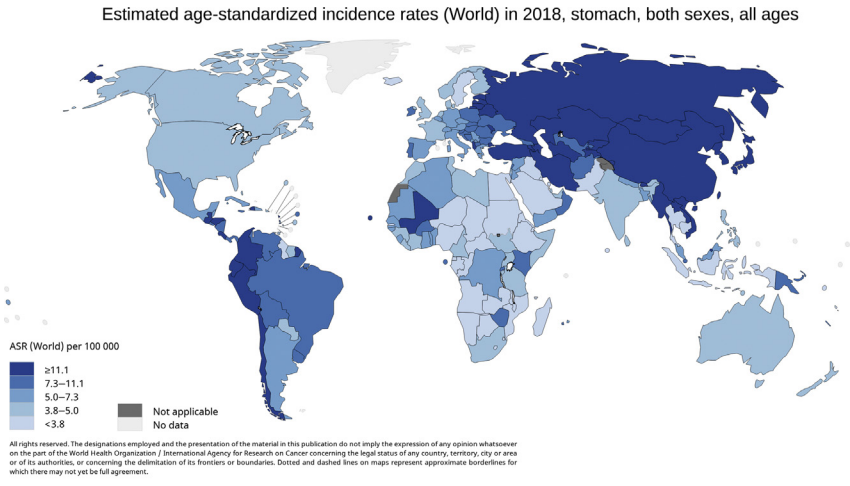

Fig. 1. Worldwide age-standardized incidence rate per 100,000 for gastric cancer in 2018. (*From* GLOBOCAN 2020; Graph production: IARC (http://gco.iarc.fr/today) World Health Organization.)

100,000 women), Central and Eastern Europe (17.1 per 100,000 men; 7.5 per 100,000 women), and South America (12.7 per 100,000; 6.9 per 100,000 women), whereas the lowest incidence rates are observed in North America (5.6 per 100,000 men; 2.8 per 100,000 women) and Africa (~5 per 100,000 men and 3–4 per 100,000 women).[1] There has been a steady decline in incidence and mortality rates for gastric cancer in Western populations since the middle of the twentieth century. In Japan and Korea, countries with historically high gastric cancer incidence rates, delayed but similar decreasing trends have been observed in recent years.[8] The highest mortality rates for gastric cancer are observed in Eastern Asia (15.9 per 100,000).[1] High mortality rates are also observed in Central and Eastern Europe and South America, whereas lowest mortality rates for gastric cancer are seen in Northern America (1.8 per 100,000).[1]

United States Trends

The epidemiology of gastric cancer in the United States has changed dramatically over time,[9] with a linear decline in incidence rates in recent decades.[10,11] For the purpose of this review, the most recent data were analyzed from the US National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) nine registries[12] (covering approximately 10% of the US population) in which 89,066 cases of invasive gastric cancer (defined using International Classification of Diseases for Oncology, Third Edition, site codes C160–C169 and histology type, excluding 9050–9055, 9140, and 9590–9992) were diagnosed between 1975 and 2017. Gastric cancer incidence rates decreased from 11.7 per 100,000 in 1975 to 6.6 per 100,000 in 2017 (**Fig. 2**). During that period, incidence of gastric cancer decreased at a rate of 1.49% per year (average annual percent change [AAPC], −1.49%; 95% confidence interval [CI], −1.43% to −1.55%). Among all gastric cancer cases in the SEER database diagnosed between 1975 and 2017, 61.4% were in men. Between 1975 and

