1

Epidemiology of gastric cancer

Mark E. Lockhart and Cheri L. Canon

Introduction

Although the incidence and mortality rate of gastric cancer are declining in the United States and Great Britain (Figures 1.1 and 1.2), gastric carcinoma remains the fourth most common cancer in the world [1] and is second only to lung cancer in terms of worldwide cancer deaths (Figures 1.3 and 1.4).The development of gastric cancer is a multifactorial process, and many conditions influence the likelihood of occurrence. An understanding of the disease process in these patients is important for the assessment of risk and prognosis. In this chapter, the epidemiologic factors of gastric cancer, including its incidence, mortality, pathogenesis, and risk factors, are discussed.

Incidence and mortality

In developing countries, there is a high incidence of gastric cancer, and more than 990 000 cases occur worldwide each year based on 2008 statistics [2, 3]. However, in the United States, gastric cancer represents only approximately 1.5% of an estimated 1.44 million new cancer cases each year [4]. There were 22 000 new cases in the United States in 2008. Despite the decreasing incidence of gastric carcinoma from a previous rate of 35/100 000 cases in 1930 to 4/100 000 cases in 2003, it carries a relatively high mortality rate when compared to other cancers: 2.96 and 5.70/100 000 for women and men, respectively. Not only is the incidence higher in men, so trends the death rate [4]. However, the mortality rate of gastric cancer in the United States has decreased by 26% and 35% since 1990 in females and males, respectively [4].

Gastric cancer is more common in older populations, usually occurring in the seventh and eighth decades of life. The mean age at diagnosis was 67 years in one large

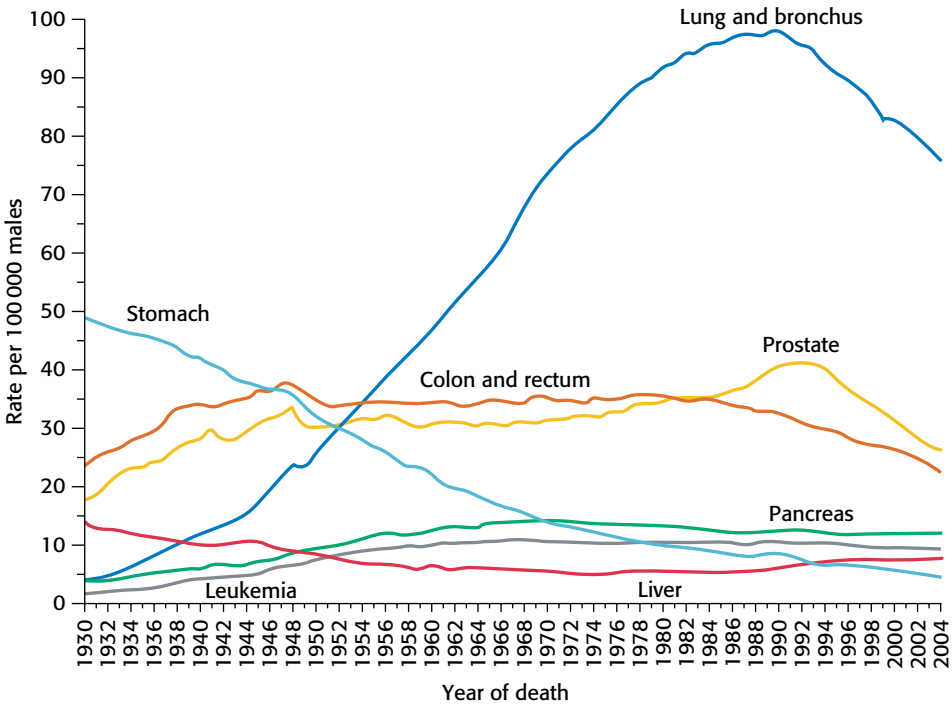


Figure 1.1. Cancer death rates in the United States. In 1930, gastric cancer was the most common cause of cancer-related deaths. By the twenty-first century, gastric cancer had become the seventh leading cause of cancer deaths in the United States.

