

REVIEW

Epidemiology of gastric cancer

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Abstract

The incidence and mortality of gastric cancer have fallen dramatically in US and elsewhere over the past several decades. Nonetheless, gastric cancer remains a major public health issue as the fourth most common cancer and the second leading cause of cancer death worldwide. Demographic trends differ by tumor location and histology. While there has been a marked decline in distal, intestinal type gastric cancers, the incidence of proximal, diffuse type adenocarcinomas of the gastric cardia has been increasing, particularly in the Western countries. Incidence by tumor sub-site also varies widely based on geographic location, race, and socio-economic status. Distal gastric cancer predominates in developing countries, among blacks, and in lower socio-economic groups, whereas proximal tumors are more common in developed countries, among whites, and in higher socio-economic classes. Diverging trends in the incidence of gastric cancer by tumor location suggest that they may represent two diseases with different etiologies. The main risk factors for distal gastric cancer include *Helicobacter pylori* (*H pylori*) infection and dietary factors, whereas gastroesophageal reflux disease and obesity play important roles in the development of proximal stomach cancer. The purpose of this review is to examine the epidemiology and risk factors of gastric cancer, and to discuss strategies for primary prevention.

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INTRODUCTION

Overall, gastric cancer incidence and mortality have

fallen dramatically over the past 70 years^[1]. Despite its recent decline, gastric cancer is the fourth most common cancer and the second leading cause of cancer-related death worldwide^[2,3]. In 2000, about 880 000 people were diagnosed with gastric cancer and approximately 650 000 died of the disease^[4].

The two main tumor sites of gastric adenocarcinoma are proximal (cardia) and distal (noncardia). Despite a decline in distal gastric cancers, proximal tumors have been increasing in incidence since the 1970s, especially among males in the Western countries^[5,6]. These gastric tumor types predominate in populations from different geographic locations, racial and socio-economic groups. They may also differ in genetic susceptibility, pathologic profile, clinical presentation, and prognosis. The observed differences between gastric cancers by anatomic site suggest that they are distinct diseases with different etiologies. Detailed epidemiological analyses of their demographic trends and risk factors will help guide future cancer control strategies.

PATHOLOGIC CONSIDERATIONS

About 90% of stomach tumors are adenocarcinomas, which are subdivided into two main histologic types: (1) well-differentiated or intestinal type, and (2) undifferentiated or diffuse type. The intestinal type is related to corpus-dominant gastritis with gastric atrophy and intestinal metaplasia, whereas the diffuse type usually originates in pangastritis without atrophy.

The intestinal type is more common in males, blacks, and older age groups, whereas the diffuse type has a more equal male-to-female ratio and is more frequent in younger individuals^[7,8]. Intestinal type tumors predominate in high-risk geographic areas, such as East Asia, Eastern Europe, Central and South America, and account for much of the international variation of gastric cancer^[9]. Diffuse type adenocarcinomas of the stomach have a more uniform geographic distribution^[10]. A decline in the incidence of the intestinal type tumors in the corpus of the stomach accounts for most of the recent decrease in gastric cancer rates worldwide^[11]. In contrast, the incidence of diffuse type gastric carcinoma, particularly the signet ring type, has been increasing^[12].

DEMOGRAPHIC TRENDS

Time trends

In the 1930s, gastric cancer was the most common cause of cancer death in US and Europe. During the past 70 years, mortality rates have fallen dramatically

