



ONCOLOGY

Changing trends in the epidemiology of gastric cancer

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Abstract

Currently being the seventh most prevalent form of cancer worldwide, and the fifth most common cause of cancer-related death, based on GLOBOCAN 2020 data, gastric cancer is still an important public health problem, despite its dropping incidence. Regions around the world are still at high-risk, mostly in populations with a high prevalence of *Helicobacter pylori* infection or a carcinogenic favorable diet. Gastric cardia cancer incidence is on the rise in some areas. Great steps were made in the last decades in understanding the pathogenesis of gastric cancer and its risk factors. Host genetic polymorphisms play a quintessential role in disease outcome. *Helicobacter pylori* eradication and endoscopic surveillance are the most effective options to further decrease gastric cancer incidence. Surgery is required for a curative treatment in most cases.

This review summarizes the latest worldwide epidemiological data of gastric cancer and aims to provide an accessible and credible source of evidence for physicians who assess risk factors for gastric cancer.

Keywords: epidemiology, prevalence, mortality, gastric cancer

Introduction

Gastric cancer (GC) is the 7th most common type of cancer worldwide, approximately 1.9 million patients being currently diagnosed with this disease, 3.6% of all cancer diagnoses, and the 4th most common cause of cancer deaths globally. A total of 1,089,103 new cases of GC were reported in 2020 (Table I) [1].

The stomach is the most dilated part of the digestive system and it is composed by 4 main parts: cardia, fundus, body and the pylorus. Its primary functions are the temporary storage of food and the initiation of food digestion [2]. The gastric mucosa is primarily formed of parietal cells, chief cells, mucus cells and neuroendocrine cells [3]. The gastric mucosal turnover is a dynamic process, defined by continuous cell proliferation which

is counterbalanced by apoptosis. The cell's turnover times vary from 3 to 60 days [4]. Having this high turnover rate, the gastric epithelial cells are prone to mutations because they are rapidly dividing. Both environmental and genetic factors influence the cancer development process.

Although GC was the leading cause of cancer deaths until the mid 1990s, its mortality and incidence have considerably declined around the world. Many reasons were linked to this decline including the introduction of commercially available refrigeration which by itself reduced other factors that influence the development of GC including the consumption of smoked and salted preserved foods and increasing the consumption of fresh fruits and vegetables, a greater use of antibiotics which reduced the *Helicobacter pylori*

DOI: 10.15386/mpr-2538

Manuscript received: 10.05.2022

Accepted: 29.05.2022

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(HP) infection, and a drop in smoking incidence in the western countries [5]. HP is considered the most important factor in the development of GC, but the GC pathogenesis cannot be induced by HP infection alone, because only 2-5% of people with this infection develop GC [6].

World Health Organization guidelines of GC include the following subtypes, adenocarcinoma, signet ring-cell carcinoma and undifferentiated carcinoma.

The more commonly used classification of GC is based on Lauren’s histo-clinical classification, which include the intestinal type, diffuse and mixed. More commonly found is the intestinal type, named because of the similar etiopathogenesis with the other digestive tract adenocarcinomas. It is more frequently seen in high-risk areas, males and older patients. The less common type is the diffuse type, defined by the loss of intracellular adhesions, which leads to a lack of glandular structures. It is more common in younger patients and has a worse prognosis [7-8]. The worldwide decline of the GC overall was counterbalanced by a rise in the incidence of cancer of the gastric cardia [8].

Epidemiology

Approximately one million patients are diagnosed with GC each year around the globe. GC is the 7th most commonly prevalent cancer and the 6th most commonly diagnosed in the world [1]. Countries with the highest incidence rates (>15 new cases /100000 patients) include Mongolia, Japan, Republic of Korea, Tajikistan, Kyrgyzstan etc (Table II). Higher than average rates countries include Eastern-European countries, Turkey, Mali, Portugal, Peru, Ecuador and Columbia. Lower rates (<5 new cases/100000 patients) are seen in western counties including France, United States, Canada, United Kingdom, Norway, Sweden, Australia and also in Central-African countries, although the latter conclusion can be partially attributed to the lower accessibility to medical care (Table III) [1]. 66% of the new cases of GC diagnosed in 2020 were in men. The men to women ratio was 2:1. No country currently has a higher of GC in women than in men and also no country currently has an increasing trend in incidence [1,9].

The cumulative risk of GC is highest in Eastern Asia (2.64%) and lowest in southern Africa (0.42%) [9].

High-HDI (Human Development Index) countries have a 2 to 3-fold increase in average incidence rates when compared to low and middle HID countries. Families with high-middle income are currently at the highest risk of developing GC, most probably correlated with the western diet [1].

Table I. Worldwide 5-year incidence and prevalence of cancers, both sexes, all ages [1].