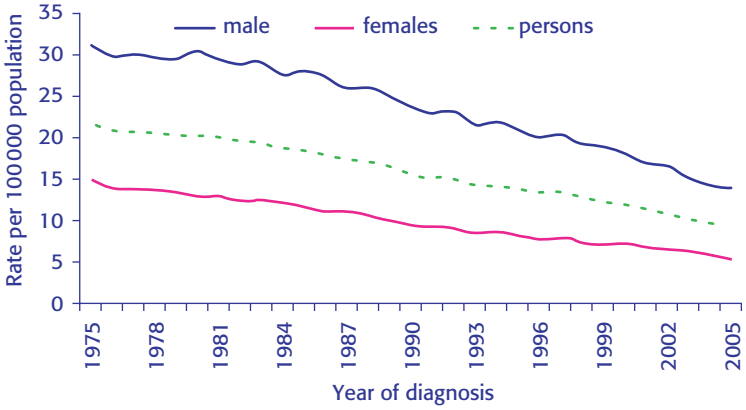


Figure 1.2. Age-standardized incidence rates of gastric cancer in Great Britain between 1975 and 2005.

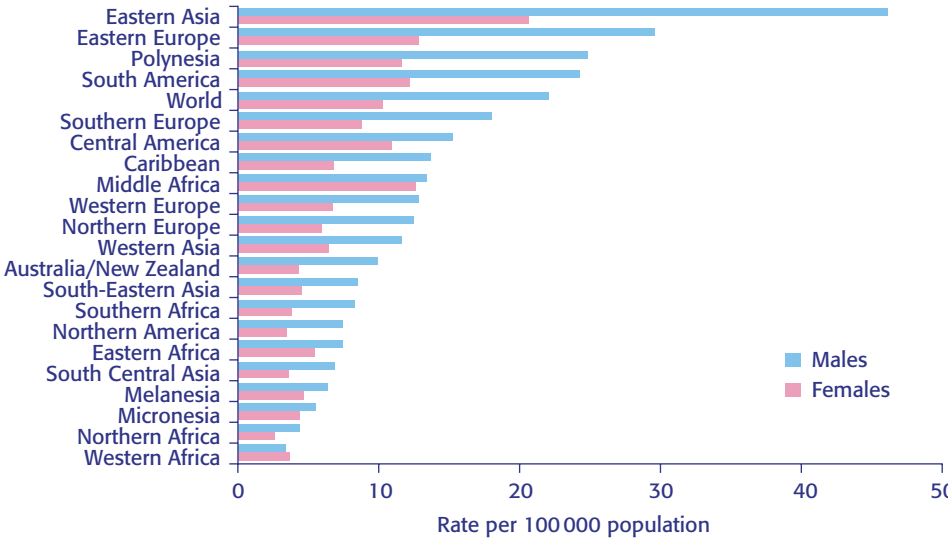


Figure 1.3. Age-standardized incidence rates of stomach cancer, by sex and region of world; 2008 estimates.

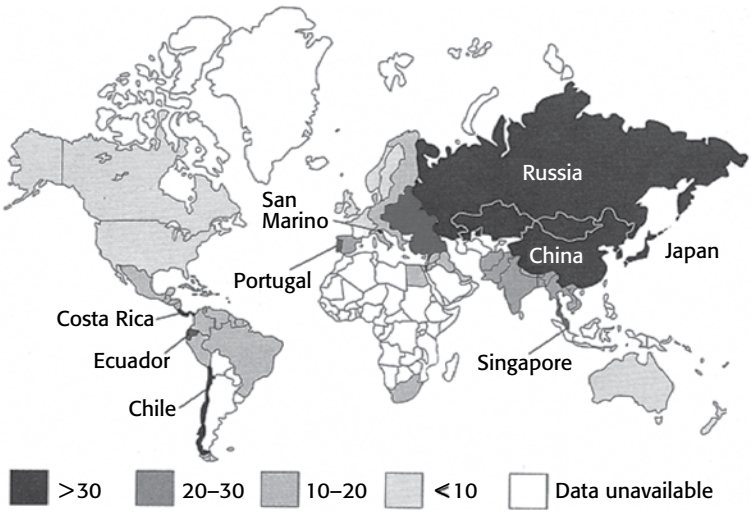


Figure 1.4. Worldwide distribution of gastric cancer age-adjusted death rates. The highest incidences are found in the Far East, Russia, and Eastern Europe, and the lowest incidence rates are found in North America, Africa, the UK, Australia, and New Zealand. From Koh TJ and Wang TC. Tumors of the stomach. In Feldman M, Brandt LJ and Sleisenger MH eds., *Gastrointestinal and Liver Disease*, 7th edn. Philadelphia, PA: WB Saunders, 2002; pp. 822–59, figure 44.1, p. 830.