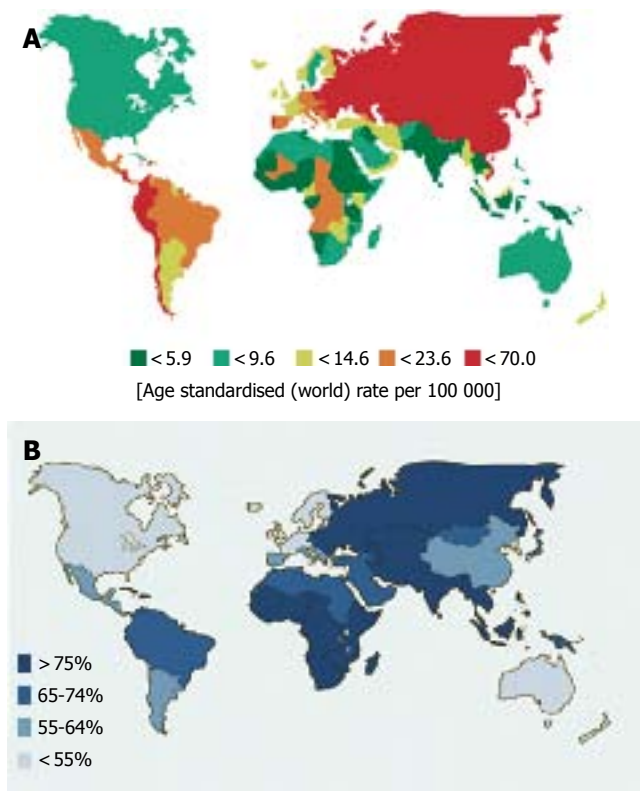


Figure 1 (A) Incidence of stomach cancer in males. (B) Prevalence of *H. pylori* infection in asymptomatic adults. (Data adopted from Parkin *et al.*^[6])

in all developed countries largely due to unplanned prevention. However, in the past 30 years, the incidence of gastric cardia adenocarcinoma rose by five- to six-fold in developed countries^[13-19]. Gastric cardia tumors now account for nearly half of all stomach cancers among men from US and UK^[6,20]. There has also been a rising trend in esophageal adenocarcinoma, in which obesity, gastroesophageal reflux disease (GERD), and Barrett's esophagus are major etiologic factors. Gastric cardia cancers share certain epidemiologic features with adenocarcinomas of the distal esophagus and gastroesophageal (GE) junction, suggesting that they represent a similar disease entity.

Geographic variation

Gastric cancer incidence rates vary by up to ten-fold throughout the world. Nearly two-thirds of stomach cancers occur in developing countries^[4]. Japan and Korea have the highest gastric cancer rates in the world^[21,22]. High-incidence areas for noncardia gastric adenocarcinoma include East Asia, Eastern Europe, and Central and South America^[20,23]. Low incidence rates are found in South Asia, North and East Africa, North America, Australia, and New Zealand (Figure 1A).

In Japan, gastric cancer remains the most common type of cancer among both men and women. Age-standardized incidence rates in Japan are 69.2 per 100 000 in men and 28.6 per 100 000 in women^[3]. In contrast to the increasing incidence of proximal tumors in the West, distal tumors continue to predominate in Japan. However, even in Japan, the proportion of proximal stomach cancers has increased among men^[24].

Migrant populations from high-risk areas such as Japan show a marked reduction in risk when they move to low-incidence regions such as the US^[25]. Subsequent generations acquire risk levels approximating those of the host country^[20,23].

Sex, race, and age distribution

Noncardia gastric cancer has a male-to-female ratio of approximately 2:1^[20,23]. Incidence rates are significantly higher among blacks and lower socio-economic groups, and in developing countries^[20]. Incidence rises progressively with age, with a peak incidence between 50 and 70 years.

In contrast, for gastric cardia carcinomas, men are affected five times more than women and whites twice as much as blacks^[26]. In addition, the incidence rates of proximal gastric cancers are relatively higher in the professional classes^[27]. Different rates of genetic polymorphisms according to tumor sub-site suggest variation in susceptibility to stomach cancer by tumor location^[28]. These findings suggest that noncardia and cardia adenocarcinomas are distinct biological entities.

