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Review article

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Global burden of gastric cancer: epidemiological trends, risk factors, screening and prevention

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Abstract

Gastric cancer remains a major cause of cancer-related mortality worldwide. The temporal trends for this malignancy, however, are dynamic, and reports from the past decade indicate important declines in some regions and demographic groups, as well as a few notable exceptions in which gastric cancer rates are either stable or increasing. Two main anatomical subtypes of gastric cancer exist, non-cardia and cardia, with different temporal trends and risk factors (such as obesity and reflux for cardia gastric cancer and *Helicobacter pylori* infection for non-cardia gastric cancer). Shifts in the distribution of anatomical locations have been detected in several high-incidence regions. *H. pylori* is an important aetiological factor for gastric cancer; importantly, the anticipated long-term findings from studies examining the effect of *H. pylori* eradication on the risk of (re)developing gastric cancer have emerged in the past few years. In this Review, we highlight the latest trends in incidence and mortality using an evidence-based approach. We make the best possible inferences, including clinical and public health inference, on the basis of the quality of the evidence available, and highlight burning questions as well as gaps in knowledge and public health practice that need to be addressed to reduce gastric cancer burden worldwide.

Sections

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Key points

- Globally, gastric cancer remains the fifth most common malignant cancer and the fourth leading cause of cancer-related mortality. Despite declining incidence rates, the global burden of this malignancy is expected to have a 62% increase by 2040.
- Overall, gastric cancer incidence rates have been decreasing over the past 5 decades in the USA, although the incidence of non-cardia gastric cancer among adults aged <50 years and that of advanced-stage gastric cancer in Hispanic individuals are both increasing.
- Worldwide, *Helicobacter pylori* infection accounts for almost 90% of distal gastric cancers; other well-established risk factors include excess body fat, cigarette smoking and diets high in salt and processed meats.
- Other possible risk factors for gastric cancer include Epstein–Barr virus infection, autoimmune gastritis and Ménétrier disease, and possible protective factors include high vegetable intake and treatment with nonsteroidal anti-inflammatory drugs and statins.
- A small proportion of all gastric cancers are diagnosed in patients not infected with *H. pylori*; other components of the gastric microbiome might have a role in the development of these cancers.
- Population-based screening and surveillance programmes and *H. pylori* eradication hold promise for reducing gastric cancer-related mortality.
- The knowledge on risk factors needs to be translated into actionable diagnostic algorithms for public health and clinical use.

Introduction

Worldwide, gastric cancer remains one of the most common malignancies and a leading cause of mortality[1]. Gastric cancer comprises two main anatomical subtypes, cardia gastric cancer and non-cardia gastric cancer, which have distinct epidemiological and risk-factor profiles. Furthermore, gastric cancer can be classified into two histological subtypes: intestinal type (which features a glandular growth pattern and includes adenocarcinomas) and diffuse type (which is characterized by poorly cohesive cells with no glandular growth pattern and includes signet ring cell carcinomas and linitis plastica)[2]. Diffuse-type gastric cancer is probably caused by mutations in genes that affect pathways related to cell–extracellular matrix interactions, whereas the intestinal type typically originates from chronic inflammatory mucosal damage (such as that caused by *Helicobacter pylori* infection)[3,4]. Intestinal gastric cancer is the most frequent type among populations with the highest overall gastric cancer rates globally. In the USA, approximately 70% of gastric cancers are of the intestinal type. A prolonged precancerous process with well-defined, consecutive stages (known as the Correa cascade) precedes the development of intestinal-type gastric adenocarcinomas[5]. *H. pylori* infection causes chronic active gastritis and, when this infection remains for decades, it can lead to chronic atrophic gastritis. This atrophy subsequently predisposes to the cascade of intestinal metaplasia, incomplete intestinal metaplasia, dysplasia and, finally, invasive adenocarcinoma.

In this Review, we use an evidence-based approach that considers study design, consistency of findings across studies and generalizability across populations at risk to summarize the global burden and distribution of gastric cancer, detailing the primary risk factors for gastric cancer. We then describe opportunities and challenges associated with primary and secondary prevention efforts for gastric cancer.

Global burden of gastric cancer

On the basis of the latest estimates released by GLOBOCAN, in 2020 the annual number of gastric cancers globally reached 1,089,000 (corresponding to an age-standardized incidence rate of 11.1 per 100,000), ranking fifth among all malignant tumours. In the same year, 769,000 deaths were caused by gastric cancer (corresponding to an age-standardized mortality rate of 7.7 per 100,000), ranking fourth among all cancer types behind lung, colorectal and liver cancers[1,6]. Despite an overall decline in incidence rates globally, the secular trends in incidence and mortality rates for gastric cancer vary between countries[7,8]. The authors of a study with results published in 2022 estimated that, globally, the number of new cases will rise by 62% to 1.77 million by 2040 (ref. 9). The incidence of gastric cancer is higher in countries with a high or very high Human Development Index (HDI); however, gastric cancer-related mortality is lower in these countries than in those with a medium or low HDI, in which this cancer type is among the top causes of cancer-related mortality[9]. The incidence rates of gastric cancer correlate with the prevalence of *H. pylori* infection. Furthermore, regions in eastern and southeastern Asia have both a high HDI and a high prevalence of the highly virulent strains of *H. pylori*[9,10]. Consequently, almost two-thirds of gastric cancers diagnosed in 2020 (n = 696,112) were diagnosed in eastern and southeastern Asia[1,11] (Fig. 1). In 2020, eastern Asia (22.4 per 100,000), central and eastern Europe (11.3 per 100,000) and South America (8.7 per 100,000) had the highest incidence rates of gastric cancer, whereas North America (4.2 per 100,000) and Africa (3–4 per 100,000) had the lowest incidence rates of gastric cancer globally[1,11]. Since the mid-twentieth century, gastric cancer incidence and mortality rates have declined linearly in most countries with a high or very high HDI, albeit with notable differences in the initiation and rate of decline. For example, in countries with the highest gastric cancer burden, such as Japan and South Korea, the downward trend started in the 1990s[8,12]. Consistent with global incidence rates, eastern Asia (14.6 per 100,000) and central and eastern Europe (8.3 per 100,000) have the highest gastric cancer mortality rates, whereas North America (1.8 per 100,000) has the lowest[1,11] (Fig. 2).