Table 1.1. Comparison of cardia and distal gastric adenocarcinoma

		Cardia adenocarcinoma	Distal adenocarcinoma
Change in incidence		++	–
Risk factors:	*H. pylori*	–	++
	Obesity	+	+/–
	Smoking	+	+
	Red meat	–	+
	Alcohol	?	?
	Low socioeconomic status	++	+
Prognosis		Worse	Better

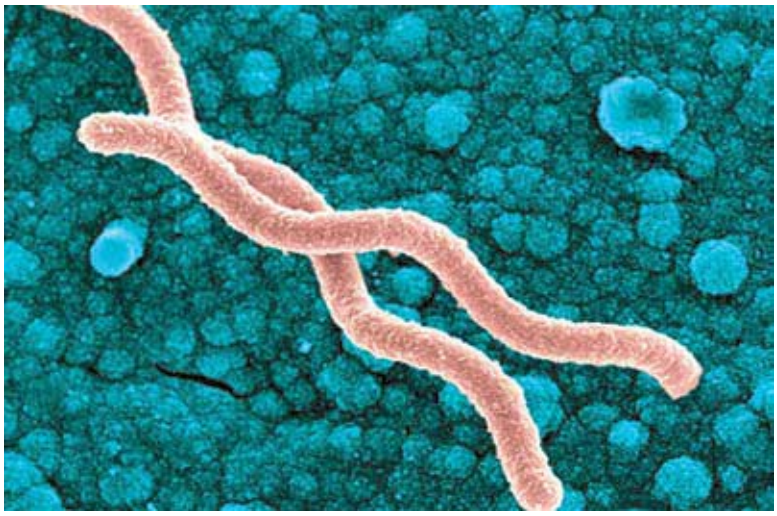
series [5]. Although previously suspected, there is current uncertainty as to whether gastric cancer in young patients is associated with a worse clinical outcome [6].

Pathogenesis

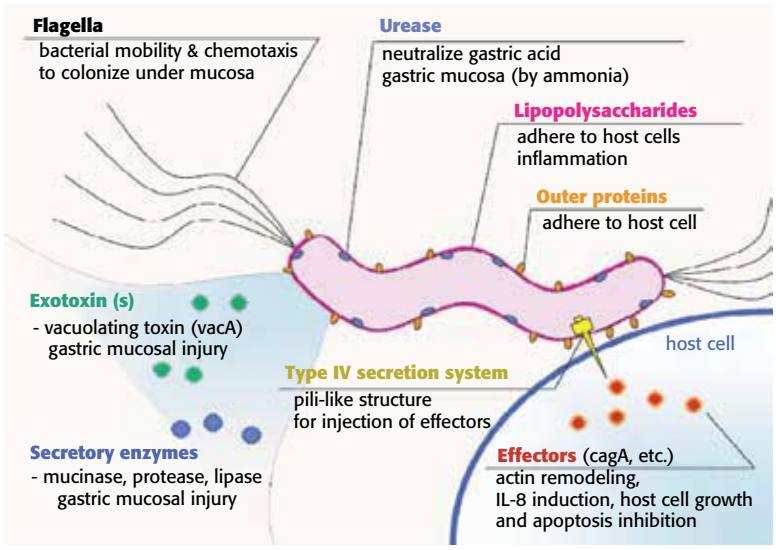
Adenocarcinoma is the most common malignancy of the stomach, accounting for nearly 90% of gastric tumors [7]. Pathologically, there are two types of gastric adenocarcinoma based upon location: cardia, or proximal, and distal, non-cardia adenocarcinomas. These should be considered as separate entities because of differing epidemiologic relationships, associated risk factors, and prognosis [8] (Table 1.1). Historically, distal gastric carcinoma was the most common type. However, because the rate of cardia tumors continues to increase while that of distal gastric cancers decreases [9, 10], the incidence of proximal adenocarcinoma has surpassed that of distal cancers in recent years. This is an unfortunate change in the epidemiology of the disease since cancers of the gastric cardia generally have worse prognosis than distal gastric cancers [7, 10].