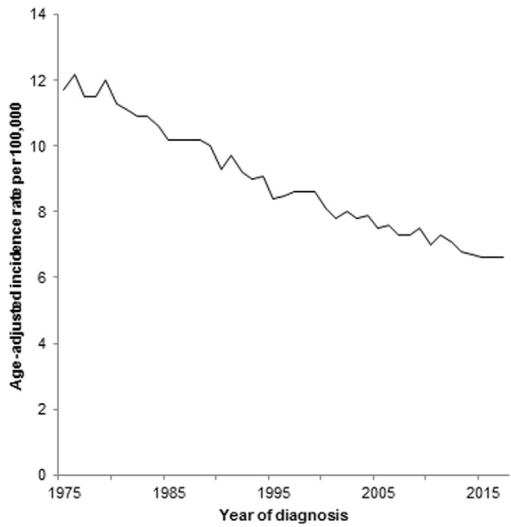

Fig. 2. Age-adjusted incidence rates of gastric cancer in the United States, 1975 to 2017. (*From* Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER Research Data, 9 Registries, Nov 2019 Sub (1975-2017) - Linked To County Attributes - Time Dependent (1990-2017) Income/Rurality, 1969-2017 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, released April 2020, based on the November 2019 submission.)

2017, gastric cancer incidence rates in the United States decreased in men (AAPC, −1.70%; 95% CI, −1.64% to −1.77%) and women (AAPC, −1.34%; 95% CI, −1.21% to −1.47%). The lifetime risk of gastric cancer in the United States is approximately 1 in 95 men and 1 in 154 women.[10]

Incidence rates for gastric cancer in the United States increase with increasing age, with, historically, low rates of gastric cancer among adults aged less than 50 years.[10] However, although rates of noncardia gastric cancer in the United States continue to decrease among adults aged greater than or equal to 50 years, the incidence of noncardia gastric cancer among persons aged less than 50 years is increasing.[13–15] In addition to established sex disparities, incidence rates for gastric cancer vary among different ethnic groups within the United States.[10] Compared with non-Hispanic Whites, incidence rates for gastric cancer are two-fold higher among Hispanics, non-Hispanic Blacks, and Asian and Pacific Islanders in the United States.[10] Divergent secular trends in gastric cancer rates by cancer stage at diagnosis between non-Hispanic Whites and Hispanics aged less than 50 years have also been reported in the United States.[10,11] Among non-Hispanic Whites, rates of localized-stage noncardia gastric cancer increased by 5.28% (95% CI, 3.94%–6.64%) per year between 2001 and 2014. Conversely, during the same period, the rates of regional- and distant-staged noncardia gastric cancer among non-Hispanic Whites aged less than 50 years decreased and remained unchanged, respectively. By contrast, there was a significant increase in distant-staged noncardia gastric cancers among Hispanics aged less than 50 years (AAPC, 1.78%; 95% CI, 0.66%–2.91%).[14]

Geographic differences in overall gastric cancer incidence rates and trends over time have been observed in the United States.[15] Data from the US Cancer Statistics registry (covering 100% of the US population in 2015)[16] show that the highest incidence rates for gastric cancer in 2001 to 2002, 2006 to 2007, and 2011 to 2012 were found in Hawaii (14.4, 10.6, and 9.1 per 100,000, respectively), whereas by 2016 to 2017 the highest rates were found in New York (8.7 per 100,000). In 2001 to 2002, 12 of the 50 states had incidence rates less than or equal to 5.7 per 100,000; this number increased to 22 states by 2016 to 2017. By contrast, the number of states with incidence rates greater than 8.4 per 100,000 decreased from seven states (Hawaii, Alaska, New York, Rhode Island, New Jersey, Connecticut, Louisiana) in 2001 to 2002 to one (New York) by 2016 to 2017 (**Fig. 3**).

For gastric cancer cases in the SEER 18 registries,[17] median relative survival has increased from 10.3 months in 2000 to 17.6 months for persons diagnosed in 2016. Overall 5-year observed survival rates increased from 18.8% for patients diagnosed with gastric cancer in 2000 to 28.4% for patients diagnosed in 2012. The greatest absolute improvement in survival trends occurred in patients with gastric cancer diagnosed with localized disease. Approximately 46% of patients diagnosed with localized gastric cancer in 2000 survived 5 years after their diagnosis, whereas the 5-year observed survival rate for patients diagnosed with localized gastric cancer in 2012 was 61% (**Fig. 4**). However, one-third of patients with gastric cancer are still diagnosed with distant-stage disease and there has been little improvement in 5-year survival rates for these patients (2.3% for patients diagnosed in 2000 vs 5.4% for those diagnosed in 2012).

