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Review

Gastric Cancer Epidemiology: Current Trend and Future Direction

Chidozie Declan Iwu [1,*] and Chinwe Juliana Iwu-Jaja [2]

[1] School of Health Systems and Public Health, Faculty of Health Sciences, University of Pretoria, Pretoria 0001, South Africa
[2] Department of Global Health, Stellenbosch University, Stellenbosch 7602, South Africa
* Correspondence: chidoziedelan@gmail.com

Abstract: Gastric cancer (GC) is a significant global public health problem. It is the third leading cause of cancer-related mortality despite its decline in incidence since the past five decades. The incidence of GC varies between regions, and this heterogeneity is attributed to multi-factors, including infectious, environmental, and genetic traits. Most of the GC cases are linked to *Helicobacter pylori* (*H. pylori*) infection. Understanding the etiology, epidemiology, and risk factors of GC is necessary for the prevention and targeted treatment of the disease. In this study, we synthesized published studies, including data from the "International Agency for Research on Cancer GLOBOCAN" to narratively provide an updated overview of the recent global trends, etiology, known risk factors, pathogenesis, hallmarks, treatment, and prevention of GC. One area that significantly advanced GC research was understanding the mechanisms by which *H. pylori* colonizes humans and mediates physiological, microbiological, immune, and histologic features of the gut. However, there are still gaps present in understanding the molecular mechanisms underlying the initiation and progression of GC.

Keywords: gastric cancer; epidemiology; *Helicobacter pylori*; risk factors; treatment; genetics

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1. Introduction

Gastric cancer (GC) is a prevalent disease that has remained one of the leading causes of cancer-related deaths globally. It was reported as the 5th most common cancer and the 4th leading cause of cancer death worldwide in 2020 [1]. Despite some progress been made in field of cancer treatments, the survival rate for gastric cancer patients remains low, highlighting the need for primary and secondary prevention strategies [2]. In most parts of the world, the incidence and mortality of GC have been on a gradual decline, particularly in developed countries [2]. However, recent studies have indicated a concerning trend of increasing incidence rates in younger adults (<50 years) [3].

The incidence of GC exhibits significant geographical variation, with over 50% of new cases emerging in developing countries. The risk of developing gastric cancer varies greatly, with a 15–20-fold difference between the highest and lowest-risk populations. The regions with the highest risk include East Asia (China and Japan), Eastern Europe, and Central and South America. Conversely, the regions with a lower risk include Southern Asia, North and East Africa, North America, Australia, and New Zealand [4].

GC is characterized by two main subsites, non-cardia and cardia [5]. Non-cardia GC refers to tumors that develop in the main part of the stomach, which is the region excluding the cardia region. The stomach, positioned in the digestive tract between the esophagus and small intestine, play a vital role in food digestion by producing enzymes, gastric acid, and intrinsic factors necessary for vitamin B12 absorption. Its inner lining consists of a mucous membrane composed of columnar epithelial cells and glands, which are susceptible to inflammation leading to gastritis, peptic ulcers, and potentially gastric cancer [6]. On the other hand, cardia GC specifically denotes cancer occurring in the cardia region, which is the top portion of the stomach where it joins the esophagus or food pipe. The term "cardia"

is derived from its proximity to the heart. [7]. Both non-cardia and cardia gastric cancers have overlapping risk factors, such as smoking, heavy alcohol consumption, and foods preserved by salting. However, these two subsites have distinct etiologies. Cardia GC is associated with gastroesophageal reflux and obesity, while non-cardia cancer is mostly attributable to *Helicobacter pylori* (*H. pylori*) infection [8]. As such, understanding the current epidemiology of GC is crucial in developing appropriate cancer control measures.

Given the strong link between GC and its modifiable risk factors, the disease is significantly preventable. This paper, therefore, presents a recent and comprehensive overview of GC, underscoring the need for continued research and prevention strategies to curb the incidence and mortality rates of the disease.

2. Materials and Methods

This study adopts an extensive narrative review approach, utilizing web search engines, snowballing, and examination of relevant reports to present an updated and comprehensive overview of the recent global trends, etiology, known risk factors, pathogenesis, hallmarks, treatments, and prevention of GC. To retrieve the relevant information, electronic databases, including Medline, PubMed, Web of Science, Scopus, and Google Scholar were searched using the following search terms: "gastric cancer", "stomach neoplasms", "etiology of gastric cancer", "risk factors for gastric cancer", "pathogenesis of gastric cancer", "molecular mechanisms of gastric cancer", "hallmarks of gastric cancer", "gastric cancer treatment options", "prevention of gastric cancer", "prognosis of gastric cancer", "gastric cancer epidemiology", "early detection of gastric cancer", "surgical treatment for gastric cancer", "chemotherapy for gastric cancer", "immunotherapy for gastric cancer", "targeted therapy for gastric cancer", "gastric cancer screening methods", "*Helicobacter pylori* and gastric cancer", "dietary factors and gastric cancer", and "genetic predisposition to gastric cancer". We included studies and reports that offered insights into the recent global trends, etiology, risk factors, pathogenesis, hallmarks, treatment options, prevention strategies, prognosis, epidemiology, and early detection methods for GC. These studies had to be conducted on human subjects including males and females across different age groups, available in English language, and published in peer-reviewed journals, reputable organization reports, and relevant conference proceedings. We excluded studies that were not directly related to GC, studies conducted on animal models or in vitro settings, studies not available in English, studies lacking sufficient data or methodological rigor, and studies published in non-peer-reviewed sources or sources of questionable credibility.

