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REVIEW ARTICLE

Epidemiology of Gastric Cancer: Global Trends, Risk Factors and Premalignant Conditions

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Abstract

This review article aims to provide a comprehensive overview of recent epidemiology, pathogenesis, risk factors, and premalignant conditions of gastric cancer. Worldwide, gastric cancer is one of the most common and most fatal cancers. The incidence and mortality remain high in regions such as East Asia and Eastern Europe. Although there is a lower incidence in the United States, it remains a deadly disease. Age, gender, and race are non-modifiable demographic risk factors for developing gastric cancer. There have been several dietary and lifestyle risk factors such as salt preserved foods, N-nitroso compounds containing foods, tobacco smoke, alcohol use, and obesity that have been shown to contribute to the development of gastric cancer. Infections have additionally been shown to have a clear role in the pathogenesis of gastric cancer as *Helicobacter pylori* eradication has shown a significant reduction in the incidence of gastric cancer as well as other pathogens such as Epstein−Barr virus. There are certain premalignant lesions that increase the risk of developing gastric cancer. These include atrophic gastritis, and intestinal metaplasia amongst others.

Keywords: Gastric cancer epidemiology, Gastric cancer demographics, Gastric cancer etiology, Gastric cancer risk factors, *Helicobacter pylori*, N-nitroso compounds, Intestinal metaplasia, Atrophic gastritis, Hereditary diffuse gastric cancer, Ménétrier's disease

1. Epidemiology

Gastric cancer (GC), is currently the fifth most common cancer diagnosed worldwide and the fourth most frequent cause of cancer-related mortality. Adenocarcinomas are the most common type of gastric cancers. Our review focuses on adenocarcinomas, and does not pertain to other gastric cancers such as mucosa-associated lymphoid tissue (MALT) lymphomas, gastrointestinal stromal tumors (GIST), and neuroendocrine tumors, unless otherwise specified. More than one million cases of GC and approximately 769,000 deaths were recorded globally in 2020; this represented a slight downward trend compared to 2018 data which included approximately 783,000 deaths.[1,2] The Global Cancer Observatory (GLOBOCAN) database coordinated by the International Agency for Research on Cancer (IARC) of the World Health Organization (WHO) reports cancer statistics worldwide. According to most recent GLOBOCAN data from 2020, the estimated incidence of new-onset GC was 5.6 per 100,000 with an associated mortality of 7.7 per 100,000.[3] According to the GLOBOCAN database GC is listed as the sixth most common cancer occurrence and the second most common cause of cancer-associated mortality followed by lung cancer. The overall incidence of GC was two-fold higher in males compared to females, although its incidence varied by geographic area. Eastern Asia (EA) and Eastern Europe (EE) exhibited the highest age-standardized incidence rates (ASIRs) of GC, at 32.5

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per 100,000 males and 13.2 per 100,000 females, and 17.4 per 100,000 males and 7.1 per 100,000 in females in EA and EE respectively. The ASIRs of GC in North America were 5.4 per 100,000 males and 3.1 per 100,000 females; these values were estimated at approximately 4.7 per 100,000 males and 3.5 per 100,000 females in Africa.[1] In 2012, Korea, Mongolia, Japan, and China (all in EA) reported the largest number of GC cases.[4] In 2020, the ASIRs trend for GC increased for males in Japan and females in Mongolia. According to the US National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER), stomach cancer is the fifteenth most common cancer in the United States and has a 5-year relative survival rate of 33.3%.[5]

2. Demographics

Age, gender, and race are non-modifiable demographic risk factors for developing GC. The American Cancer Society estimates that in the United States in 2023, 15,930 men and 10,570 women will be diagnosed with GC and 6690 men and 4440 women are expected to die of GC.[6] Globally, GC is much more prevalent in men as rates are 2-fold higher in men than in women particularly in several South-Central Asian countries, where GC is the leading cause of cancer related death in men.[1]

In previous years, the incidence of GC was reported to increase with age, with higher rates reported in groups with a mean age of 75 years. More recently, a higher incidence has been reported among younger adults with a median age of 40 years at the time of diagnosis.[7-9] The underlying cause of this trend has not been identified yet, but it is thought that it may be related to lifestyle changes in youth, more specifically the intake of high salt diet and prevalence of obesity in America.