Histologically, gastric cancer is divided into two main types: well-differentiated, intestinal type, and undifferentiated, diffuse type [8]. The latter occurs in the setting of diffuse gastritis without atrophy. This histologic type is seen throughout the world, whereas the intestinal type occurs in areas with a high incidence of gastric cancer and follows a predictable stepwise progression of cancer development from metaplasia.

In 1994, the International Agency for Research on Cancer and The World Health Organization classified *Helicobacter pylori* (Figure 1.5) as a type I carcinogen, but



a



b

Figure 1.5. ***Helicobacter pylori.*** **(a) Scanning electron micrograph image showing the wavy, thin, rod-shaped bacterium attached to the foveolar epithelium of the stomach. (b) Schematic diagram depicting the virulence factors of** ***Helicobacter pylori.*** **cagA, cytotoxin associated gene A.**

the exact mechanism leading to gastric carcinoma is not clearly understood. The effects of *H. pylori* infection on gastric cancer appear multifactorial, involving host and environmental factors as well as differing bacterial strains. *H. pylori* is most closely associated with intestinal gastric cancers, which follow a stepwise pathway

toward malignancy, similar to that in the colon. In the Correa model of gastric carcinogenesis, gastric inflammation leads to mucosal atrophy, metaplasia, dysplasia, and, ultimately, carcinoma [11]. Studies have shown that *H. pylori* infection is an independent risk factor for distal gastric cancer, with a 3- to 6-fold increased risk relative to those without the infection [12, 13, 14]. However, the great majority of infected individuals will never develop gastric neoplasia: approximately 40% of patients infected with *H. pylori* will develop gastric metaplasia but fewer than 1% will develop cancer [15].

Gastric atrophy also increases susceptibility of the cells to carcinogens. In patients with *H. pylori*, the presence of specific gene polymorphisms increases the risk of developing gastric carcinoma. Genes that encode tumor necrosis factor alpha (TNF-α), and interleukins IL-1, IL-8, and IL-10 have each been associated with higher cancer rates in the setting of *H. pylori* [16, 17]. While intestinal gastric cancer is strongly associated with chronic *H. pylori*, this strong link is not seen in diffuse gastric cancer. Diffuse or cardia gastric cancer, however, has been associated with other risk factors such as higher socioeconomic class [18], obesity [19, 20], and type A blood [21].

Risk factors

The risk factors for gastric cancer are protean and detailed in Table 1.2.

Ethnic and geographic factors

There is a higher incidence of gastric cancer in non-Caucasian populations. In the United States, the highest incidence is found in the Native American (21.6/100 000) and Asian (20/100 000) populations. Both race and sex affect the risk of disease development and subsequent mortality rate. The highest mortality rate based upon ethnic/sex combination is African-American males (12.4/100 000) [4]. However, there are similar overall 5-year survival rates among the different races.

The incidence of gastric carcinoma also varies dramatically by geographic location. In contrast to the American population, the societal burden of gastric cancer is much higher in Japan where it is the most common tumor type, accounting for approximately 19% of new tumor diagnoses based upon 2001 cancer registry data [22]. In Japanese men, the incidence rate is 116/100 000 [22]. A study by the American Cancer Society suggests that Japanese patients living within the United States who develop gastric cancer may even have differences in pathophysiology