In the USA, the overall gastric cancer incidence rate has declined linearly in past decades[12–14], and the epidemiology of gastric cancer has changed[15]. To represent current trends in gastric cancer incidence in the USA, we extracted data from the eight registries of the Surveillance, Epidemiology, and End Results (SEER) Program, the population cancer registry programme overseen by the US National Cancer Institute (NCI)[16]. The eight SEER areas (SEER 8) cover ~10% of the US population. Incidence rates of gastric cancer dropped from 11.6 per 100,000 in 1975 to 6.1 per 100,000 in 2019 (Fig. 3). Based on joinpoint regression, a common tool used to analyse trends in epidemiology, gastric cancer incidence rates decreased by 1.46% per year between 1975 and 2019. Rates decreased among both men and women (with average annual percentage change (AAPC) of −1.69% and −1.28%, respectively) in the USA during that period. In the USA, gastric cancer rates are highest among older age groups and, historically, gastric cancer incidence is the lowest in individuals <50 years of age[15]. In contrast to the continued decline in the incidence of non-cardia gastric cancer in adults aged ≥50 years

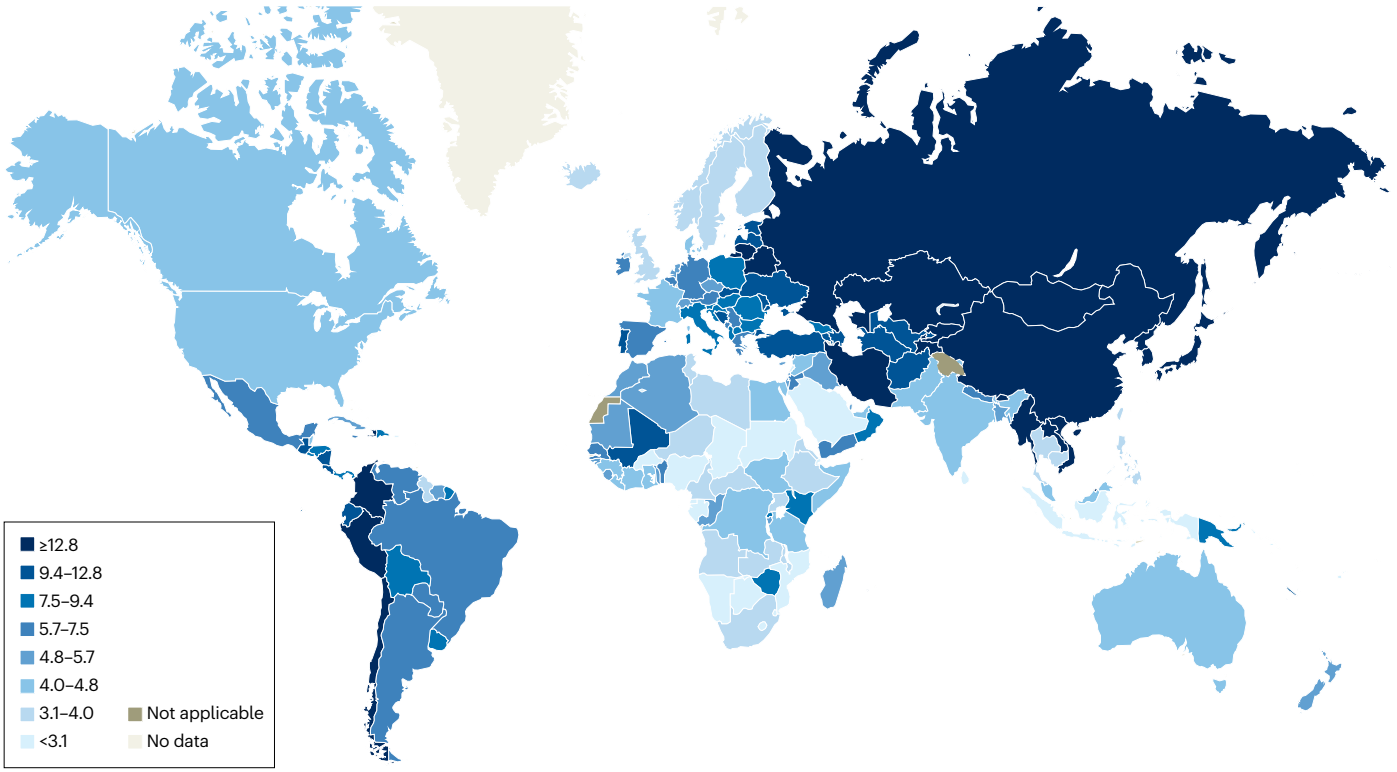

Fig. 1 | Worldwide gastric cancer incidence in 2020. The shading indicates estimated age-standardized incidence rates per 100,000 persons based on data from GLOBOCAN 2020 (ref. 1), https://go.nature.com/3JoIkd5 (accessed 26 July 2022; ©International Agency for Research on Cancer, 2020).

in the USA, non-cardia gastric cancer rates are increasing in those <50 years of age[13,15,17]. Gastric cancer burden and secular trends also vary by ethnicity in the USA, with twofold higher incidence rates observed for minority populations (such as Hispanic, non-Hispanic Black, and Asian and Pacific Islander individuals) versus non-Hispanic white individuals[12]. We and others have also reported differences in the long-term trends in incidence rate for stage-specific early-onset (<50 years) gastric cancer between non-Hispanic white and Hispanic individuals[12,15,17]. From 2001 to 2014, the incidence rates of distant-stage non-cardia gastric cancer remained unchanged in non-Hispanic white individuals <50 years of age (AAPC 0.68%, 95% CI −0.63% to −2.00%) but increased significantly among Hispanic individuals in the same age group (AAPC 1.78%, 95% CI 0.66%–2.91%). The incidence of localized-stage non-cardia gastric cancer in individuals aged <50 years increased in both ethnic groups (AAPC 5.28%, 95% CI 3.94%–6.64%, and AAPC 2.90%, 95% CI 1.21%–4.62%, in non-Hispanic and Hispanic individuals, respectively), whereas that of regional-stage non-cardia gastric cancer decreased (AAPC −2.22%, 95% CI −3.28% to −1.57%, and AAPC −2.73%, 95% CI −3.98% to −1.47%)[17].

According to data from patients with gastric cancer identified among all cancer records in 17 SEER areas (SEER 17)[18], covering ~28% of the US population, between 2000 and 2018, the median relative survival of patients with gastric cancer increased from 8.8 months to 16.2 months. Patients diagnosed with localized gastric cancer had the greatest absolute improvement in median relative survival during this period: whereas <40% of those diagnosed in 2000 survived 5 years after diagnosis, this rate was 55.8% for patients diagnosed in 2014 (Fig. 4). Nonetheless, approximately 40% of all patients diagnosed with gastric cancer each year in the USA are diagnosed at an advanced stage (such as distant stage) and their outcomes did not improve substantially (5-year survival rate of 2.7% versus 4.7% for patients diagnosed in 2000 and 2014, respectively).

Main risk factors for gastric cancer

Infection with *H. pylori*

In 1994, the International Agency for Research on Cancer (IARC) classified *H. pylori* as a carcinogen (that is, as a group 1 agent) for non-cardia gastric cancer on the basis of epidemiological evidence[19]. IARC reconfirmed this classification in 2009 (ref. 20). Chronic infection with *H. pylori* is the main cause of non-cardia and intestinal-type gastric cancers. According to immunoblot-based data, which have a reported sensitivity of 95.6% and specificity of 92.6%, almost 90% of distal gastric cancers globally are caused by *H. pylori* infection[21–25]. Most individuals infected with *H. pylori* are exposed during childhood and, once established, *H. pylori* infection persists for life unless treated. The population prevalence of *H. pylori* infection varies worldwide, with the highest prevalence in Central and South America (~60%) and in parts of Asia (for example, ~55% in China and South Korea) and eastern Europe (~50%)[26]. In general, the worldwide population prevalence of *H. pylori* infection correlates with the incidence rates of gastric cancer[27,28].