RISK FACTORS

Helicobacter pylori Infection

Chronic infection with *H pylori* is the main cause of gastric cancer, accounting for approximately 89% of distal gastric cancer cases worldwide.[18] In 1994, the International Agency for Research on Cancer classified *H pylori* as a class I carcinogen for

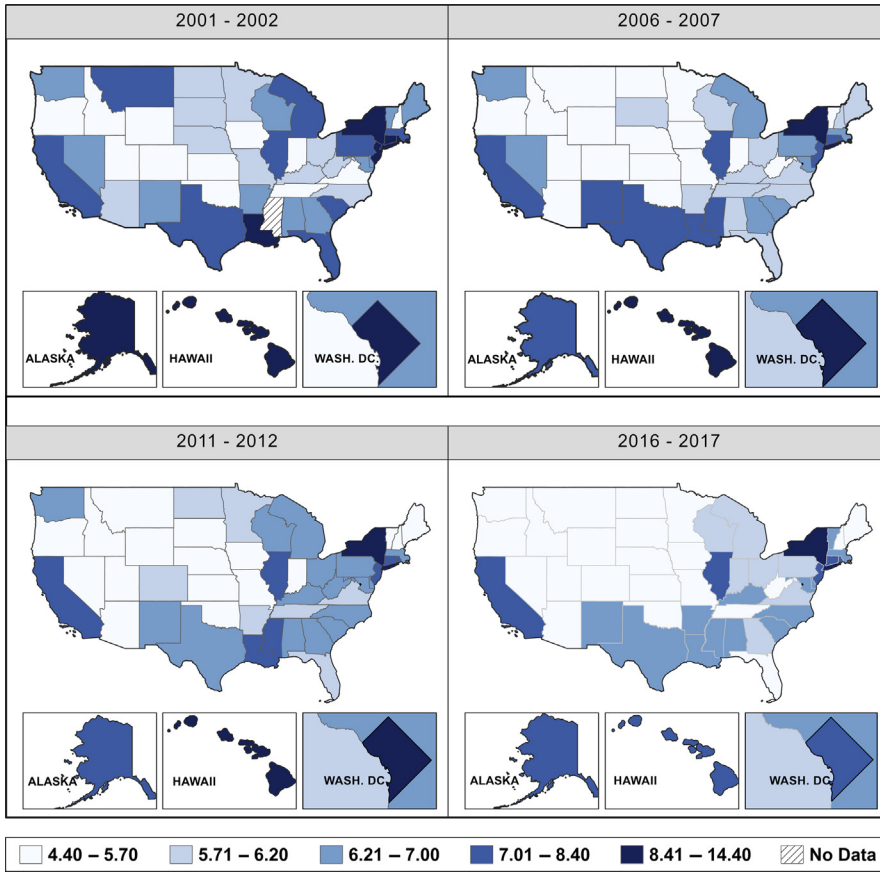

Fig. 3. State-level heat maps showing age-adjusted incidence rates of gastric cancer in the United States, 2001 to 2017. (*From* National Program of Cancer Registries and Surveillance, Epidemiology, and End Results SEER*Stat Database: NPCR and SEER Incidence - U.S. Cancer Statistics 2001-2017 Public Use Research Database, 2019 Submission (2001-2017), United States Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute. Released June 2020. Accessed at www.cdc.gov/cancer/uscs/public-use.)