Table 1.2. Risk factors for development of gastric cancer

Precursor conditions
Helicobacter pylori infection
Gastric adenomatous polyps
Chronic atrophic gastritis and intestinal metaplasia
Pernicious anemia
Partial gastrectomy for benign disease
Dietary
Highly salted food
Smoked foods, high fat or contaminated oil intake
Low consumption of fruits and vegetables
Habits
Smoking
Consumption of sake or contaminated whiskey
Cultural
Low socioeconomic status
Environmental
Acidic or peaty soil
High nitrate content in water
Elevated lead or zinc in water
Volcanic rock background
Exposure to environmental talc
Extensive use of nitrate fertilizers
Urban residency
Genetic
Family history of gastric cancer
Blood type A
Hereditary non-polyposis colon cancer syndrome
Familial adenomatous polyposis syndrome
Peutz–Jeghers syndrome
Li–Fraumeni syndrome
Hyperplastic gastric polyposis
Familial diffuse gastric carcinoma
Occupational
Workers in mines and quarries
Painters
Fishermen
Ceramic, clay, and stone workers
Metal industry workers
Agricultural workers
Textile workers
Printers and bookbinders

compared with their Caucasian counterparts. The percentage of cardia tumors in Japanese patients (11%) was less than half the percentage for the overall population in the study (28%) [5]. The study also showed that although gastric cancer is still more common in Japanese men than women, there was a smaller difference in the male-to-female ratio for Japanese patients compared with other Americans.

The rate of gastric cancer in other Asian countries such as Korea and China is also high. It is interesting to note that in similar parts of the world, incidence rates of gastric cancer can vary significantly. For example, within the European Union the highest mortality rate is found in Iceland and the lowest mortality rate is in Poland [23]. The mortality differs by the severity of disease at the time of diagnosis, and there is generally delayed diagnosis in Western populations as compared to in Japan. Still, there has been a long-term worldwide decrease in both the incidence and mortality associated with gastric cancer [24].

Genetics

There are a variety of genes that increase the risk of gastric cancer that are detailed in Table 1.3 and Figure 1.6. Specific genes such as MCC, APC, and p53 tumor suppressor genes have been identified in a large percentage of gastric cancers [25]. Several studies have identified E-cadherin, a calcium-dependent adhesion molecule that is responsible for cellular binding to adjacent cells, as an important component in the gastric carcinogenesis cascade [26, 27, 28]. Genetic susceptibility involves hereditary transmission of a single mutated CDH1 allele. If there is an acquired mutation of the second allele in the E-cadherin gene, then loss of intracellular adhesion leads to increased intracellular permeability [29]. A wide variety of mutations in this domain have been identified in gastric cancer families [30].

Multiple syndromes are associated with gastric carcinoma; most are associated with gastrointestinal polyp formation and have increased risk of cancer at other sites as well. These include familial adenomatous polyposis (FAP) and Cowden disease. The FAP genetic defect is located in the APC gene involved in the Wnt tumor-signaling pathway. This gene is located on chromosome 5q and involves development of different tumor types, including colonic and gastric cancers [31].

In FAP a significant proportion of adenomatous polyps in the stomach will develop into carcinoma. Hamartomatous polyps, such as are found in Peutz–Jeghers disease and juvenile polyposis, have exceedingly low malignant potential. However, patients with these syndromes tend also to have an increased incidence of adenomatous polyps, which do carry the risk of malignant transformation.