The prevalence of *H. pylori* infection also varies depending on the method used to test for the infection[26]. Histological examination of non-malignant gastric samples is associated with false-negative results derived from sampling errors and reduced bacterial load in individuals

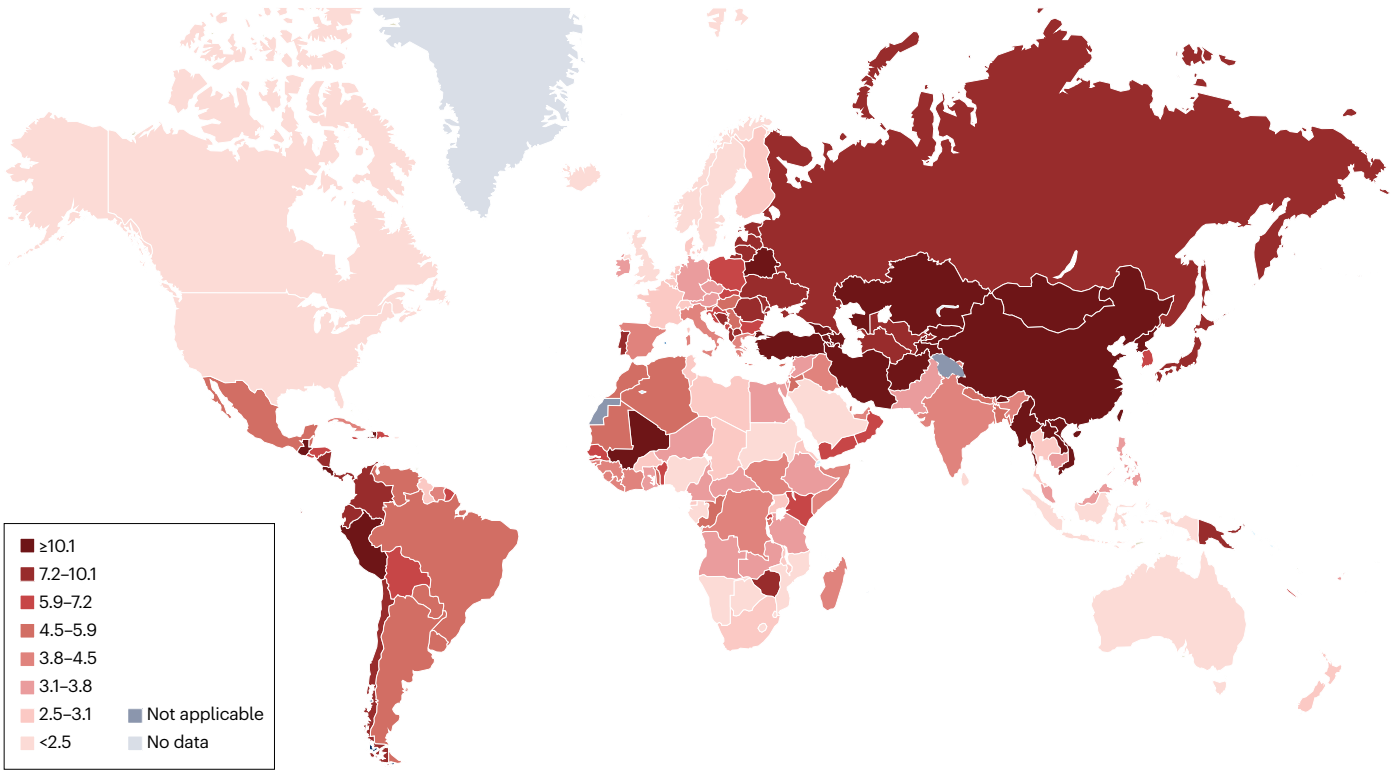

Fig. 2 | Worldwide gastric cancer mortality in 2020. The shading indicates estimated age-standardized mortality rates per 100,000 persons based on data from GLOBOCAN 2020 (ref. 1), https://go.nature.com/3YUjJCE (accessed 26 July 2022; ©International Agency for Research on Cancer, 2020).

with atrophic gastritis. Compared with histological examination, serological testing for antibodies has lower sensitivity for identifying active infection but greater sensitivity for the detection of lifetime infection[29–31]. The strength of association with gastric cancer varies between one- and tenfold across studies depending on the method of *H. pylori* testing in individuals with and without infection[21,32–34]. In one report that pooled individual level data from eight international studies, the odds ratio (OR) for the association with non-cardia gastric cancer increased from 1.45 (95% CI 0.87–2.42) using histological examination to 4.79 (95% CI 2.39–9.60) when serological testing was used to reclassify individuals with *H. pylori*-negative results[35].

Although *H. pylori* infection is the main cause of gastric cancer, only an estimated 17% of individuals with this infection develop gastric cancer[36]. One explanation is that oxyntic atrophy of the gastric fundus or body is necessary for the development of gastric cancer. Indeed, oxyntic atrophic gastritis reduces gastric acid secretion, which seems to enable *H. pylori* infection to propagate gastric carcinogenesis[37,38]. In addition, the various *H. pylori* strains and antigens have different carcinogenic potential. *cagA*$^+$ *H. pylori* has been observed to have a stronger effect on risk of non-cardia gastric cancer relative to *cagA*$^-$ *H. pylori*. Furthermore, low titres of anti-CagA antibodies confer a higher risk of non-cardia gastric cancer (relative risk (RR) 3.9, 95% CI 2.1–7.0) than high titres of these antibodies (RR 2.0, 95% CI 1.3–3.2), probably reflecting a reduced bacterial load of *H. pylori* in the setting of severe corpus atrophy[39]. Additionally, tyrosine phosphorylation sites in CagA with key roles in host cell transformation differ between eastern and western *cagA*$^+$ *H. pylori* strains, which might explain geographical variations in the incidence of non-cardia gastric cancer[40]. East Asian strains of *cagA*$^+$ *H. pylori* contain the EPIYA motif variant D (EPIYA-D), which binds to the pro-oncogenic SHP2 phosphatase with an affinity twice that of the EPIYA-C motif, present in western strains[41]. CagA seropositivity confers a higher risk of non-cardia gastric cancer in non-Japanese Brazilians (OR 4.5, 95% CI 2.6–7.9) relative to Japanese Brazilians (OR 2.1, 95% CI 1.2–3.6). However, this effect might be caused by geographical variations in the titre of anti-CagA antibodies instead of in tyrosine phosphorylation motifs[42]. Weaker but significant associations with risk of non-cardia gastric cancer have been reported for other *H. pylori* antigens, including HyuA (OR 1.42, 95% CI 1.13–1.79), HP0305 (OR 1.72, 95% CI 1.32–2.25), Omp (OR 1.83, 95% CI 1.30–2.58) and VacA (OR 2.05, 95% CI 1.67–2.52)[43]. Additionally, the *H. pylori babA2* gene has been associated with a two- to threefold increase in the risk of non-cardia gastric cancer in case–control studies conducted in Asian populations[44]. Evidence also supports the fact that host genetic factors, including polymorphisms in genes encoding certain cytokines (such as IL-1β), are associated with increased risk of *H. pylori*-related gastric cancer[45] (Table 1).

