Chapter 2
Epidemiology

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Incidence and Mortality

Gastric cancer, with 984,000 new cases and 841,000 deaths estimated to have occurred in 2013, is the fifth most common malignancy and the second leading cause of cancer death worldwide [1]. This disease used to be the leading cause of cancer deaths until 1980s, when it was exceeded by lung cancer [2].

Approximately 80–90% of gastric carcinomas develop in a sporadic setting, and the remaining show familial clustering, with approximately 1–3% exhibiting a clear inherited genetic susceptibility [3].

Worldwide, both the incidence of the disease and overall survival rates vary significantly. Incidence is strongly affected by ethnic and geographical factors: it is higher in Eastern Asia, Eastern Europe, and South America, while North America and Africa show the lowest rates [1, 4].

Recent decades have seen a progressive reduction in the incidence of gastric cancer across the globe (Fig. 2.1) [1]. This reduction began in those countries that had the lowest rate, while the decline rate is lower in countries with higher incidences [1]. Distal cancer (antrum and pylorus) are more common in high-incidence and high-mortality areas, and the incidence of this type of gastric cancer has decreased significantly [5]. This trend is attributed to the knowledge and control of risk factors such as *Helicobacter pylori* and other dietary and environmental factors [1]. In the USA, from 1977 to 2006, the incidence of noncardia gastric cancer declined among all race and age groups except for whites aged 25–39 years [6]. While the incidence of gastric cancer has decreased worldwide in recent decades, the incidence of signet-ring cell carcinoma (SRCC) has remained unchanged or even risen in certain parts of the globe [7].

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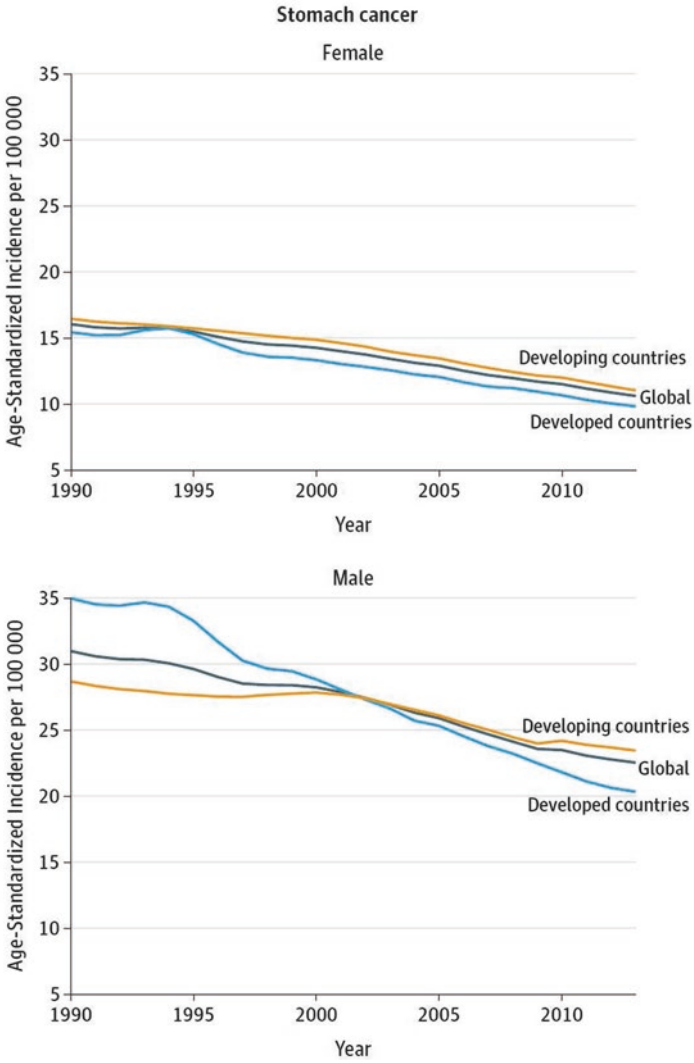

Fig. 2.1 Trends in age-standardized incidence rates for stomach cancer, 1990–2013. (Source: Global Burden of Disease Cancer Collaboration [1])

Age-standardized incidence rates (ASIRs) per 100,000 and age-standardized death rates (ASDRs) per 100,000 for both sexes in 2013 were higher in developing compared to developed countries for stomach cancer (ASIR: 17 vs. 14; ASDR: 15 vs. 11) [7]. Analysis of mortality rates from 1980 to 2005 showed a slower decline in Latin America compared to developed countries (USA, Japan, and Australia) [5].