noncardia gastric cancer and reconfirmed this classification in 2009.[19] Most *H pylori* infections are acquired during childhood and, once established, usually persist for life unless treated. There is substantial regional variation in prevalence,[20] with highest prevalence in Central and South America and in parts of Asia and Eastern Europe, regions with highest rates of gastric cancer.[20] A stronger effect of *H pylori* on the risk of noncardia gastric cancer is observed among individuals with the CagA-positive *H pylori* strain compared with the CagA-negative strain.[21] Likely because of a reduced bacterial load in severe corpus atrophy, positive low CagA antibody titers may confer higher risk for noncardia gastric cancer (relative risk [RR], 3.9; 95% CI, 2.1–7.0) than high antibody titers (RR, 2.0; 95% CI, 1.3–3.2).[22] Geographic variation in noncardia gastric cancer incidence may be explained by global variability in the prevalence of CagA-positive *H pylori* strains, and by functional differences in CagA tyrosine phosphorylation sites between Eastern and Western CagA-positive *H pylori* strains.[23]

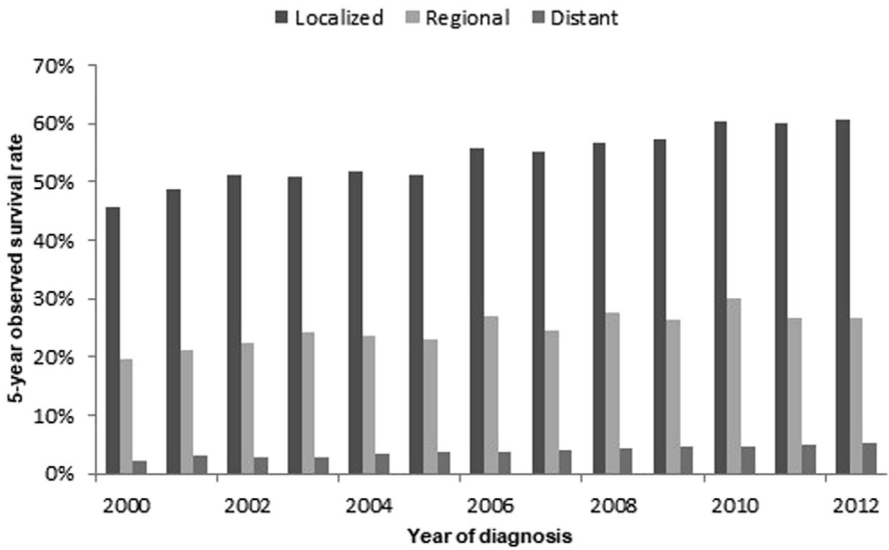

Fig. 4. Five-year survival rates for gastric cancer in the United States, 2000 to 2012, by stage at diagnosis (localized, regional, and distant stage). (*From* Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER Research Data, 18 Registries, Nov 2019 Sub (2000-2017) - Linked To County Attributes - Time Dependent (1990-2017) Income/Rurality, 1969-2018 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, released April 2020, based on the November 2019 submission.)

Studies show that the CagA EPIYA-D in East Asian strains of *H pylori* bind to the pro-oncogenic SHP2 phosphatase two-fold more strongly than the CagA EPIYA-C in Western strains.[24] However, a case-control study found that the odds of noncardia gastric cancer in CagA seropositives was higher in non-Japanese Brazilians (odds ratio [OR], 4.5; 95% CI, 2.6–7.9) than in Japanese Brazilians (OR, 2.1; 95% CI, 1.2–3.6), which may reflect geographic variations in the frequency rather than oncogenic potential of CagA-positive *H pylori* strains.[25]

Cigarette Smoking

In 2002, International Agency for Research on Cancer concluded that there was sufficient evidence for a causal relationship between smoking and gastric cancer.[26] In a meta-analysis, compared with never smoking, current smoking was associated with increased risk of cardia gastric cancer (RR, 1.87; 95% CI, 1.31–2.67; nine studies) and noncardia gastric cancer (RR, 1.60; 95% CI, 1.41–1.80; nine studies).[27] A recent pooled analysis of data from 10,290 gastric cancer cases and 26,145 control subjects in the Stomach Cancer Pooling Project (StoP) found that current smokers had 25% higher risk of gastric cancer compared with never smokers (OR, 1.25; 95% CI, 1.11–1.40).[28] Smoking conferred increased risk regardless of tumor location; however, the magnitude of association seemed stronger for cardia gastric cancer than noncardia gastric cancer. Risk increased linearly with increasing number of cigarettes per day (P for trend <0.01) and duration of smoking (P for trend <0.01). Importantly, this study found evidence that, among ever smokers, gastric cancer risk declined with increased years of smoking cessation (P for trend <0.01). Gastric cancer risk in former smokers became similar to that of never smokers after 10 years of smoking