Age and sex

Similar to other cancer types, the incidence of gastric cancer increases with advancing age. Furthermore, gastric cancer incidence rates are two- to threefold higher in men than in women[1,9]. Globally, in 2020 gastric cancer was the fourth most common cancer in men (with an incidence rate of 15.8 per 100,000) and the seventh most common cancer in women (incidence rate 7.0 per 100,000)[1,9]. In older men

(≥65 years of age) intestinal-type gastric cancer is more common than the diffuse type, whereas patients with diffuse-type gastric cancer are more likely to be younger (<70 years of age, 50.9% versus 33.7% for intestinal-type gastric cancer) and/or female (46.6% versus 35.4% for intestinal-type gastric cancer)[46,47]. In SEER data from 1992–2004, both cardia and non-cardia gastric cancer were more common in men than in women. The male-to-female ratio was much higher among patients with cardia gastric cancer (male-to-female incidence rate ratio 4.2, 95% CI 4.1–4.4) relative to non-cardia gastric cancer (male-to-female incidence rate ratio 1.6, 95% CI 1.6–1.6)[48]. Men aged 75–84 years (23.7 per 100,000 person-years) and men aged ≥85 years (54.2 per 100,000 person-years) had the highest incidence rate of cardia and non-cardia gastric cancer, respectively[48].

Cigarette smoking

According to the 2002 report from the IARC, sufficient evidence now supports the fact that tobacco smoking causes gastric cancer[49–51]. In a meta-analysis involving data from 32 published studies (27 cohort and five nested case–control) published up until 2007, current smokers had an increased risk of both cardia (RR 1.87, 95% CI 1.31–2.67; nine studies) and non-cardia (RR 1.60, 95% CI 1.41–1.80; nine studies) gastric cancer relative to never smokers[52]. Current smokers (OR relative to never smokers 1.25, 95% CI 1.11–1.40) also had a higher risk than former smokers (OR relative to never smokers 1.12, 95% CI 0.99–1.27). This risk increases in correlation with the number of cigarettes smoked per day (OR 1.32 for >20 cigarettes per day) as well as with duration of regular smoking (OR 1.33 for >40 years of use)[53]. Any history of smoking, whether a former smoker or current smoker, was associated with a higher risk of intestinal-type (RR 2.0 and 2.1, respectively), but not diffuse-type gastric cancer[54]. Importantly, smoking cessation can reduce the future risk of gastric cancer. In a study from the Stomach Cancer Pooling (StoP) Project, a consortium of case–control studies of gastric cancer established in 2012 that aimed to examine the role of lifestyle, environmental and genetic determinants in gastric cancer[55], examinations only of individuals who have ever smoked revealed that the risk of gastric cancer decreases with increasing years of smoking cessation (P for trend < 0.01) such that the risk of gastric cancer is not different from that of never smokers in former smokers >10 years after smoking cessation[53]. A sex difference might exist in the association between current smoking and risk of gastric cancer (RR for men relative to women 1.30, 95% CI 1.05–1.63)[56]. Although data for other forms of tobacco use, including opium and hookah, are limited and mixed, they might also indicate an association with a higher risk of gastric cancer[57].

Obesity and metabolic dysfunction

Results from studies examining the relationship between excess body weight and risk of gastric cancer are conflicting. In a meta-analysis of 24 prospective studies published through 2012, overweight (BMI 25 to <30 kg/m^2) and obesity (BMI ≥30 kg/m^2) were not associated with gastric cancer[58]. In the same meta-analysis, however, stratification by tumour site revealed an association between obesity and increased risk of cardia gastric cancer (RR 1.21, 95% CI 1.08–1.36, and RR 1.82, 95% CI 1.32–2.49, for overweight and obesity, respectively) but not with non-cardia gastric cancer risk (RR 0.93, 95% CI 0.82–1.05, and RR 1.00, 95% CI 0.87–1.15, respectively)[58]. This relationship is affected by ethnicity. In a meta-analysis involving data from ten cohort studies, excess body weight (BMI ≥ 25 according to the WHO classification for overweight and obesity) was associated with an increased risk of gastric cancer in non-Asian individuals (OR 1.24, 95% CI 1.14–1.36) but not in Asian individuals (OR 1.17, 95% CI 0.88–1.56)[59]. The Asia–Pacific classification system defines obesity as BMI ≥ 25 kg/m^2, which might explain these divergent findings. In a meta-analysis of seven Asian cohort studies using the Asia–Pacific classification system, obesity was significantly associated with the risk of gastric cancer but the effect size was nonetheless marginal (RR 1.03, 95% CI 1.01–1.06)[60]. In a study from the Asia Cohort Consortium (involving 8,997 patients with gastric cancer) that examined gastric cancer by histological subtype, underweight and obesity were associated with a higher risk of intestinal-type (HR 1.14, 95% CI 1.01–1.28, and HR 1.11, 95% CI 0.98–1.25, for underweight and obesity, respectively) but not diffuse-type (HR 0.99, 95% CI 0.63–1.55, and HR 1.27, 95% CI 0.85–1.89, for underweight and obesity, respectively) intestinal gastric cancer[61].

Associations of other features of metabolic dysfunction with gastric cancer is less consistent than that of BMI. For example, in a systematic review of data from five studies, serum levels of glycosylated haemoglobin (HbA1c; a diabetes marker) were associated with a marginally increased risk of gastric cancer (HR 1.36, 95% CI 1.06–1.74), but serum glucose levels were not (HR 1.11, 95% CI 0.98–1.26)[62]. In another pooled analysis of data from the SToP consortium, no association was found between a diagnosis of diabetes and risk of gastric cancer (OR 1.01, 95% CI 0.94–1.07)[63]. However, the authors reported an association with higher risk of cardia gastric cancer in individuals with type 2 diabetes (OR 1.16, 95% CI 1.02–1.33)[63].

Dietary factors

Published data regarding diet and gastric cancer risk are conflicting, probably owing to the longstanding challenges identified in the design and execution of nutritional epidemiological studies[64]. For example,

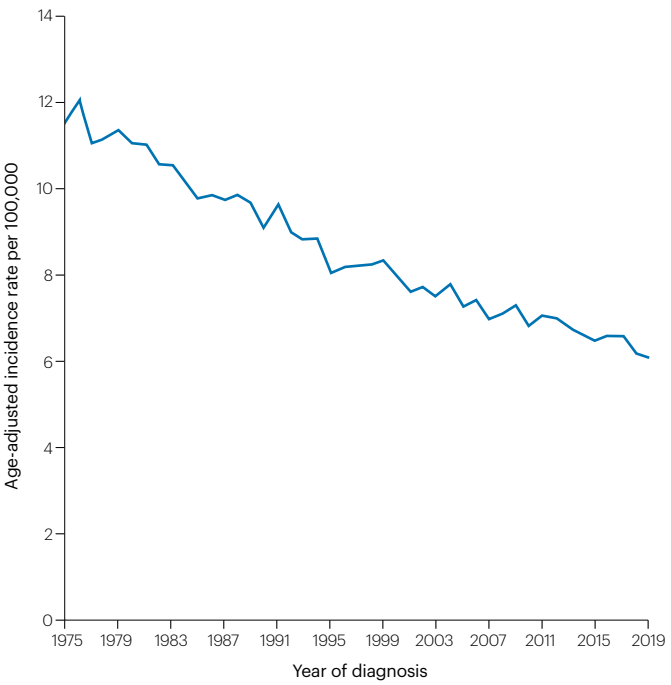

Fig. 3 | Gastric cancer incidence in the USA 1975–2019. The chart provides age-adjusted incidence rates obtained from the Surveillance, Epidemiology, and End Results (SEER) Program[16]. In total, we identified 76,861 invasive gastric cancers (defined using the third edition of the *International Classification of Diseases for Oncology*[154] site codes C160–C169 and ICD-O-3 histology type, excluding 9050–9055, 9140 and 9590–9992) diagnosed from 1975 to 2019 in SEER 8.