Cancer	Incidence (No of cases /5 years)	Prevalence (No of cases /5 years)
Breast	2 261 419	7 790 717
Non-melanoma skin cancer	1 198 073	6 458 885
Colorectum	1 931 590	5 253 335
Prostate	1 414 259	4 956 901
Lung	2 206 771	2 604 791
Thyroid	586 202	1 984 927
Stomach	1 089 103	1 805 968
Cervix uteri	604 127	1 495 211
Liver	905 677	994 539
Oesophagus	604 100	666 388

Table II. Estimated age-standardized highest incidence rates in 2020, both sexes, all ages [1].

Population	Value (per 100.000)
Mongolia	32.5
Japan	31.6
Republic of Korea	27.9
Tajikistan	23.4
China	20.6
Kyrgyzstan	19.7
Cabo Verde	18.4
Bhutan	17.7
Islamic Republic of Iran	17.5
Vietnam	15.5

Table III. Estimated number of prevalent cases in all continents in 2020 [1].

Populations	5-year	Proportions (per 100000)
Asia	1397478	30.1
Europe	213013	28.4
Africa	44194	3.3
Northern America	50387	13.7
Oceania	5389	12.6
Latin America and the Caribbean	95507	14.6

GC is also the 4th most common cause of cancer death worldwide, accounting for 783,793 deaths in 2020 alone [1], out of which 502,788 were in men. Asia had the highest mortality in GC related death (575,206 people), followed by Europe (96,997 people) and Latin America and Caribbean (53,392 people) [1]. The annual percent change (APC) in gastric cancer mortality decreased between 3 to 4 percent in European counties, Korea, Japan and Australia between 1980 to 2005 [10]. In Latin America the APC was lower but still constant: Brazil and Chile (-1.6%); Argentina and Mexico (-2.3%). Currently, the only reported country to have an increasing trend in mortality in men is Thailand (AAPC, 3.92; 95% CI, 2.14-5.74; P = .001) [9].

In the United States, the 5-year survival rate for GC is 31%. Most diagnosed cases are already metastatic, which lowers survival rates. When the diagnosis is made in the pre-metastatic phase, the 5-year survival rate rises to 67% [11]. Asian patients tend to have a better prognosis than Caucasians, having higher survival rates [12]. UK's 5-year survival rates currently stands at 20.8%, while Europe's is slightly higher, at 26% [13].

The 5-year survival rates of gastric cancer according to TNM staging system are mentioned in table IV.

Table IV. 5-year survival rates of GC – TNM staging system [14].

AJCC TNM staging system of GC- 8 th edition	5-year overall survival rates
IA	94.7%
IB	89.9%
IIA	80.7%
IIB	72.5%
IIIA	58.4%
IIIB	40.8%
IIIC	20.2%
IV	8.8%

Risk factors

Risk factors can be further classified as exogenous and endogenous. Due to the fact that the pathogenesis of GC is a multifactorial and multi-step process, there is a considerable interdependence of these risk factors for gastric cancer (Table V).

1. Genetics

The *TP53* gene is currently described as the highest mutated gene in GC, over 50% of cases presenting abnormalities. Its role as a tumor suppressor gene is well-documented [15]. Important pathogenically mutations have also been observed in *KRAS*, *CTNBB1*, *PIK3CA* oncogenes and in *SMAD4*, *APC* tumor suppressor genes.

Somatic copy number alterations (SCNAs) is a major mechanism of activating oncogenes or inactivating tumor suppressor genes and is seen in GC as well. *RTK/RAS/MAPK* signaling, including *HER2*, *EGFR*, *MET*, *FGFR2* *și* *RAS*, is a pathway altered in 30-40% of cases [16,17]. *CCND1*, *CCNE1* *și* *CDK6* are genes that regulate cell-cycle and can be amplified in GC [18].

DNA methylation is another pathogenical factor that can induce genetic alterations. Methylation of *CDHI*, *RUNX3*, *p16*, and *hMLH1* is described in GC [19,20]. It was also confirmed that the way that Epstein-Barr virus induces GC is by DNA methylation [21].

Recent studies described mutations in the *ARID1A* tumor suppressor gene, which encodes SW1/SNF chromatin remodeling complex [22]. *IL-17* and *IL-10* mutations were described in Asian populations.

2. Preexisting conditions

Chronic gastric atrophy and intestinal metaplasia are considered as the most relevant processes in GC pathogenesis. Mucosal atrophy is characterized by the loss of the glandular elements, thus being replaced by areas of metaplasia and areas of fibrosis. Intestinal metaplasia is considered a precancerous condition, with an abundance of goblet and mucosal, similar to those found in the intestinal mucosa. The chronic inflammation induces the transcription factor *NF-κB*, one of the key mediators of inflammation. It also induces oxidative stress, reactive oxygen species and nitrosamines being generated by leukocytes and macrophages [23-26].