Diffuse-Type Gastric Carcinoma

The majority of gastric cancers are adenocarcinomas that were classically grouped in the intestinal and diffuse types by the histoclinical Laurén classification in 1965 [8]. Gastric carcinomas represent a biologically and genetically heterogeneous group of tumors with multifactorial etiologies, both environmental and genetic. They are characterized by broad morphological heterogeneity with respect to patterns of architecture and growth, cell differentiation, histogenesis, and molecular pathogenesis.

The World Health Organization (WHO) has categorized gastric cancer into five major histologic types: tubular, papillary, mucinous, poorly cohesive carcinomas (with or without signet ring cell), and mixed. Poorly cohesive carcinoma refers to the diffuse type [9].

Recently, The Cancer Genome Atlas (TCGA) Research Network proposed a molecular gastric cancer classification system that includes four subtypes: Epstein–Barr virus (EBV) positive, microsatellite-unstable, genomically stable, and chromosomal instability (CIN) tumors [10].

The third group, named genomically stable (20% of cases), lacked extensive somatic copy number aberrations, and biopsies often presented a diffuse-type histology. This subtype frequently presented alterations in genes involved in cell adhesion, such as *RHOA* (15%), *CDH1* (26%), and *CLDN18/ARHGAP* (15%). Moreover, these tumors also exhibited elevated expression of cell adhesion and angiogenesis-related pathways [10].

Nevertheless, although the WHO and TCGA classifications brought considerable contributions to the field, Laurén classification is still extensively used in clinical practice.

Compared to intestinal gastric adenocarcinoma, patients with diffuse gastric carcinoma are significantly younger at diagnosis and do not have sex predominance. Patients with diffuse gastric cancer have more advanced and less differentiated tumors, as well as greater invasion depth and lymphovascular invasion [11]. The incidence of intestinal adenocarcinoma decreased faster than that of diffuse carcinoma between 1990 and 2009 in Iceland (0.92/100,000 vs. 0.12/100,000). Median survival rates of diffuse carcinoma were significantly lower than those of intestinal adenocarcinomas [11].

Evaluation of incidence or histologic types among resettlers from the former Soviet Union and the general population in Germany showed that the ASIR of intestinal gastric cancer decreased over time, whereas the ASIR of diffuse gastric cancer remained unchanged [12].

Risk Factors

Environmental Factors

Helicobacter pylori

Helicobacter pylory is a Gram-negative bacterium that colonizes the gastric mucosa. In 1994, the International Agency for Research on Cancer (IARC) categorized *H. pylori* as a Group 1 carcinogen for gastric cancer [13]. *H. pylory* infection is a risk factor for both intestinal and diffuse gastric cancer types [14]. However, in contrast to intestinal-type gastric cancers, diffuse-type gastric cancers have no clearly defined precancerous lesion [15].

Ford et al. (2016) found limited and moderate-quality evidence that searching for and eradicating *H. pylori* reduces the incidence of gastric cancer in healthy asymptomatic infected Asian individuals [16].

There is a risk of developing gastric cancer of both the intestinal and diffuse types even after the eradication of *H. pylori* infection and cessation of gastric inflammation. One survey showed that during follow-up, gastric cancer developed in 28 of 1674 patients up to as much as 13.7 years following the cure of *H. pylori* infection. The risk of developing gastric cancer was 0.30% per year. Histologically, 16 gastric cancers were of the intestinal type and 12 the diffuse type; the risk of each cancer type was 0.17% and 0.13% per year, respectively [17].

Smoking

Smoking causes stomach cancers. Multiple studies in regions with high levels of stomach cancer have shown a small, but significant, increased risk for stomach cancer among smokers [18].

Dietary Habits and Nitroso Compounds

N-nitroso compounds (compounds containing an NO group) are recognized as important dietary carcinogens. N-nitroso compounds are generated following the ingestion of nitrates. Dietary nitrate intake is determined by the type of vegetable consumed, the levels of nitrate in the vegetables (including the nitrate content of fertilizer), the amount of vegetables consumed, and the level of nitrate in the water supply. Diets with high exposure to N-nitroso compounds such as processed meat, smoked and cured fish, and beer have been associated with an increased risk of gastric carcinoma [19]. The IARC reviewed the evidence supporting the linkage between a high intake of processed meat and a variety of cancer sites and concluded that there was a positive association between the consumption of processed meat and stomach cancer [20].