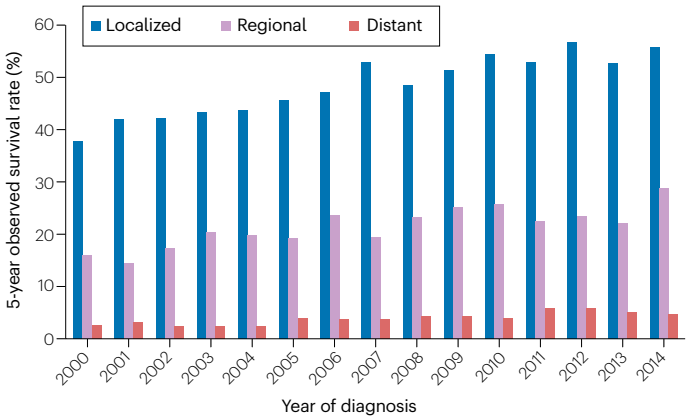

Fig. 4 | Gastric cancer survival in the USA 2000–2014. The chart provides 5-year survival rates by stage at diagnosis (localized, regional and distant stage), based on data from the Surveillance, Epidemiology, and End Results (SEER) Program[18]. For additional details, see legend of Fig. 3.

the authors of a meta-analysis published in 2017 found that higher consumption of red meat conferred a high risk of gastric cancer in 24 case–control studies (RR 1.67, 95% CI 1.36–2.05)[64], but did not find such an association in four cohort studies (RR 1.14, 95% CI 0.97–1.34)[64]. Analysis of white meat consumption provides similar findings: in a meta-analysis of data from nine case–control studies, the risk of gastric cancer was lower with consumption of white meat (RR 0.75, 95% CI 0.61–0.93) but such an association was not found in a meta-analysis of five cohort studies (RR 0.85, 95% CI 0.63–1.16)[65]. Evidence from studies of the association of processed meat with risk of gastric cancer, however, is more robust. Such an association has been described in both case–control studies (RR 2.17, 95% CI 1.51–3.11; 12 studies) and cohort studies (RR 1.21, 95% CI 1.04–1.41; seven studies)[65]. Nonetheless, this increased risk was seen only for non-cardia gastric cancer and not for cardia gastric cancer. In a case–control study from the USA that stratified gastric cancer by histological subtype, increased red meat and processed meat consumption did not confer a difference in the risk of intestinal-type (OR 1.2, 95% CI 0.9–1.7, and OR 1.4, 95% CI 0.9–2.0, for red and processed meat, respectively) or diffuse-type gastric cancer (OR 1.2, 95% CI 0.8–1.6, and OR 1.3, 95% CI 0.8–2.1, for red and processed meat, respectively)[66].

Investigators have proposed that nitrates and nitrites — particularly *N*-nitrosodimethylamine (NDMA), which is a type of nitrosamine produced by chemical reactions of nitrates and nitrites and is a food additive often used for processed meats — might be a risk factor for gastric cancer[67]. In a meta-analysis of data from 11 studies, the risk of gastric cancer was higher in individuals with the highest NDMA consumption relative to those with the lowest intake (RR 1.34, 95% CI 1.02–1.76; seven cohort and four case–control studies)[68]. Furthermore, an increase in NDMA intake ≥0.12 μg/day was associated with a higher risk of gastric cancer (*P* for non-linearity < 0.001).

A high-salt diet can lead to an excessive intake of sodium chloride. In animal studies, a diet with a high sodium chloride content can lead to hypergastrinaemia, initial gastric tissue damage and cancer cell proliferation[69]. In a meta-analysis of data from seven cohort studies, a high-salt diet was associated with a higher risk of gastric cancer relative to a low-salt diet (RR 1.68, 95% CI 1.17–2.41)[70]. In a separate large case–control study from Portugal, a high-salt diet (>3,960.1 mg/day) was associated with an increased risk of non-cardia gastric cancer (OR 2.26, 95% CI 1.27–4.04) but not of cardia gastric cancer (OR 1.50, 95% CI 0.50–4.52)[71]. Only one study in the aforementioned meta-analysis[70] adjusted for *H. pylori* infection, demonstrating that the positive association might be caused by confounding. In particular, researchers found that ethnic groups that tend to have a higher prevalence of *H. pylori* infection also tend to consume high-salt diets[70,72]. A meta-analysis of data from 25 case–control studies in the SToP consortium found a higher risk of gastric cancer among individuals with a salty taste preference than among individuals with a preference for tasteless (OR 1.59, 95% CI 1.16–1.54 for salty versus tasteless) and those in the highest tertile of intake of a high-salt diet and salt-preserved foods (OR 1.24, 95% CI 1.01–1.51). This association was detected and consistent across strata of individuals with and without *H. pylori* infection[73]. The results of preclinical studies suggest that salt and *H. pylori* infection might synergistically activate signalling pathways that result in the upregulation of inducible nitric oxide synthase, prostaglandin G/H synthase 2 (also known as cyclooxygenase 2) and IL-2, which can promote gastric carcinogenesis[74,75].

A report by the World Cancer Research Fund–American Institute for Cancer Research on dietary factors and cancer prevention stated that the consumption of non-starchy vegetables probably protects against gastric cancer[76]. Therefore, the current high availability of fresh fruit and vegetables has been hypothesized to contribute to decreasing trends in the incidence of gastric cancer. A meta-analysis found that high consumption of white vegetables (such as potatoes, cauliflowers, turnips, onions, parsnips, mushrooms, white corn and kohlrabi) confers a decreased risk of gastric cancer (RR 0.67, 95% CI 0.47–0.95; six cohort studies); however, no association was found between gastric cancer risk and high consumption of all vegetables (RR 0.98, 95% CI 0.91–1.05; 22 studies)[77]. In addition, no association between vegetables and gastric cancer risk was found when data were stratified into cardia (RR 0.88, 95% CI 0.76–1.01) and non-cardia (RR 0.92, 95% CI 0.77–1.09) gastric cancer[77]. In a pooled analysis of data from 30 cohort studies, consumption of fruit had a protective effect against gastric cancer (RR per 100 g/day 0.95, 95% CI 0.92–0.99); however, stratification by anatomical location of gastric cancer revealed no association between fruit consumption and cardia gastric cancer (RR 1.08, 95% CI 0.93–1.26; seven studies) as well as non-cardia gastric cancer (RR 0.98, 95% CI 0.82–1.16; seven studies)[77]. In a prospective cohort study from the Japan Public Health Center (involving 404 patients with gastric cancer), those in the highest quintile of vegetable consumption had lower risk of intestinal-type gastric cancer relative to those in the lowest quintile (RR 0.54, 95% CI 0.31–0.96), and gastric cancer risk decreased with increasing vegetable consumption (*P* for trend 0.03)[78]. No association between vegetable consumption and diffuse-type gastric cancer was found[78]. In a case–control study from the USA (91 and 132 individuals with and without cancer, respectively), increased fruit consumption was associated with a decreased risk of both intestinal-type (OR 0.5, 95% CI 0.3–0.9) and diffuse-type (OR 0.5, 95% CI 0.2–0.99) gastric cancer[66].