Ménétrier disease is a hypertrophic gastropathy, characterized by massive growth of mucous cells in the gastric mucosa. While the cause is currently not well-understood, it is linked with a 10% risk of malignant transformation [27-29].

Gastric stump cancer is defined as a primary GC that arises at a minimum of five years after a partial gastrectomy. The five-year mark was appointed in case an inappropriate initial diagnosis was made. Post-procedural hypochlorhydria causes bacterial overgrowth which leads to the accumulation of nitroso compounds. A 1.66-fold increase of the risk of developing GC compared to general population has been attributed to gastric stump cancer. Clinical and endoscopic surveillance are the best strategies for prevention and early detection [30].

Gastric polyps are most-often incidental findings during upper G.I. tract endoscopy. Histology is required to exclude malignancy. Hyperplastic polyps have malignant potential through a dysplasia/carcinoma sequence and the risk of malignancy is increased in polyps >1cm and pedunculated. An estimate of 8-59% of gastric adenomas occur at the same time with GC. Size, villous contour and degree of dysplasia are associated with the presence of invasive carcinoma [31,32].

Table V. Risk factors – GC.

Exogenous	Endogenous	
HP infection	Preexistent gastric disease	Hereditary factors
Nitroso-compound rich diet	Chronic atrophic gastritis	Family history of GC
Smoking	Ménétrier disease	'A' Blood group
Epstein-Barr virus infection	Gastric ulcer	Lynch Syndrome
Socioeconomic status	Subtotal gastrectomy	
Obesity	Gastric adenomatous polyps	
	Gastroesophageal Reflux Disease	

3. *Helicobacter pylori* infection

In 1995, HP infection was classified by the International Agency for Research on Cancer as a group I carcinogen. Although the causality is certain, there are important interpersonal variation in the course of infection.

The complex interaction between environmental, genetic and bacterial factors suggests an unpredictable evolution [33,34]. The classical carcinogenesis sequence – superficial gastritis, chronic atrophic gastritis, intestinal metaplasia, dysplasia, carcinoma – is pathognomonic for the intestinal type. The diffuse subtype is also linked with GC [35].

Neutrophil migration is triggered by HP. One at the mucosal site, the neutrophils induce the nitric oxide synthase and reactive oxygen species which in turn leads to DNA damage [36]. Severe DNA damage triggers apoptosis, represented as gastric atrophy. It was shown that treating the infection normalizes the rate of apoptosis [36,37].

HP eradication reduces GC risk. A meta-analysis of 27 studies, with 48,606 HP positive patients, of which 715 developed GC, has shown that patients that were cured of HP infection had lower incidence of GC [38-40]. Gastric cancer prevention can be achieved by H. pylori screen-and-treat strategies with selection of the most effective timing for intervention [40]. No consensus has yet been reached regarding the population screening. Some guidelines suggest that it may be beneficial in populations that have an increased risk.

4. Diet

Excess salt was proven to have a direct carcinogenic effect in GC. There is also synergistic effect of salt consumption and HP infection in GC patients. The decline in GC incidence is attributed to the changes made in food preservation in the last 50 years, commercially available refrigeration replacing salt as the main preserving method [41-44].

Nitrates are chemical compounds which contain the -NO group and are not only taken from diet and smoking, but also endogenous sources. Processed meats and dairy products are rich in nitrates. Once absorbed in the stomach, the nitrates react with amines, amides or aminoacids to form N-Nitro compounds. High gastric N-Nitro levels were associated with the presence of advanced premalignant lesions. Processed meat was classified in 2015 by the World Health Organization as a group I carcinogen [43,45-47].

Multiple studies have showed the association between smoking and GC. A meta-analysis showed a 1.53-fold increased risk of GC in smokers compared to non-smokers. The European EPIC study showed a similar risk, which decreases after 10 years of quitting. Currently, approximately 18% of GC cases are linked with smoking [48].

Non-steroidal anti-inflammatory drugs were proven to decrease the risk of GC. The effect is even more favorable in HP positive patients [49,50].

Conclusions

Although a significant decrease in GC incidence, prevalence and mortality in GC patients was seen in the last thirty years, gastric cancer still remains an important public health problem. This process is the final consequence of a complex interaction between environmental, hereditary and host factors.

HP infection and the western diet are important risk factors, especially for non-cardia cancers, that are difficult to control at a global scale. Smoking is also important in carcinogenesis. Host genetic polymorphisms are quintessential in the pathogenic process.

Management of HP infection should be prioritized in every patient with a positive test. Endoscopic surveillance in patients with chronic atrophic gastritis and intestinal metaplasia would increase survival of patients if early gastric cancer is discovered. Structuring a genetic carcinogenic sequence may be the key to discovering a gene therapy.

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