3. Risk factors

3.1. Dietary and lifestyle factors

Salt and salt-preserved foods are known causes of GC. A Japanese prospective study showed a higher incidence of GC in the population that consumed >16 g of salt per day.[10] A meta-analysis confirmed the direct association between the incidence of GC and dietary salt intake; this relationship was particularly strong in the Japanese population.[11] In another meta-analysis the risk of developing GC increased by 12% with each additional 5 g of dietary salt per day.[12]

Foods that contain N-nitroso compounds (NNC) such as cured meat and preserved vegetables have been associated with an increased risk of GC. Literature dating back to the 1990s included information on the role of NNC in the development of precancerous gastric lesions.[13] A prospective study published in 2013 showed a positive association between the intake of NNC containing foods and the risk of developing gastric non-cardia adenocarcinoma in men (Hazard Ratio [HR] 1.06; 95% CI: 1.01−1.10; P-trend = 0.09) while no positive associations were identified in women in the setting of low level NNC exposure.[14] Similarly, a 45% increase in the risk of developing GC with the increased consumption of red meat (relative risk (RR) = 1.45, 95% confidence interval (CI) = 1.22−1.73) were obtained from a meta-analysis published by Zhu et al.[15]

In the meta-analysis published by Larsson et al. no clear link between GC and low dietary intake of folate were identified.[16] However, the authors reported an increased risk of developing GC among individuals with the methylenetetrahydrofolate reductase (MTHFR) 677 TT genotype. Low folate levels have been associated with increased serosal invasion in patients already diagnosed with this disease and this subject warrants further study.[16,17] Low levels of cobalamin have also been associated with an increased risk of developing GC; this has been attributed to its decreased absorption secondary to atrophic gastritis which frequently precedes GC.[18]

Numerous studies have reported the association of smoking with an increased risk of gastric GC. The release and intake of carcinogens via smoking may promote dysplastic changes in the gastric mucosa. The results of a meta-analysis revealed that the RR of developing GC increased from 1.3 to 1.7 in individuals with a smoking history of 30 cigarettes per day.[19] The results of this study also showed that smoking was associated with both cardia (RR: 1.87; 95% CI: 1.31−2.67; I^2 73.2%; n = 9 studies) and non-cardia GC (RR: 1.60; 95% CI: 1.41−1.80; I^2 18.9%; n = 9 studies). Another multicenter cohort study reported the association of smoking with an increased risk of developing GC. However, in contrast to the previous meta-analysis, the results of this study showed an increased risk of cardia versus non-cardia GC.[20] Similarly, the study by Praud et al. demonstrated that the risk of developing GC increased by 32% among those with a history of 20 cigarettes per day and by 35% among those who smoked 40 cigarettes per day compared with non-smokers.[21] Furthermore, a smoking history of >40 cigarettes per day was associated with an increased risk of developing cardia as opposed to non-cardia GC.

While alcohol use has also been identified as a risk factor associated with the development of GC,

this association varied with geographic distribution. A pooled analysis published in 2017 that included GC cases reported in Europe, Asia, and North America demonstrated that individuals who consumed >4 and > 6 alcoholic drinks developed GC with odds ratios (ORs) of 1.26 and 1.48, respectively, compared with non-drinkers.[22] Another study that was published in 2018 that prospectively analyzed members of the US population reported no increased risk of GC when comparing alcoholics versus non-alcoholics.[23]

Obesity has been implicated as a risk factor for developing GC. Results from a meta-analysis showed an increased risk of developing GC among the patients categorized as obese (body mass index (BMI) > 30 kg/m^2). While there was no significant overall increase in the risk of developing GC for those categorized as overweight (BMI 25–30 kg/m^2), it was associated with an increased risk of cardia GC. Obesity among non-Asians and males was associated with an increased risk of developing GC, with an increased risk specifically with cardia as opposed to non-cardia GC.[24,25]