cessation.[28] Other forms of tobacco use have been associated with an increased risk of gastric cancer, although this has not been consistent across studies.[29]

Excess Body Weight

Studies examining the association between excess body weight and gastric cancer risk have reported conflicting results. A meta-analysis of 13 cohort and three case-control studies found that obesity (body mass index [BMI] $\geq$30 kg/m^2; OR, 1.13; 95% CI, 1.03–1.24) was associated with a modest increased risk for gastric cancer.[30] When examined separately by tumor location, obesity was associated with increased risk for cardia gastric cancer (OR, 1.61; 95% CI, 1.15–2.24) but not noncardia gastric cancer (OR, 0.83; 95% CI, 0.68–1.01).[30] Notably, a meta-analysis of 10 cohort studies found that excess body weight (using the World Health Organization classification of overweight and obese) was associated with an increased risk of gastric cancer in non-Asians (BMI $\geq$25; OR, 1.24; 95% CI, 1.14–1.36), but not in Asians (OR, 1.17; 95% CI, 0.88–1.56).[31] Using the Asia-Pacific classification system of obesity (BMI $\geq$25 kg/m^2), a meta-analysis of seven Asian cohort studies found that obesity was associated with only 3% increased risk of gastric cancer (RR, 1.03; 95% CI, 1.01–1.06).[32]

Dietary Factors

There is strong evidence that diet influences risk of cancer; however, reported associations of dietary factors with gastric cancer are conflicting. These variations might reflect true differences in exposure–disease outcome associations but might also be a result of inherent challenges in the design and conduct of nutritional epidemiology studies. For example, when stratified by study design, a meta-analysis found that red meat was associated with increased risk for gastric cancer in 24 case-control studies (RR, 1.67; 95% CI, 1.36–2.05) but there was no association in four cohort studies (RR, 1.14; 95% CI, 0.97–1.34).[33] Similarly, increased white meat consumption was associated with lower risk of gastric cancer when assessed in population-based case-control studies (RR, 0.75; 95% CI, 0.61–0.93; nine studies) but not in cohort studies (RR, 0.85; 95% CI, 0.63–1.16; five studies).[34] There is, however, stronger evidence for processed meat. In a meta-analysis, high consumption of processed meat was associated with increased risk for gastric cancer whether assessed in cohort (RR, 1.21; 95% CI, 1.04–1.41; seven studies) or case-control (RR, 2.17; 95% CI, 1.51–3.11; 12 studies) studies.[34] When stratified by anatomic subtype, high processed meat consumption conferred increased risk for noncardia gastric cancer but not cardia gastric cancer. Given the association between a diet high in processed meats and increased risk of noncardia gastric cancer, attention has been placed on nitrates and nitrites, and, in particular, *N*-nitrosodimethylamine (NDMA), a type of nitrosamine produced by chemical reactions of nitrates and nitrites. NDMA occurs in dietary foods as a food additive often used in processed meats and is a potential carcinogen.[35] A meta-analysis of seven cohort and four case-control studies found that those with the highest NDMA consumption had 34% increased risk of gastric cancer compared with lowest intake (RR, 1.34; 95% CI, 1.02–1.76).[36] A nonlinear trend toward gastric cancer risk was seen with increasing NDMA intake greater than 0.12 μg/day (*P* for nonlinearity <0.001).