SURVIVAL

For the past few decades, gastric cancer mortality has decreased markedly in most areas of the world^[29,30]. However, gastric cancer remains a disease of poor prognosis and high mortality, second only to lung cancer as the leading cause of cancer-related death worldwide. In general, countries with higher incidence rates of gastric cancer show better survival rates than countries with lower incidence^[31]. This association is largely due to a difference in survival rates based on tumor location within the stomach. Tumors located in the gastric cardia have a much poorer prognosis compared to those in the pyloric antrum, with lower 5-year survival and higher operative mortality^[32].

In addition, the availability of screening for early detection in high-risk areas has led to a decrease in mortality. In Japan where mass screening programs are in place, mortality rates for gastric cancer in men have more than halved since the early 1970s^[33]. When disease is confined to the inner lining of the stomach wall, 5-year survival is on the order of 95%. In contrast, few gastric cancers are discovered at an early stage in US, leading to 5-year relative survival rates of less than 20%^[34]. Similarly in European countries, the 5-year relative survival rates for gastric cancer vary from 10% to 20%^[35,36]. Host-related factors may also affect prognosis, as a US study demonstrated that gastric cancers in persons of Asian descent had a better prognosis compared to non-Asians^[37].

RISK FACTORS

Gastric cancer is a multifactorial disease. The marked geographic variation, time trends, and the migratory effect on gastric cancer incidence suggest that environmental or lifestyle factors are major contributors to the etiology of this disease.

Helicobacter pylori infection

H. pylori is a gram-negative bacillus that colonizes the stomach and may be the most common chronic bacterial

infection worldwide^[38]. Countries with high gastric cancer rates typically have a high prevalence of *H pylori* infection, and the decline in *H pylori* prevalence in developed countries parallels the decreasing incidence of gastric cancer^[39,40] (Figure 1B). In US, the prevalence of *H pylori* infection is <20% at the age 20 years and 50% at 50 years^[41]. In Japan, it is also <20% at 20 years, but increases to 80% over the age of 40 years^[42] and in Korea, 90% of asymptomatic adults over the age of 20 years are infected by *H pylori*^[43]. The increase in prevalence with age is largely due to a birth cohort effect rather than late acquisition of infection. *H pylori* infection is mainly acquired during early childhood, likely through oral ingestion, and infection persists throughout life^[44]. Prevalence is closely linked to socio-economic factors, such as low income and poor education, and living conditions during childhood, such as poor sanitation and overcrowding^[45-49].

The association between chronic *H pylori* infection and the development of gastric cancer is well established^[50-53]. In 1994, the International Agency for Research on Cancer classified *H pylori* as a type I (definite) carcinogen in human beings^[54]. In Correa's model of gastric carcinogenesis, *H pylori* infection triggers the progressive sequence of gastric lesions from chronic gastritis, gastric atrophy, intestinal metaplasia, dysplasia, and finally, gastric adenocarcinoma^[55]. Several case-control studies have shown significant associations between *H pylori* seropositivity and gastric cancer risk, with about a 2.1- to 16.7-fold greater risk compared to seronegative individuals^[56-62]. Prospective studies have also supported the association between *H pylori* infection and gastric cancer risk^[50-52,63]. Perhaps the most compelling evidence for the link between *H pylori* and gastric cancer comes from a prospective study of 1 526 Japanese participants in which gastric cancers developed in 2.9% of infected people and in none of the uninfected individuals^[64]. Interestingly, gastric carcinomas were detected in 4.7% of *H pylori*-infected individuals with non-ulcer dyspepsia.

The vast majority of *H pylori*-infected individuals remain asymptomatic without any clinical sequelae. Cofactors, which determine that *H pylori*-infected people are at particular risk for gastric cancer, include bacterial virulence factors and proinflammatory host factors. Gastric cancer risk is enhanced by infection with a more virulent strain of *H pylori* carrying the cytotoxin-associated gene A (*cagA*)^[65,66]. Compared to *cagA*- strains, infection by *H pylori cagA+* strains was associated with an increased risk of severe atrophic gastritis and distal gastric cancer^[67-70]. In the Western countries, about 60% of *H pylori* isolates are *cagA+*^[71], whereas in Japan, nearly 100% of the strains possess functional *cagA*^[72,73]. Host factors associated with an increased risk of gastric cancer include genetic polymorphisms which lead to high-level of expression of the proinflammatory cytokine, interleukin-1 β ^[74,75].