3.2. Infections

Helicobacter pylori (Hp) is a gram-negative bacterium that has a known impact on intestinal-type GC. The pathophysiology is believed to encompass an immune-mediated reaction in the gastric mucosal cells. While the prevalence of Hp infection varies with geographic region, the association between Hp infection and the incidence of GC is particularly evident in Asian countries, including Korea and Japan. A prospective study conducted in Japan demonstrated a direct association between the risk of developing GC and Hp infection along with significant reduction in the incidence of GC following eradication of Hp.[26] In this study, 36 of 1246 (2.9%) of the patients infected with Hp developed GC, compared to none (0%) in the uninfected group ($p < 0.001$). The results of numerous randomized studies and meta-analyses confirmed this finding.[27,28] Results from a meta-analysis published in 2020 revealed that eradication of Hp not only reduced the incidence of GC (RR: 0.54; 95% CI: 0.40–0.72; Number-Needed-to-Treat [NNT]: 72), but also reduced mortality associated with this disease (RR: 0.61; 95% CI: 0.40–0.92; NNT: 135).[29]

Epstein–Barr virus (EBV) is a double-stranded DNA virus and has been implicated in multiple malignancies, including nasopharyngeal carcinoma, Burkitt lymphoma, Hodgkin's and non-Hodgkin's lymphoma. A 1991 study demonstrated that this pathogen could be detected in 16% of patients diagnosed with GC in a predominantly American population.[30] A Korean study conducted in 1996 revealed EBV in 13% of the patients diagnosed with GC.[31] The mechanism underlying EBV-mediated induction of GC is multifactorial and appears to be the result of the upregulation of genes with pro-tumor and anti-apoptotic activity. A systematic review and meta-analysis published in 2020 considered the association of EBV with GC. Two separate analyses were performed in this study that included data from case–control studies with matched and non-matched pairs designed to calculate the pooled estimates of the ORs. Among the 20,361 GC patients who were included in this study, the prevalence of EBV was determined at 8.77% (95% CI: 7.73–9.92%; $I^2 = 83.2\%$). The prevalence of EBV-positive GC was significantly higher among males compared to females (10.83% vs 5.72%).[32]

3.3. Genetic factors

Hereditary GC contributes approximately 1–3% of total cases of GC. Hereditary diffuse gastric cancer (HDGC), Peutz-Jeghers Syndrome (PJS), juvenile polyposis syndrome (JPS), Lynch syndrome, familial adenomatous polyposis (FAP), gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS), Li-Fraumeni syndrome, and familial gastric cancer are all genetic disorders that have been associated with the development of GC. Among these disorders, HDGC is the one that is detected most frequently.[33] HDGC is an autosomal dominant disorder characterized by a germline mutation in the gene encoding epithelial cadherin known as CDH1. Mutations in CTNNA1, which is the gene encoding alpha-1 catenin, have also been detected in patients with HDGC.[34] HDGC typically develops at a younger age and is characterized by diffuse signet ring cells. The updated International Gastric Cancer Linkage Consortium (IGCLC) criteria in 2020 recommends CDH1 testing for individuals fulfilling criteria for HDGC genetic testing.[34] If CDH1 mutation is not detected, CTNNA1 analysis should be considered. Genetic counseling, endoscopic surveillance, and prophylactic gastrectomy along with mastectomy to prevent lobular breast cancer are among the recommendations for patients at risk for developing HDGC.[35]

4. Premalignant conditions

4.1. Chronic atrophic gastritis

Chronic atrophic gastritis is caused by chronic inflammation triggering thinning of the gastric

mucosa due to the rate of cell loss exceeding the rate of cell turnover. The loss of glandular cells ensues a decrease in gastric secretions and function. This leads to achlorhydria and ultimately the development of GC.[36] Not only is there evidence that atrophic gastritis increases the risk for GC, but also the extent of gastric mucosal involvement has correlated with an increased risk in a positive linear relationship.[37,38]

Broadly there are 2 types of atrophic gastritis. There is the environmental type which is typically found in the gastric body and predominantly caused by Hp infection. The other is the autoimmune type found in the gastric body and fundus and caused by antibodies against parietal cells and intrinsic factor.[39] Autoimmune atrophic gastritis is associated with pernicious anemia and although it has an increased risk of GC, the risk is not as high as the environmental type. The overall prevalence of atrophic gastritis in Hp infected individuals was found to be >80% compared to 9.8% among uninfected individuals in a large Japanese multicenter study. Additionally, there has been an increase in atrophic gastritis from 9.4% to >70% when comparing patients less than 20 years of age to those greater than 60 years of age, respectively.[40] Certain Hp virulence factors increase the risk of GC development. The presence of a chromosomal region known as the Cag pathogenicity island has been associated with a higher incidence of GC. This produces cytotoxin associated gene A (CagA) which produces an exaggerated inflammatory response.[41] Furthermore, environmental factors such as high-salt diet, processed meats and tobacco smoking also increase the risk for GC development from Hp.[42]