High salt intake has been hypothesized to promote gastric mucosal damage, hypergastrinemia, and cell proliferation, and several prospective studies have been performed to evaluate the relationship between salt intake and risk of gastric cancer.[37] A meta-analysis of seven cohort studies found that high salt intake was associated with 68% higher risk of gastric cancer compared with low intake (RR, 1.68; 95% CI, 1.17–2.41).[38] Stratified analysis was not performed for anatomic subtype of gastric

cancer in the meta-analysis; however, a large case-control study from Portugal found that high salt intake (>3960.1 mg/day) was associated with increased risk of noncardia gastric cancer (OR, 2.26; 95% CI, 1.27–4.04) compared with low intake (<3067.5 mg/day), whereas no association was found for cardia gastric cancer.[39] Although these data suggest that salt intake is a risk factor for gastric cancer, only one study in the meta-analysis adjusted for *H pylori* infection, and the positive association may be caused by confounding because those ethnicities with high prevalence of *H pylori* infection may also have diets high in salt.[38,40]

Decreasing trends in the incidence of gastric cancer has been hypothesized to be partly caused by the increased availability of fresh fruit and vegetables. A meta-analysis of six cohort studies found an inverse relationship with high white vegetable consumption versus low (RR, 0.67; 95% CI, 0.47–0.95), but no association was seen with total vegetables and gastric cancer risk (22 studies; RR, 0.98; 95% CI, 0.91–1.05) and stratified by cardia and noncardia cancer.[41] Total fruit consumption was found to be inversely associated with risk of gastric cancer in pooled analysis of 30 cohort studies (RR, 0.93; 95% CI, 0.89–0.98); however, this was not seen in pooled analyses stratified by cardia (RR, 1.08; 95% CI, 0.93–1.26; seven studies) and noncardia (RR, 0.98; 95% CI, 0.82–1.16; seven studies).[41]

Alcohol Consumption

Alcohol may affect gastric cancer cell proliferation[42] and has been examined as a risk factor for gastric cancer with inconsistent results. A meta-analysis of 23 cohort studies published through 2016 found some evidence for a modest increased risk of gastric cancer associated with ever alcohol consumption (RR, 1.17; 95% CI, 1.00–1.34; I^2 = 79.6%).[43] Among alcohol drinkers, risk increased by 7% with every 10 g/day increment in alcohol consumption (RR, 1.07; 95% CI, 1.02–1.12).[43] Likewise, a meta-analysis of 56 case-control and 17 cohort studies also reported increased risk of gastric cancer with high alcohol consumption (vs low; RR, 1.25; 95% CI, 1.15–1.37) with a curvilinear dose-response.[44] Notably, subgroup analysis for type of alcohol demonstrated increased risk of gastric cancer with high consumption of beer (RR, 1.13; 95% CI, 0.98–1.39) and liquor (RR, 1.22; 95% CI, 1.06–1.40), but not wine. When stratified by anatomic subtype, there was a significant association between high alcohol consumption and risk of noncardia gastric cancer (18 studies; RR, 1.19; 95% CI, 1.01–1.40) but not cardia gastric cancer (15 studies; RR, 1.16; 95% CI, 0.98–1.39).[44] In pooled analyses of data from StoP, heavy alcohol drinking (>6 drinks/day) conferred increased risk for cardia (OR, 1.61; 95% CI, 1.11–2.34) and noncardia (OR, 1.28; 95% CI, 1.13–1.45) gastric cancer.[45]