The effects of *H pylori* on gastric tumor development may vary by anatomical site. The falling incidence of *H pylori* infection and noncardia gastric cancer in developed countries has been diametrically opposed to the rapid increase in the incidence of gastric cardia adenocarcinoma^[76]. Based on a meta-analysis of prospective cohort studies, *H pylori* infection was associated

with the risk of noncardia gastric cancer, but not cardia cancer^[77]. Other studies demonstrated a significant inverse association between *H pylori* infection, particularly *cagA+* strains, and the development of gastric cardia and esophageal adenocarcinomas^[78,79]. In the Western countries, where the prevalence of *H pylori* infection is falling, GERD and its sequelae are increasing. Studies have shown that severe atrophic gastritis and reduced acid production associated with *H pylori* infection significantly reduced the risk of GERD^[80-83]. However, recent studies have found conflicting results on whether *H pylori* eradication therapy increases the risk of esophagitis and gastric cardia adenocarcinoma^[84-91]. Thus, the protective effect of *H pylori* against cardia tumors remains controversial.

Dietary factors

It is unlikely that *H pylori* infection alone is responsible for the development of gastric cancer. Rather, *H pylori* may produce an environment conducive to carcinogenesis and interact with other lifestyle and environmental exposures. There is evidence that consumption of salty foods and *N*-nitroso compounds and low intake of fresh fruits and vegetables increases the risk of gastric cancer. *H pylori* gastritis facilitates the growth of nitrosating bacteria, which catalyze the production of carcinogenic *N*-nitroso compounds^[92]. In addition, *H pylori* infection is known to inhibit gastric secretion of ascorbic acid, which is an important scavenger of *N*-nitroso compounds and oxygen free radicals^[93].

Salt-preserved foods and dietary nitrite found in preserved meats are potentially carcinogenic. Intake of salted food may increase the risk of *H pylori* infection and act synergistically to promote the development of gastric cancer. In animal models, ingestion of salt is known to cause gastritis and enhance the effects of gastric carcinogens^[94,95]. Mucosal damage induced by salt may increase the possibility of persistent infection with *H pylori*^[96]. Several case-control studies have shown that a high intake of salt and salt-preserved food was associated with gastric cancer risk^[97-103], but evidence from prospective studies is inconsistent^[104-107]. *N*-nitroso compounds are carcinogenic in animal models and are formed in the human stomach from dietary nitrite. However, case-control studies have shown a weak, nonsignificant increased risk of gastric cancer for high vs low nitrite intake^[97,108-110]. Prospective studies have reported significant reductions in gastric cancer risk arising from fruit and vegetable consumption^[111-114]. The worldwide decline in gastric cancer incidence may be attributable to the advent of refrigeration, which led to decreased consumption of preserved foods and increased intake of fresh fruits and vegetables.

Animal studies have shown that polyphenols in green tea have antitumor and anti-inflammatory effects. In preclinical studies, polyphenols have antioxidant activities and the ability to inhibit nitrosation, which have been implicated as etiologic factors of gastric cancer^[115-117]. Although various case-control studies have shown a reduced risk of gastric cancer in relation to green tea consumption^[118-121], recent prospective cohort studies found no protective effect of green tea on gastric cancer risk^[122-125].