Socioeconomic disparities have a role in the incidence of gastric cancer, and a strong inverse relationship exists between high education level and risk (OR 0.60, 95% CI 0.44–0.84), for both non-cardia and cardia gastric cancer[79]. The StoP Project attempted to establish whether dietary and lifestyle factors mediate the association between education and gastric cancer. In a meta-analysis of data from ten case–control studies, these researchers defined a lifestyle score (based on smoking, alcohol consumption, fruit and vegetable intake, processed meat intake and salt consumption), which explained about 10.1% (95% CI 7.1%–15.4%)

of the association between high versus low levels of education and risk of gastric cancer[80]. This mediation effect was limited to men only.

Other dietary factors have been associated with gastric cancer risk. In a meta-analysis of data from 14 case–control studies, the risk of gastric cancer was greater in subgroups with the highest cholesterol intake relative to those with the lowest intake (OR 1.35, 95% CI 1.29–1.62)[81]. In a meta-analysis of data from ten cohort studies and 29 case–control studies, a nonsignificant association was observed between high consumption of dairy products and risk of gastric cancer (RR 1.06, 95% CI 0.95–1.18)[82]. In a meta-analysis of data from 22 case–control studies, a weak inverse association was found between risk of gastric cancer and regular tea consumption relative to no consumption (OR 0.91, 95% CI 0.85–0.97), which was more robust for cardia gastric cancer only (OR 0.64, 95% CI 0.49–0.84)[83]. This association was stronger in China and Japan, where green tea is consumed regularly (OR 0.67, 95% CI 0.49–0.91) and in individuals with *H. pylori* infection (OR 0.68, 95% CI 0.58–0.80)[83]. Increased carbohydrate intake is associated with an increased risk of intestinal-type gastric cancer (second tertile relative to first tertile: OR 6.89, 95% CI 1.28–22.94), but with a decreased risk of diffuse-type gastric cancer (third tertile relative to first tertile: OR 0.17, 95% CI 0.04–0.66)[84]. Finally, high intake of chili peppers (or capsaicin) has been associated with an increased risk of gastric cancer (OR 1.51, 95% CI 1.02–2.00)[85].

Alcohol use

Acetaldehyde, the by-product of alcohol, has been classified by the IARC as a group 1 agent[86]. In preclinical and clinical studies, alcohol consumption has been linked to the risk of gastric cancer through increased generation of reactive oxygen species, which contribute to the activation of carcinogens, as well as promotion of folate deficiencies, which results in aberrant DNA methylation and leads to gastric cancer[87,88]. In a meta-analysis of data from 81 epidemiological studies (68 case–control and 13 cohort studies), the risk of gastric cancer was higher in individuals with any alcohol consumption relative to those with no consumption (OR 1.20, 95% CI 1.12–1.27)[89]. A dose-dependent response was also seen, with no risk among those consuming 10 g/day of alcohol, a slight risk at 50 g/day (OR 1.14, 95% CI 1.06–1.21) and the highest risk at 100 g/day (OR 1.32, 95% CI 1.18–1.48)[89]. Furthermore, a meta-analysis that included studies published before 2017 showed an association between high consumption (defined as ≥3 drinks/day) of beer (RR 1.13, 95% CI 0.98–1.39; 17 case–control and seven cohort studies) and liquor (spirits) (RR 1.22, 95% CI 1.06–1.40; 20 case–control and eight cohort studies) but not wine[90]. In analyses that examined gastric cancer outcomes according to anatomical subtype, high alcohol consumption was statistically significantly associated with the risk of non-cardia gastric cancer (RR 1.19, 95% CI 1.01–1.40; 18 studies) but not with the risk of cardia gastric cancer (RR 1.16, 95% CI 0.98–1.39; 15 studies) although these risk estimates were very close to each other[90]. Analyses of pooled data from the StoP Project revealed that consuming large amounts of alcohol (defined as >6 drinks/day) is associated with a higher risk of both cardia (OR 1.61, 95% CI 1.11–2.34) and non-cardia (OR 1.28, 95% CI 1.13–1.45) gastric cancer[91]. When examined separately, one study found no association between alcohol use and the risks of intestinal-type or diffuse-type gastric cancer[54].

Medications

Nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin, have been hypothesized to reduce the risk of gastric cancer owing to the inhibition of the activity of cyclooxygenase 2 (ref. 92), which is overexpressed in gastric carcinogenesis[93]. In one meta-analysis, the risk of gastric cancer was lower in individuals who used any NSAID relative to those who never used NSAIDs (RR 0.78, 95% CI 0.72–0.85; 24 observational studies)[94]. Furthermore, the risk of gastric cancer decreased by 11% for every 2 additional years of NSAID use (RR 0.89, 95% CI 0.83–0.96). Use of aspirin only and no other NSAIDs was also associated with a decreased risk of gastric cancer (RR 0.70, 95% CI 0.62–0.89). When stratified by anatomical subtype of gastric cancer, the use of any type of NSAID was associated with a 30% lower risk of non-cardia gastric cancer (RR 0.70, 95% CI 0.59–0.84). Furthermore, evidence supported a dose–response relationship between NSAID use and risk of non-cardia gastric cancer (in 2-year increments of NSAID use; RR 0.83, 95% CI 0.72–0.96; *P* for linear trend < 0.01). No association was

Table 1 | Direction and strength of association between various risk factors and gastric cancer

Risk factor	Association with non-cardia gastric cancer	Association with cardia gastric cancer	Association with gastric cancer with *H. pylori*	Association with gastric cancer without *H. pylori*
H. pylori infection	RR 4.79	RR 1.98 (in China, South Korea and Japan)		
Cigarette smoking	RR 1.60	RR 1.87	HR 11.41	NS
BMI ≥ 30 kg/m^2	NS	RR 1.82	Unknown	Unknown
Dietary factors				
Salt	OR 2.26	NS	OR 14.2	NS
Processed meats	RR 1.34	NS	OR 2.00	NS
Red meat	NS	NS	NS	NS
White meat	NS	NS	NS	NS
Vegetables	NS	NS	NS	NS
Fruit	NS	NS	NS	NS
Alcohol consumption	RR 1.19	NS	OR 1.38	NS
NSAID use	RR 0.70	NS	Unknown	Unknown

H. pylori, *Helicobacter pylori*; HR, hazard ratio; NS, nonsignificant; NSAID, nonsteroidal anti-inflammatory drug; OR, odds ratio; RR, relative risk.

found between cardia gastric cancer and NSAID use[94]. In a cohort study from the USA involving 643 and 168,649 individuals with and without cancer, respectively, regular aspirin use was associated with a decreased risk of intestinal-type gastric cancer (HR 0.66, 95% CI 0.47–0.95), with increased protection with ≥6 years of regular use (HR 0.48, 95% CI 0.26–0.88; *P* for trend 0.01)[95]. The use of any NSAID was also associated with a decreased risk of intestinal-type gastric cancer (HR 0.70, 95% CI 0.50–0.97), but the use of non-aspirin NSAIDs was not (HR 0.97, 95% CI 0.64–1.47)[95]. Furthermore, the use of aspirin or any NSAID was not associated with diffuse-type gastric cancer risk (HR 0.92, 95% CI 0.53–1.60, and HR 0.89, 95% CI 0.54–1.48, respectively)[95].