The consumption of total fruit and white vegetables was inversely associated with gastric cancer risk [21]. The protection afforded by vegetables and fruits is most likely related to the presence of dietary nitrosation inhibitors, including vitamin C, which reduce the formation of carcinogenic N-nitroso compounds inside the stomach [22].

Dietary fiber may reduce the risk of gastric cancer, and the association was similar for diffuse-type gastric cancer (OR 0.62, 95% CI 0.42–0.92) and intestinal-type gastric cancer (OR 0.63, 95% CI 0.45–0.89) [23].

Positive associations exist between salt and high-salt foods and gastric cancer risk [21]. The declining incidence of gastric cancer worldwide in recent decades has been attributed in part to the spread of refrigeration [24]. Furthermore, a strong effect of alcohol consumption, particularly beer and liquor but not wine, on gastric cancer risk was observed compared with nondrinkers [21].

Obesity

A meta-analysis showed that excess body weight (body mass index ≥ 25 kg/m^2) was associated with an increased risk of gastric cancer (OR = 1.22, 95% CI = 1.06–1.41) [25]. Specifically, a stratified analysis showed that excess body weight was associated with an increased risk of cardia gastric cancer (OR = 1.55, 95% CI = 1.31–1.84) and gastric cancer among non-Asians (OR = 1.24, 95% CI = 1.14–1.36) [25].

Epstein–Barr Virus

EBV-associated gastric carcinoma is one of the four subtypes of gastric carcinoma, as defined by the novel classification recently proposed by TCGA [8]. It has been estimated that 10% of gastric cancers worldwide are associated with EBV [26].

EBV-associated gastric cancers have male predominance, preferential proximal location, lymphocytic infiltration, less advanced pathologic stage, a diffuse type of histology in most series, and better prognosis [27, 28].

Host Factors

Blood Group

An increased risk of gastric cancer among individuals with blood group A has been identified (incidence ratio = 1.20, 95% CI:1.02–1.42) [29].

CDH1 Gene

Germline pathogenic variants of the *CDH1* gene, which encodes E-cadherin, constitute the genetic causal event of hereditary diffuse gastric cancer (HDGC) [30]. There is evidence that not only germline mutations but also epigenetic changes (e.g., gene promoter hypermethylation) in *CDH1* are associated with the development of gastric cancer, particularly of the diffuse type [31].

HDGC is an inherited form of diffuse-type gastric cancer determined by germline truncating mutations in the *CDH1* gene. Individuals with HDGC face a lifetime cumulative risk of gastric cancer of 70% in men and 56% in women [32].

A model of early development of diffuse gastric cancer in *CDH1* mutation carriers has been proposed, encompassing precursor (intraepithelial) lesions (in situ carcinoma and pagetoid spread of signet ring cells), early intramucosal carcinoma, and advanced cancer [33].

Differences Between Intestinal and Diffuse Subtypes

During data review of the epidemiology of gastric cancer, a range of classic information appears almost constantly: the worldwide incidence varies widely, with developed Western countries tending to have lower incidence; Asian countries have the highest incidence in the world; and, more importantly, gastric cancer incidence and mortality are decreasing due to the reduction of cases of the intestinal subtype [1].

The decrease in the intestinal subtype is usually explained using historical arguments: (a) improvements in food conservation as a consequence of the widespread availability of refrigerators and reduced use of salted food and (b) a decrease in *H. pylori* infection rates caused by improved sanitary conditions and widespread use of antibiotics [21, 24].

These explanations are widely accepted by the scientific community and seem to account for the reduction of intestinal-type incidence and the stable incidence of the diffuse type, which is attributed less to environmental factors and more to genetic factors [30, 31].

Nevertheless, infection with *H. pylori*, recognized by WHO as the strongest known risk factor for gastric cancer, is associated with the development not only of the intestinal type but also of diffuse-type adenocarcinomas [13]. At the same time, some attempts to prove the impact of changes in dietary habits that modify diffuse-type gastric cancer incidence fail to demonstrate significant evidence. In addition, sequential histopathological changes related to the development of diffuse-type gastric cancer remain poorly defined [15].