Table 1 Epidemiologic differences between cardia and noncardia gastric cancer

	Cardia Increasing	Noncardia Decreasing
Incidence		
Geographic location		
Western countries	+	-
East Asia	-	+
Developing countries	-	+
Age	++	++
Male gender	++	+
Caucasian race	+	-
Low socio-economic status	-	+
<i>H pylori</i> infection	?	+
Diet		
Preserved foods	+	+
Fruits/vegetables	-	-
Obesity	+	?
Tobacco	+	+

NOTE: ++, strong positive association; +, positive association; -, negative association; ?, ambiguous studies.

Tobacco

Prospective studies have demonstrated a significant dose-dependent relationship between smoking and gastric cancer risk^[126,127]. The effect of smoking was more pronounced for distal gastric cancer, with adjusted rate ratios of 2.0 (95% CI, 1.1-3.7) and 2.1 (95% CI, 1.2-3.6) for past and current smokers, respectively^[128]. There is little support for an association between alcohol and gastric cancer^[129].

Obesity

Obesity is one of the main risk factors for gastric cardia adenocarcinoma^[130,131]. Obesity can promote GE reflux disease which predisposes to Barrett's esophagus, a metaplastic precursor state for adenocarcinoma of the esophagus and GE junction^[132,133]. A Swedish study found that the heaviest quarter of the population had a 2.3-fold increased risk for gastric cardia adenocarcinoma compared to the lightest quartile of the population^[134]. A recent prospective study from US found that body mass index was significantly associated with higher rates of stomach cancer mortality among men^[135]. Thus, risk factors positively associated with adenocarcinoma of the esophagus and gastric cardia include obesity, GE reflux, and the presence of Barrett's esophagus. A summary of the main differences between cardia and noncardia gastric cancer can be found in Table 1.

Other

Less common risk factors for gastric cancer include radiation^[136], pernicious anemia^[137], blood type A^[138], prior gastric surgery for benign conditions^[139], and Epstein-Barr virus^[140-142]. In addition, a positive family history is a significant risk factor, particularly with genetic syndromes such as hereditary nonpolyposis colon cancer and Li-Fraumeni syndrome^[143-145].

PREVENTION OF GASTRIC CANCER

Lifestyle modifications

Because gastric cancer is often associated with a poor

prognosis, the main strategy for improving clinical outcomes is through primary prevention. Reduction in gastric cancer mortality is largely due to unplanned prevention. The widespread introduction of refrigeration has led to a decrease in the intake of chemically preserved foods and increased consumption of fresh fruits and vegetables^[98,146]. A decline in the prevalence of *H pylori* infection may be due to improvements in sanitary and housing conditions, as well as the use of eradication therapy^[54]. In addition, reduced tobacco smoking at least in males may have contributed to the decline in gastric cancer incidence^[147]. Therefore, modifiable risk factors, such as high salt and nitrite consumption, low fruit and vegetable intake, cigarette smoking, and *H pylori* infection, may be targeted for prevention.

Helicobacter pylori eradication

Public health measures to improve sanitation and housing conditions are the key factors in reducing the worldwide prevalence of *H pylori* infection. *H pylori* eradication therapy is another potential strategy for gastric cancer chemoprevention. A 7 to 14 d course of two antibiotics and an antisecretory agent has a cure rate of about 80% with durable responses^[148]. However, higher reinfection rates are seen in developing countries after people have had effective eradication therapy^[149]. In Japanese patients treated for early gastric cancer, *H pylori* eradication therapy resulted in a significantly lower rate of gastric cancer recurrence^[150]. A randomized controlled chemoprevention trial showed that antimicrobial therapy directed against *H pylori* or dietary supplementation with antioxidants increased the regression rate of gastric atrophy and intestinal metaplasia compared to placebo^[151]. In a randomized, placebo-controlled primary prevention trial conducted in a high-risk region of China, 1 630 healthy carriers of *H pylori* infection were randomized to a 2-wk course of eradication treatment or placebo^[152]. Although the incidence of gastric cancer was similar in both groups after 7.5 years of follow-up, post hoc analysis of a subgroup of *H pylori* carriers without precancerous lesions at baseline showed a significant decrease in the development of gastric cancer with eradication therapy.