Statins, which are pharmacological inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A reductase, are a class of drugs that reduce serum lipid levels and have been proposed as a chemopreventive therapy against gastric cancer. Studies in gastric cancer-derived cell lines have shown that statins have anti-proliferative, pro-apoptotic, anti-angiogenic and immunomodulatory effects[96]. One meta-analysis found an association between statin use and decreased risk of gastric cancer (OR 0.83, 95% CI 0.76–0.90; I^2 = 0% among six case–control studies)[97]. In a pooled analysis of individual data from three case–control studies, longer statin use (≥2 years) had an increased protective effect against gastric cancer (OR 0.35, 95% CI 0.16–0.76) relative to shorter durations of statin use (<2 years: OR 0.73, 95% CI 0.51–1.05)[97]. In a meta-analysis of data from 27 randomized controlled trials, statin use was associated with a decreased risk of gastric cancer (RR 0.73, 95% CI 0.58–0.92); however, this protective effect was attenuated but remained significant after excluding individuals with diabetes (RR 0.85, 95% CI 0.80–0.91)[98]. In a population-based matched study, use of the anti-diabetic medication metformin had no effect on the risk of early-onset gastric cancer (OR 0.44, 95% CI 0.14–1.44)[99]. Likewise, that study also found no association between use of NSAIDs (unadjusted OR 1.00, 95% CI 0.52–1.92) or statins (unadjusted OR 1.10, 95% CI 0.47–2.59) and early-onset gastric cancer[99].

Proton-pump inhibitors (PPIs), a class of medications that inhibit gastric acid secretion thereby reducing gastric acidity, have been hypothesized to promote carcinogenesis via hypergastrinaemia. A systematic review and meta-analysis of data from nine case–control and five cohort studies published through July 2020 found an increased risk of gastric cancer in users of PPIs relative to non-users (OR 1.94, 95% CI 1.47–2.56)[100]. However, longer durations of PPI use (>3 years relative to <1 year or 1–3 years) did not confer a greater risk. Anatomical subtype stratification revealed an increase in risk of non-cardia gastric cancer (OR 2.20, 95% CI 1.44–3.36) but not cardia gastric cancer (OR 1.77, 95% CI 0.72–4.36). However, the studies included had a high level of statistical heterogeneity (I^2 = 82%) and, overall, a moderate risk of bias[100]. More studies examining causation rather than associations between PPI use and gastric cancer are warranted.

Host genetics

Despite most gastric cancers being sporadic, they can also be hereditary and associated with specific mutational profiles. The risk of gastric cancer is higher in individuals with a family history of gastric cancer (OR 2–10 depending on the region)[101]. Three major heritable syndromes are primarily related to gastric cancer: hereditary diffuse gastric cancer (involving mutations in *CDH1* or *CTNNA1*)[102,103], gastric adenocarcinoma and proximal polyposis of the stomach (involving mutations in the promoter 1B region of *APC*[104]), and familial intestinal gastric cancer (involving mutations in *IL12RB1* (ref. 105)). Gastric cancer might develop as part of a familial cancer syndrome, such as Lynch syndrome (especially in individuals that harbour germline mutations in *MLH1* or *MSH2* (ref. 106)), familial adenomatous polyposis, Peutz–Jeghers syndrome or Li–Fraumeni syndrome[107].

Other risk factors

Other risk factors account for approximately 10% of gastric cancers globally. Here, we present the most important among such risk factors.

Epstein–Barr virus infection. In an international pooled analysis of 15 cross-sectional studies involving 5,081 patients with gastric cancer, approximately 8% harboured Epstein–Barr virus (EBV) in tumour tissue[108]. However, epidemiological evidence of a clear aetiological role for EBV infections in gastric carcinogenesis is currently insufficient[20].

Autoimmune disorders. Autoimmune gastritis, which causes pernicious anaemia in its severe form owing to malabsorption of vitamin B12, leads to the replacement of parietal and principal cells of the gastric mucosa with cells similar to intestinal cells that secrete mucus (that is, intestinal metaplasia or spasmolytic polypeptide-expression metaplasia (SPEM))[109,110]. These processes lead to total glandular atrophy of the oxyntic mucosa of the gastric body, predisposing to gastric cancer[111]. The incidence rate of gastric adenocarcinoma in patients with intestinal metaplasia is 0.72 per 1,000 person-years, and 7.7 per 1,000 person-years for patients with intestinal metaplasia with low-grade dysplasia[112]. Autoimmune gastritis is greater than twofold more common in women than in men[113] and is associated with disease progression to gastric carcinoid tumours or gastric adenocarcinomas in >10% of men[114]. Other autoimmune diseases, including but not limited to dermatomyositis, Addison disease and lupus erythematosus, have been linked with an increased risk of gastric cancer, with RR 3.69, 95% CI 1.74–7.79; RR 2.11, 95% CI 1.26–3.53, and RR 1.37, 95% CI 1.01–1.84, respectively[115].

Ménétrier disease. Ménétrier disease is a rare, acquired gastric disorder of hypertrophic gastropathy with no known prevalence or incidence, which is characterized by foveolar hyperplasia, tortuosity and cystic dilation of glands, smooth muscle hyperplasia and atrophy of oxyntic gland mucosa that leads to decreased production of gastric acid[116]. The aetiology of this disease is unknown, although a small-cohort study suggests a link between childhood Ménétrier disease and cytomegalovirus infection[117]. *H. pylori* infection has also been postulated as a potential risk factor for Ménétrier disease[118,119]. The incidence of gastric cancer in individuals with Ménétrier disease might be as high as 6–10%, although the exact incidence rate is unknown because most published data are from case reports and small series[120,121].

***H. pylori*-negative gastric cancer.** *H. pylori*-negative gastric cancers tend to be diagnosed at a younger age (56.0 years versus 59.3 years for *H. pylori*-positive gastric cancers), at a more advanced stage (at stage >1 in 39.3% and 33.7%, respectively) and are located more frequently in the proximal stomach or in the cardia (14.3% and 5.3%, respectively)[122]. The prevalence of *H. pylori*-negative gastric cancer has increased from 50% in 2007–2010 to 70% in 2015–2018 in the USA[123]; however, this prevalence is much lower in Japan (0.42–13.9%)[124]. Gut microbiota other than *H. pylori*, including *Neisseria*, *Peptostreptococcus*, *Streptococcus* and *Fusobacterium*, all might have a role in the carcinogenesis of *H. pylori*-negative gastric cancer[125–127]. The main causes of *H. pylori*-negative gastric cancer are unclear but probably include EBV infection, microsatellite instability and chromosomal instability[128,129].