Medications

Nonsteroidal anti-inflammatory drugs (NSAIDs), including nonselective NSAIDs (aspirin), have been proposed as potential chemopreventive therapy for gastric cancer given increased cyclooxygenase-2 expression found in gastric cancer tissue.[46] A meta-analysis of 24 studies demonstrated that any NSAID use was associated with 22% lower risk of gastric cancer compared with never use (RR, 0.78; 95% CI, 0.72–0.85).[47] For every 2 years of incremental NSAID use, gastric cancer risk decreased by 11% (RR, 0.89; 95% CI, 0.83–0.96). Aspirin alone was also inversely related to gastric cancer risk (RR, 0.70; 95% CI, 0.62–0.89). In subgroup analysis for anatomic subtype, any NSAID use was associated with lower risk of noncardia gastric cancer (RR, 0.70; 95% CI, 0.59–0.84), with evidence for a dose–response relationship (per 2-year increments; RR, 0.83; 95% CI, 0.72–0.96; *P* for linear trend <0.01), but not associated with cardia gastric cancer.[47] However, a meta-analysis of nine randomized

controlled trials found no statistically significant association between NSAID use and gastric cancer risk (RR, 0.84; 95% CI, 0.65–1.10).[48]

Statins (HMG CoA reductase inhibitors), one of the most widely used medications for hyperlipidemia, have also been proposed as chemopreventive therapy, because studies have shown that statins have antiproliferative, proapoptotic, antiangiogenic, and immunomodulatory effects in human gastric cancer–derived cell lines.[49] A meta-analysis of six case-control studies demonstrated an inverse relationship between statin use and risk of gastric cancer (OR, 0.83; 95% CI, 0.76–0.90; I^2 = 0%).[50] Pooled analysis of three case-control studies found a dose-duration response with long statin duration use (≥2 years of daily use) having more chemopreventive effect (OR, 0.35; 95% CI, 0.16–0.76) than short statin duration use (<2 years of daily use; OR, 0.73; 95% CI, 0.51–1.05).[50] Another meta-analysis of 26 randomized controlled trials found that statin use was associated with 27% lower risk of gastric cancer (RR, 0.73; 95% CI, 0.58–0.92), which was attenuated but remained significant after excluding subjects with diabetes (RR, 0.85; 95% CI, 0.80–0.91).[51]

Genetics

Although most gastric cancers are sporadic, risk of gastric cancer is up to 10-fold higher in persons with a family history of gastric cancer.[52] Gastric cancer may also develop as part of a familial cancer syndrome, such as hereditary diffuse gastric cancer syndrome, Lynch syndrome (in particular patients with an MLH1 or MSH2 mutation),[53] familial adenomatous polyposis, Peutz-Jeghers syndrome, and Li-Fraumeni syndrome.[54]

Other

Up to 10% of gastric cancers are attributed to less common causes, including infection with Epstein-Barr virus (EBV), autoimmune gastritis, and Ménétrier disease. A recent international pooled analysis of 15 studies reported that approximately 8% of gastric cancers harbor EBV,[55] but there is insufficient epidemiologic evidence of a clear etiologic role for EBV in gastric carcinogenesis.[19]

PREVENTION

Gastric cancer maintains a high case fatality rate of 75% throughout most of the world[56] and is a main contributor to global disability-adjusted life-year burden.[57] Mass screening for gastric cancer is generally not included in national strategies for cancer prevention because of high cost; decreasing incidence; and a lack of data on whom, when, and how to screen. To date, the clinical practice of gastric cancer prevention has focused on screening and surveillance and *H pylori* screening and eradication. However, incorporating multiple risk factors into a clinical prediction rule could lead to more efficient selection for screening of patients at risk for gastric cancer. Several models have been developed[58]; however, none of these models is perfect and they require further examination in larger, external populations before clinical implementation is recommended.[59]

Primary Prevention with Helicobacter pylori Screening and Eradication

A systematic review and meta-analysis of six international randomized controlled trials found that adults who have tested positive for *H pylori* and received eradication therapy had 34% lower risk of developing incident gastric cancer compared with *H pylori*–positive control subjects who received placebo or no therapy (RR, 0.66; 95% CI, 0.46–0.95)[60]; corresponding to a number needed to treat to prevent one gastric cancer of 124 (95% CI, 78–843).[60] A phase 3 randomized controlled trial in

school-aged *H pylori*–naive children reported successful prevention of *H pylori* infection with a prophylactic oral *H pylori* vaccine (vaccine efficacy, 71.8%).[61] A large community-based intervention trial in China demonstrated that *H pylori* eradication is feasible and acceptable; however, eradication was not uniformly achieved in the population.[62]