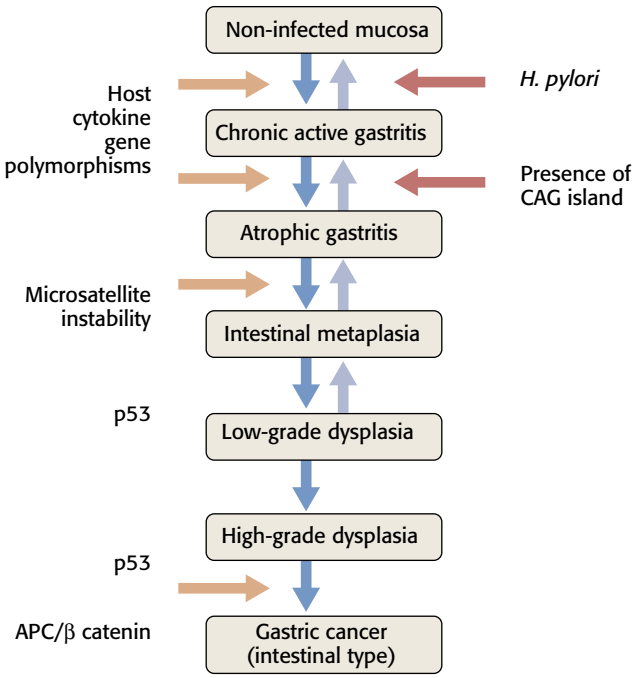


Figure 1.6. Proposed multistep pathway in the pathogenesis of gastric cancer. Infection with *Helicobacter pylori* is the common initiating event in most cases, and the presence of the *cag* pathogenicity island is associated with more severe disease. Host genetic polymorphisms, resulting in high production of interleukin-1β and tumor necrosis factor-α and low production of interleukin-10, contribute to gastric cancer risk. Accumulation of genetic defects within gastric lesions such as alterations in p53, microsatellite instability, and abnormalities in the adenomatous polyposis coli/β-catenin pathway may play a role in later steps. Gray arrows represent steps that are potentially reversible. (From Koh TJ, Wang TC: Tumors of the stomach. In Feldman M, Brandt LJ and Sleisenger MH eds., *Gastrointestinal and Liver Disease*, 7th edn. Philadelphia, PA: WB Saunders, 2002; pp. 822–59, Figure 44–4, p. 832.)

Hereditary diffuse gastric carcinoma is an autosomal dominant trait on chromosome 16p22 and has an associated 67%–83% lifetime risk of gastric carcinoma [32]. Families are identified if there are two first- or second-degree relatives who develop gastric cancer before age 50 or if there are three such relatives regardless of age. Due to the high risk of malignancy, genetic screening of patients' families is recommended if a patient is diagnosed with diffuse cancer before age 35, if the patient is diagnosed with gastric and breast carcinoma, or if family members have both diffuse gastric cancer and breast cancer [29].

In the absence of a defined familial syndrome, increased risk of gastric cancer is present in relatives of patients with breast cancer [33]. Also, the Li–Fraumeni

Table 1.3. Genetic alterations in gastric carcinomas and their relative frequency

Genes and alterations	Well-differentiated adenocarcinoma	Poorly differentiated adenocarcinoma
Telomerase activity	+++	+++
CD44 (abnormal transcript)	+++	+++
TGFA (overexpression)	++	++
DNA repair error	++	++
TP53 (LOH, mutation)	++	++
Beta catenin (mutation)	+	++
TP16 (reduced expression)	++	+
c-*met* (amplification)	+	++
VEGF (overexpression)	++	+
EGF (overexpression)	++	+
EGFR (overexpression)	++	+
APC (LOH, mutation)	++	+
DCC (LOH)	++	
BCL2 (LOH)	++	
E-cadherin/*CDH1* gene		++
K-*ras* mutation	+	+
Cyclin E (amplification)	+	+
c-erbB-2 (amplification)	+	

The number of crosses defines the relative frequency, from + (infrequent) to +++ (very common genetic alteration); APC, adenomatous polyposis coli; EGF, epidermal growth factor; EGFR, EGF receptor; LOH, loss of heterozygosity; VEGF, vascular endothelial growth factor.

syndrome has an increased risk of breast and gastric cancer in addition to more commonly seen melanoma, leukemia, brain tumors, and sarcomas. The syndrome is autosomal dominant in inheritance and demonstrates high penetrance in the cancer predisposition. This cancer risk is associated with mutations involving tumor suppressor genes, specifically germline TP53 mutations [34].

Hereditary non-polyposis colorectal cancer (HNPCC, Lynch syndrome II) is a risk factor for stomach cancer. In nearly one-quarter of these patients with gastric cancer, chromosomal mutations result in microsatellite instability [35]. In this syndrome, there is an approximately 4-fold increase in stomach cancer relative to the general population [36]. The disease is transmitted in an autosomal dominant pattern and has a high degree of penetrance [37]. Patients with Lynch syndrome II more typically present with early onset of colorectal cancer, and patients are also at increased risk of uterine carcinoma [38].