Several large-scale chemoprevention trials of *H pylori* eradication therapy with gastric cancer endpoints are ongoing. Potential downsides of widespread eradication therapy in asymptomatic carriers include developing antibiotic-resistant strains of *H pylori* and perhaps increasing the risk of GERD and adenocarcinoma of the esophagus and gastric cardia.

Antioxidants

High intake of antioxidants, such as vitamins C and E and β -carotene, may have a protective effect on the risk of gastric cancer. High serum levels of α -carotene, β -carotene, lycopene, and vitamin C were significantly associated with reduced risk of gastric cancer in a cohort from Shanghai, China^[153]. A randomized trial in Linxian, China showed a reduced risk of both cardia and noncardia gastric cancers in individuals supplemented with a combination of selenium, β -carotene, and α -tocopherol^[154]. However, a randomized trial from

Finland showed no association between α -tocopherol or β -carotene supplementation and the prevalence of gastric cancer in elderly men with atrophic gastritis^[155]. Another prospective study from the US Cancer Prevention Study II cohort found that vitamin supplementation did not significantly reduce the risk of stomach cancer mortality^[156]. Therefore, dietary supplementation may only play a preventive role in populations with high rates of gastric cancer and low intake of micronutrients.

COX-2 inhibitors

Cyclooxygenase-2 (COX-2) plays a role in cell proliferation, apoptosis, and angiogenesis, and may be involved in gastric carcinogenesis^[157,158]. Increasing levels of COX-2 are present in the progression from atrophic gastritis to intestinal metaplasia and adenocarcinoma of the stomach^[159]. Exposure to cigarette smoke, acidic conditions, and *H pylori* infection all induce COX-2 expression^[160-162]. Furthermore, McCarthy *et al.* showed that COX-2 expression in the antral mucosa was reduced in the epithelium after successful eradication of *H pylori*^[163].

Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) are thought to inhibit cancer cell growth primarily through the inhibition of COX-2, and evidence is mounting that COX-2 inhibitors may be beneficial in preventing upper gastrointestinal malignancies. Compared to colorectal cancer, the association between NSAID use and the development of gastric cancer has been studied less extensively^[164-166]. A recent meta-analysis showed that NSAID use was associated with a reduced risk of noncardia gastric adenocarcinoma^[167]. Thus, COX-2 inhibitors may provide a chemopreventive strategy against gastric carcinogenesis.

Endoscopic screening and surveillance

Because of the high risk of gastric cancer in Japan, there has been a national endoscopic surveillance program within the commercial workforce. Annual screening with a double-contrast barium technique and endoscopy is recommended for persons over the age of 40 years^[168]. With mass screening, about half of gastric tumors are being detected at an early stage in asymptomatic individuals and the mortality rate from gastric cancer has more than halved since the early 1970s^[33]. An intervention study in China is underway which involves a comprehensive approach to gastric cancer prevention, including *H pylori* eradication, nutritional supplements, and aggressive screening with double contrast X-ray and endoscopic examination. In the first four years after intervention, the relative risk of overall mortality with this intervention for a high-risk group was 0.51 (95% CI, 0.35-0.74)^[169]. This study suggests that targeting high-risk populations for aggressive screening and prevention may decrease gastric cancer mortality.

CONCLUSION

In summary, cardia and noncardia gastric cancers exhibit unique epidemiologic features characterized by marked geographic variation, diverging time trends, and differences based on race, sex, and socio-economic status. *H pylori*

infection and dietary factors appear to be the main causative agents for distal gastric cancer, whereas GERD and obesity play a primary role in proximal gastric cancer. Future directions in primary prevention should target modifiable risk factors in high-risk populations. In the planning and evaluation of gastric cancer control activities, detailed demographic analyses will inform future screening and intervention studies.

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