Taking into consideration that the prevalence of *H. pylori* has been declining in highly industrialized countries of the Western world [34] due to urbanization, sanitation, access to clean water, and improved socioeconomic status, the obvious

expected consequence should be a reduction in both the intestinal and diffuse types of gastric cancer.

Based on these data, it is recognized that the reduction in the incidence of gastric cancer is predominantly due to the intestinal subtype. Some differences between the two subtypes is still under investigation, and these differences will be discussed in the following sections.

Age of Occurrence

It is widely known that the diffuse-type gastric cancer seems to occur earlier than the intestinal type [11]. Since it takes many years from *H. pylori* infection to gastric cancer onset, the required time for diffuse-type carcinogenesis should be shorter than that for the occurrence of the intestinal type (a "genetic factor"), and treatment of *H. pylori*, usually prescribed to adult patients, might be irrelevant to diffuse-type tumors, since the necessary molecular steps were already achieved before bacteria eradication. However, the incidence of infection in children has been shown to significantly decrease [34], so the load of the diffuse type could be influenced by this reduction.

Location of Tumors

Intestinal-type gastric cancers are more frequent in the distal stomach, while the diffuse type predominates in proximal regions [11]. Distal tumors incidence decreased and this contributed to reduction of intestinal type cancers, but since distal tumors are not exclusively from the intestinal type, at least a modest decrease in diffuse tumors should be expected.

H. pylori *Infection*

H. pylori infection predominates in the antrum (distal stomach), so a reduction in *H. pylori* infection could explain the reduction of cancer in this part of the stomach. Nevertheless, the carcinogenic pathway attributed to this bacterium is based on corpus infection leading to atrophy, reduced acid secretion, increasing pH, and the subsequent events of carcinogenesis [35].

This mechanism of corpus atrophy, eventually followed by metaplasia, dysplasia, and cancer, as proposed by Correa [35], is thought to partially explain the role of *H. pylori* infection in intestinal-type cancers, but many gaps remain to be filled in our knowledge of diffuse-type carcinogenesis related to *H. pylori* infection.

Reducing microenvironmental acidity is recognized as an important factor favoring gastric carcinogenesis and can be a consequence of both secondary to infection atrophy and medical inhibition of acidity, as largely practiced around the world [36].

The role of reduced acidity via medical therapy in gastric cancer risk remains unproved since pH modification, without additional carcinogenic events, appears to be insufficient to cause cancer [37]. Linking these data to massive *H. pylori* treatment and abusive utilization of proton pump inhibition, a remarkable consequence is a drastic modification in the gastric microenvironment, including the microbiome, which could play a role in the epidemiology of diffuse gastric cancer.

Stomach Microbiome

Before the discovery in 1983 of the occurrence and understanding of the details of *H. pylori* infection pathology, the stomach was thought to be sterile. In 2015, mainly due to new-generation sequencing technologies, a wide variety of microorganisms were discovered to be present in the human stomach; collectively the microorganisms have come to be known as the human gastric microbiota. Increasing evidence supports the hypothesis that, although *H. pylori* may be the most relevant, it is not the only local bacterial culprit leading to gastric diseases [38]. The importance of the gastric microbiome on cancer incidence and even on benign diseases is still under investigation.

Interfering with the Diffuse-Type Gastric Cancer Burden

Many attempts to control the cancer burden have been proposed. For gastric cancer, the treatment of *H. pylori* infection, avoiding salted food, and monitoring patients at risk (relatives of gastric cancer patients, patients with intestinal metaplasia and hereditary cancer syndromes) are the most common measures. Except for HDGC syndrome related to *CDH1* mutations, in which cases prophylactic gastrectomy is recommended, none of the preventive strategies seem to work on diffuse-type tumors since the incidence of these tumors has remained stable [39, 40].

The expected reduction of diffuse-type incidence due to *H. pylori* infection control did not occur, as discussed earlier. Changes in alimentary habits also failed to have an effect, and there are no preneoplastic lesions for diffuse-type cancers, as is the case for metaplasia for the intestinal type.

Diffuse gastric cancer has distinct characteristics of the intestinal subtype. Its incidence remains relatively stable. Further investigation is necessary to elucidate the carcinogenesis and the environmental risk factors that contribute to its development.

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