4.2. Intestinal metaplasia and dysplasia

Intestinal metaplasia (IM) is characterized as replacement of the gastric epithelium by mucosa that resembles intestinal epithelium. It represents the subsequent step of GC progression from atrophic gastritis. As the low pH environment further escalates the barrier defect, gastric stem cells grow into cells more common in the small bowel such as absorptive cells, goblet cells and Paneth cells. Using the Filipe classification, IM is classified into the complete and incomplete groups. Type I (complete) contains small intestinal mucosa with goblet cells that secrete sialomucins, a brush border, and eosinophilic enterocytes. Types II and III (incomplete) types are described by the presence of colonic type epithelium with irregular mucin droplets of variable size in the cytoplasm and absence of brush border. Type II contains a mixture of gastric mucins and intestinal sialomucins whereas Type III expresses sulfomucins.[43,44] The presence of IM has shown to have a ten-fold increase in risk for GC with type II and an even greater risk with Type III.[44] However, it may be that the increased risk of GC is more closely linked to the location and degree of metaplasia in the stomach rather than the subtype.[45] IM can progress to low-grade or high-grade dysplasia. It has been shown that low-grade dysplasia may regress in over 60% of cases whereas it progressed in less than 20% of cases.[46] Once progressed to high-grade dysplasia the lesion rarely regresses. High-grade dysplasia is associated with a forty-fold increased risk of GC and an annual incidence of GC of 6% in 5 years compared to 0.6% in mild-moderate dysplasia.[47]

4.3. Gastric polyps

Some gastric polyps are considered premalignant lesions; however, most have low neoplastic potential. Fundic gland polyps, hyperplastic polyps, and inflammatory polyps are typically benign, however, adenomatous polyps have a high rate of malignant conversion. Fundic gland polyps are common in patients with familial adenomatous polyposis (FAP). It is difficult to distinguish the difference between FAP and sporadic fundic gland polyps, however, FAP polyps are typically seen throughout the stomach.[48] Although hyperplastic polyps have low malignant transformation, there is increased risk of cancer elsewhere in the stomach if it is associated with chronic gastritis. If associated with Hp, once Hp is effectively treated 80% of hyperplastic polyps regress.[49] If an adenomatous polyp is identified or there are signs of dysplasia, polypectomy should be performed.[50] Hamartomatous polyps associated with PJS, JPS, and Cowden syndrome carry increased risk of GC and require further investigation.[50]

4.4. Peptic ulcer disease

The association between peptic ulcer disease (PUD) and GC has been well established. A large cohort study from a Swedish population found that patients with gastric ulcers have a nearly ten-fold increased risk of developing GC when compared to the general population.[51] Interestingly, these findings were limited to gastric ulcers as the association with GC was not found in duodenal ulcers. Similar findings have been demonstrated in broader populations in more recent studies.[52] The mechanism of GC development in gastric ulcers remains unclear, but it is thought to be explained by the similarities

in etiology, specifically *H. pylori* and the cascade of chronic inflammation.[53]

4.5. Previous gastrectomy

GC is also reported at the site of anastomosis (after resection of gastric cancer and gastrectomy performed for benign conditions). Cancer development could be explained by hypochlorhydria leading to bacterial overgrowth or due to the effects of increased exposure of the alkaline bile and pancreatic enzymes.[54,55] In partial gastrectomy for benign conditions, studies have shown that there is not an increased risk in the early years after surgery, but there has been an increased risk after 20 years or more.[56] Over the last several decades, the need for elective surgery for peptic ulcer disease has significantly declined given the appropriate treatment of *H. pylori*, development of efficacious antisecretory agents, and development of endoscopic treatments.[57] More recent studies focussed on gastrectomy in bariatric surgery have re-demonstrated that there is no increased risk of GC in the early years after surgery.[58] However, future studies will have to revisit the increased risk in the long term.

4.6. Ménétrier's disease

Ménétrier's disease is another condition that carries a substantial risk of GC.[59] In a case–control study from 2021, GC developed in GC developed in 8.9% of patients with Ménétrier's disease vs 3.7% of controls in a 10-year period ($P = 0.09$).[60] However, due to low incidence of the condition the pathogenesis of this association remains unclear.

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