Prevention

The worldwide case mortality rate for gastric cancer remains at 75%[6]. As such, gastric cancer continues to be a major contributor to the burden of global disability-adjusted life-years[130]. However, owing to the cost of screening procedures, decline in overall global incidence and uncertainty about who, when and how to screen, national strategies for cancer prevention do not include population-wide screening for gastric cancer. Thus far, initiatives for gastric cancer prevention have involved screening and surveillance methods in selected populations as well as screening for and eradication of *H. pylori*. In theory, information on a suite of key risk factors should be incorporated into any prediction algorithm developed to more efficiently identify patients for gastric cancer screening and/or surveillance. Although several such predictive models have been developed that show promise[131], they are not perfect. Additional testing in large-sized external cohorts is needed before the clinical adoption of these tools and models[132].

Primary prevention

Treating and eradicating *H. pylori* reduces the risk of gastric cancer. *H. pylori* eradication regimens contain an anti-secretory drug and one or more antibiotics, followed by stool antigen testing for confirmation of eradication[133]. A systematic review and meta-analysis of data from ten international randomized controlled trials (nine of which were performed in East Asia) published through 2020 compared the risk of gastric cancer in adults who have tested positive for *H. pylori* and received eradication therapy, placebo or no therapy[134]. The risk of developing incident gastric cancer was 46% lower among individuals who received eradication therapy relative to the other groups (RR 0.54, 95% CI 0.40–0.72). According to these data, clinicians would need to treat and eradicate *H. pylori* in 72 individuals (95% CI 56–119) to prevent one gastric cancer[134]. *H. pylori* eradication therapy is associated with a reduction in mortality from gastric cancer (RR 0.61, 95% CI 0.40–0.92; number needed to treat = 135) but not in all-cause mortality (RR 0.97, 95% CI 0.85–1.12)[134]. Subsequently, three major publications reporting evidence from a randomized controlled trial conducted in Taiwan[135], a prospective cohort study in Columbia[136] and a US national retrospective cohort study[137] all indicated significant reductions in gastric cancer risk among patients successfully treated with medications against *H. pylori*. A similar benefit was reported in a meta-analysis of data from eight cohort studies published through 2015, with a pooled RR of 0.46 (95% CI 0.32–0.66) favouring eradication therapy[138]. Despite not achieving complete eradication in the study population, a community-based intervention trial conducted in China showed that acceptable levels of *H. pylori* eradication are feasible (73%)[139]. The benefit of eradicating *H. pylori* seems to extend to metachronous gastric cancer. Indeed, in a meta-analysis of four randomized controlled trials published through 2019 that involved patients with early gastric cancer who underwent endoscopic mucosal resection, the incidence of metachronous gastric cancer was reduced among those who received medication for *H. pylori* eradication (OR 0.47, 95% CI 0.33–0.67)[140]. In this meta-analysis, *H. pylori* eradication was also associated with regression of atrophic gastritis and gastric intestinal metaplasia (OR 2.61, 95% CI 1.41–4.81, and OR 2.61, 95% CI 1.66–4.11, respectively), both of which are precursor lesions for gastric cancer[140]. In a phase III randomized controlled trial involving school-aged children not infected with *H. pylori*, prevention of *H. pylori* infection with a prophylactic oral *H. pylori* vaccine was achievable, with a vaccine efficacy of 71.8%[141].

Although the WHO recommends population-wide screening for *H. pylori* to reduce gastric cancer risk, only a few organized efforts exist. The potential benefit of a gastric cancer prevention programme that includes *H. pylori* screening and eradication is dependent on the population prevalence of *H. pylori* infection and each individual's cancer risk at the time of eradication. Population-based serology screening for *H. pylori* and eradication of the infection has been shown to be cost-effective (defined as an incremental cost-effectiveness ratio of US $6,264–25,881 per quality-adjusted life-year, which is below the cost-effectiveness threshold of $50,000) when performed in individuals >50 years of age in geographical regions with a high gastric cancer burden[142,143]. By contrast, in countries with a low incidence of gastric cancer such a population-based screening strategy is not cost efficient, although under favourable assumptions, population-based serology screening for *H. pylori* is cost-effective for populations with gastric cancer rates as low as 4.2 per 100,000[143]. Targeted screening in high-risk subpopulations residing within countries with a generally low incidence of gastric cancer could be cost-effective but has not been examined thus far. Studies are needed that could enable identification of those individuals with the highest risk of gastric cancer, who could participate in targeted screening for *H. pylori* in an effort to prevent future gastric cancer. In the USA and other countries with low rates of gastric cancer, however, additional research is required to determine whether such targeted screening initiatives are cost-effective[144].

Secondary prevention

The results of several studies have shown that, among all screening modalities, the highest detection rates are achieved with upper gastrointestinal endoscopy[49]. Although the gastric cancer detection rate for gastric radiography is 0.05–0.32%, the detection rate for upper gastrointestinal endoscopy is 0.30–0.87%[145]. The evidence available thus far suggests that endoscopy-based screening is cost-effective in high-incidence countries[143]; however, additional research is required before recommending such a screening approach for primary prevention[146]. Two modelling studies showed that endoscopy-based screening in the general US population would not be cost-effective[147,148]; however, these studies did not account for ethnic variations in the risk of gastric cancer, or the prevalence of *H. pylori* or pre-neoplastic gastric intestinal metaplasia and atrophy. Another modelling study determined that endoscopic gastric cancer screening using endoscopic surveillance every 3 years for any given 50-year-old individual with gastric intestinal metaplasia would be cost-effective for those of Asian, Hispanic or non-Hispanic Black ethnicity but not for non-Hispanic white individuals[149]. These gaps in knowledge necessitate an evaluation of age-specific, and possibly ethnicity-specific, risk-stratified screening for gastric cancer to determine the optimal approach. Upper gastrointestinal radiography is another method that can be considered for gastric cancer detection; however, the studies performed thus far have not demonstrated any comprehensive benefit over endoscopy[150].

National-level screening programmes have been adopted in only a few countries. In 2001, national guidelines for gastric cancer screening in South Korea were established by the Korean Gastric Cancer Association and National Cancer Center. According to these guidelines, both men and women ≥40 years of age should undergo biennial gastric cancer screening via upper endoscopy or upper gastrointestinal radiography to identify higher-risk patients with precancerous lesions (such as gastric intestinal metaplasia or dysplasia) for surveillance and early detection when minimally invasive endoscopic resection with curative intent is feasible[151]. In 2013, the Japanese government approved insurance coverage for a national gastric cancer prevention programme that involves *H. pylori* screening and treatment (primary prevention) as well as post-*H. pylori* treatment surveillance (secondary prevention for individuals with atrophic gastritis)[152,153].

Conclusions

The epidemiology of gastric cancer has changed globally. Despite overall reductions in incidence and mortality, gastric cancer remains a leading cause of mortality worldwide. Increasing evidence indicates that *H. pylori* infection, excess body fat, cigarette smoking and diets high in salt and processed meats affect an individual's lifetime risk of gastric cancer. This knowledge on gastric cancer risk factors can also be used to establish clinical prediction rules for risk stratification, a premise that has not yet materialized. The implementation of such predictive rules in routine clinical management requires their development, optimization and validation in external cohorts. In addition, risk communication should be a central feature of research and implementation. As we discuss in this Review, the risk of gastric cancer (based on the presence of gastric histological lesions) in a given population can change rapidly. Given that *H. pylori* eradication eliminates the risk of most gastric cancer subtypes, screening programmes and *H. pylori* eradication are imperative to reduce gastric cancer-related mortality worldwide[141].

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