These studies show that under conditions of low bacterial burden and acute infection, persistent *H pylori* infection can be prevented, and eradication of *H pylori* may lead to reduced incidence of gastric cancer. Additionally, under various assumptions about effectiveness and costs, population-based screening and eradication of *H pylori* has been shown to be cost-effective.[63,64] In particular, for geographic regions with high gastric cancer burden, population-based *H pylori* serology screening is cost-effective when performed in persons aged greater than 50 years. There is some evidence that population-based *H pylori* serology screening is cost-effective for populations with gastric cancer rates as low as 4.2 per 100,000.[64] Further studies are needed to establish whether screening in high-risk subpopulations residing in countries with low gastric cancer incidence, such as the United States, is cost-effective.[65]

Secondary Prevention with Screening and Surveillance

Upper gastrointestinal endoscopy studies have shown the highest detection rates among the screening modalities and are considered the gold standard for the diagnosis of gastric cancer.[66] Although the available evidence shows that endoscopic population screening is cost-effective in areas with high gastric cancer burden,[64] further studies are needed to evaluate the impact of this technique before recommending its broad use as a primary screening test.[67] Upper gastrointestinal series has continuously been analyzed as a rivaling modality for cancer detection but has not shown clear benefits over endoscopy.[68]

Several countries have implemented national screening programs. For example, in South Korea, the Korean Gastric Cancer Association and National Cancer Center established national guidelines for gastric cancer screening in 2001. These guidelines recommend biennial gastric cancer screening via upper endoscopy or upper gastrointestinal series for men and women aged greater than or equal to 40 years, which started in 2002.[69] In 2013, the Japanese government approved insurance coverage for a gastric cancer prevention program that includes *H pylori* screening and treatment (primary prevention) and post–*H pylori* treatment surveillance (secondary prevention for people with atrophic gastritis).[70] In the United States, there are no population-based mass screening programs aimed at reducing the incidence of gastric cancer.

FUTURE DIRECTIONS

Biomarkers for screening and risk triaging and clinical prediction rules that combine these biomarkers with established clinical and lifestyle factors for risk stratification need to be derived, optimized, and then validated in external populations. Future biomarker studies should aim to state the *a priori* plan for building statistical models; consider interactions, transformations, and splines; refrain from categorizing predictors; use and report model coefficients; aim for external validation; use informed and *a priori* stated criteria for desired sensitivity and specificity; and assess model performance by incorporating population disease risk. Finally, at the public health level and clinically, risk communication should be a central feature of research and implementation.

SUMMARY

Further improvements in screening, treatment, and early diagnosis are needed for gastric cancer, which remains the third most common cause of cancer-related mortality worldwide. Although mass screening strategies could be beneficial, current modalities are not yet readily implementable in organized screening settings. Conversely, because the population risk (based on histology) can change rapidly, and *H pylori* eradication is effective, population-based programs of screening and treatment of *H pylori* may hold greatest promise for reducing the burden of gastric cancer.[61]

CLINICS CARE POINTS

- Although rates of noncardia gastric cancer in the United States continue to decrease among adults aged ≥50 years, the incidence of noncardia gastric cancer among persons aged less than 50 years is increasing, particularly among Hispanics, non-Hispanic Blacks, and Asian and Pacific Islanders.
- Chronic infection with *H pylori* is the main cause of gastric cancer, accounting for approximately 89% of distal gastric cancer cases worldwide, and data demonstrate that eradicating *H pylori* reduces the incidence of gastric cancer.
- Although studies show that endoscopic population screening is cost-effective in areas with high gastric cancer burden, further studies are needed before recommending the broad use of upper endoscopy as a primary screening test in the United States and other low-incidence countries.

DISCLOSURE

The authors have nothing to disclose.

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