Data on the most recently estimated age-standardized global incidence rates and mortality rates of GC were obtained from the Global Cancer Observatory (GCO) [9]. The GCO is an interactive web-based platform that was specifically designed to provide global cancer statistics and support cancer control and research efforts. It primarily utilizes data from the International Agency for Research on Cancer's (IARC) Cancer Surveillance Branch (CSU), including key sources such as GLOBOCAN, Cancer Incidence in Five Continents (CI5), International Incidence of Childhood Cancer (IICC), and various cancer survival benchmarking projects, like SurvCan and SURVMARK. The GCO's interactive platform allows for the visualization and exploration of cancer indicators, thereby providing valuable insights for this study on GC [9].

3. Current Global Trends in Measures of Gastric Cancer

According to the latest available data from 2020 [10], GC remains a significant public health burden globally. An estimated 1.1 million cases of GC were diagnosed worldwide, with 720,000 cases occurring in males and 370,000 cases in females, respectively. GC ranks among the top three most common cancers in 19 countries, with four of these countries (Bhutan, Kyrgyzstan, Cape Verde, and Tajikistan, respectively) having GC as the most common cancer. GC incidence displays a substantial global variation, with a nearly 40-fold difference between the countries with the highest and lowest rates. The incidence rates are markedly elevated in Eastern Asian and Eastern European countries, while

North American, North European, and African countries exhibit lower rates, as shown in Figure 1 [1]. The underlying reasons for such global heterogeneity are likely multifactorial, implicating diverse environmental, genetic, and infectious factors. Notably, dietary habits have emerged as a crucial risk factor in GC development, with marked intercontinental variations likely contributing significantly to the disease burden. Additionally, specific *H. pylori* genotypes may account for the augmented incidence of GC in specific populations with high rates of infection, while other similar populations exhibit lower cancer rates [11]. Furthermore, variations in the use of tobacco and alcohol may also modulate cancer risk profiles across different regions. Studies examining the risk of GC in migrants from high-incidence to low-incidence countries revealed a decreasing trend in cancer risk over successive generations, further substantiating the role of environmental factors in carcinogenesis and global variation [12].

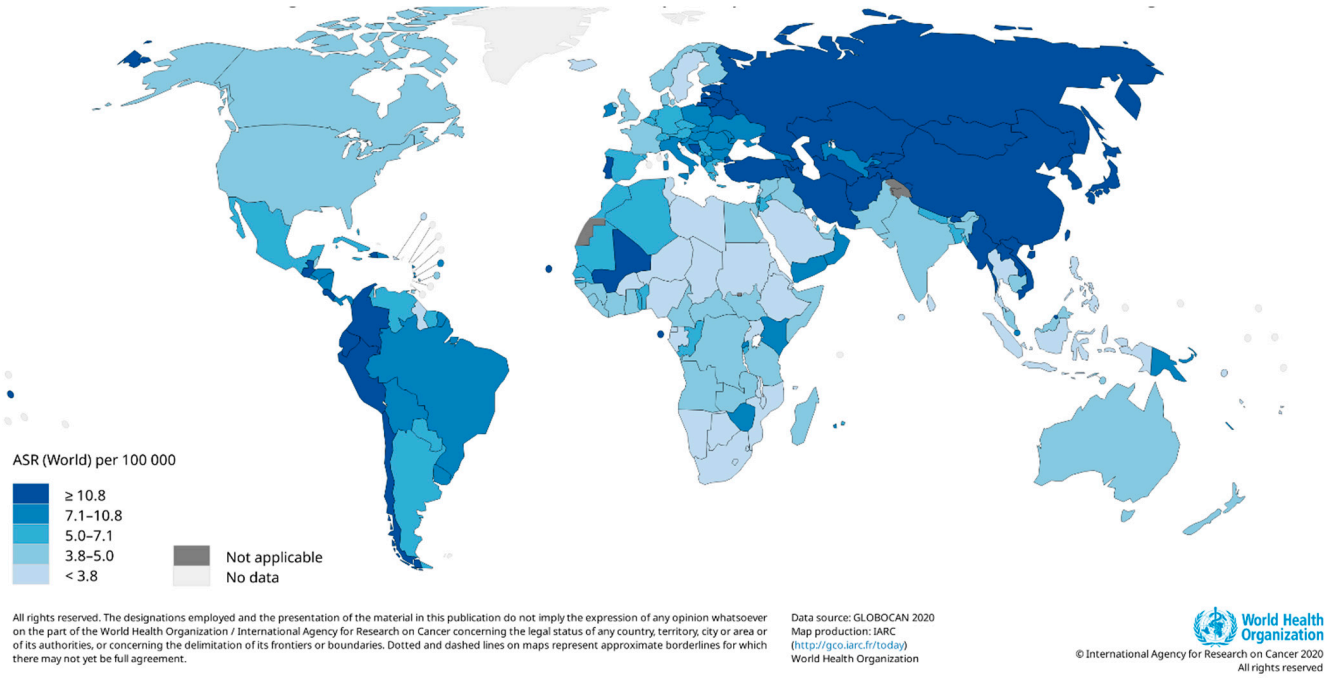

Figure 1. Estimated age-standardized global incidence rates of GC in 2020. Source: [9].

Gastric cancer continues to be a leading cause of cancer-related mortality worldwide. In 2020, 770,000 deaths were attributed to gastric cancer [10]. In 42 countries, gastric cancer was among the three most common causes of cancer death, with 13 countries having it as the primary cause. As shown in Figure 2, the highest mortality rates were observed in Eastern Asia, where 56.6% of all global deaths occurred, and China alone accounted for 48.6% of all global deaths. Mongolia and Tajikistan had the highest mortality rates for males and females, respectively, with 36.5 and 15.4 deaths per 100,000 people [10].

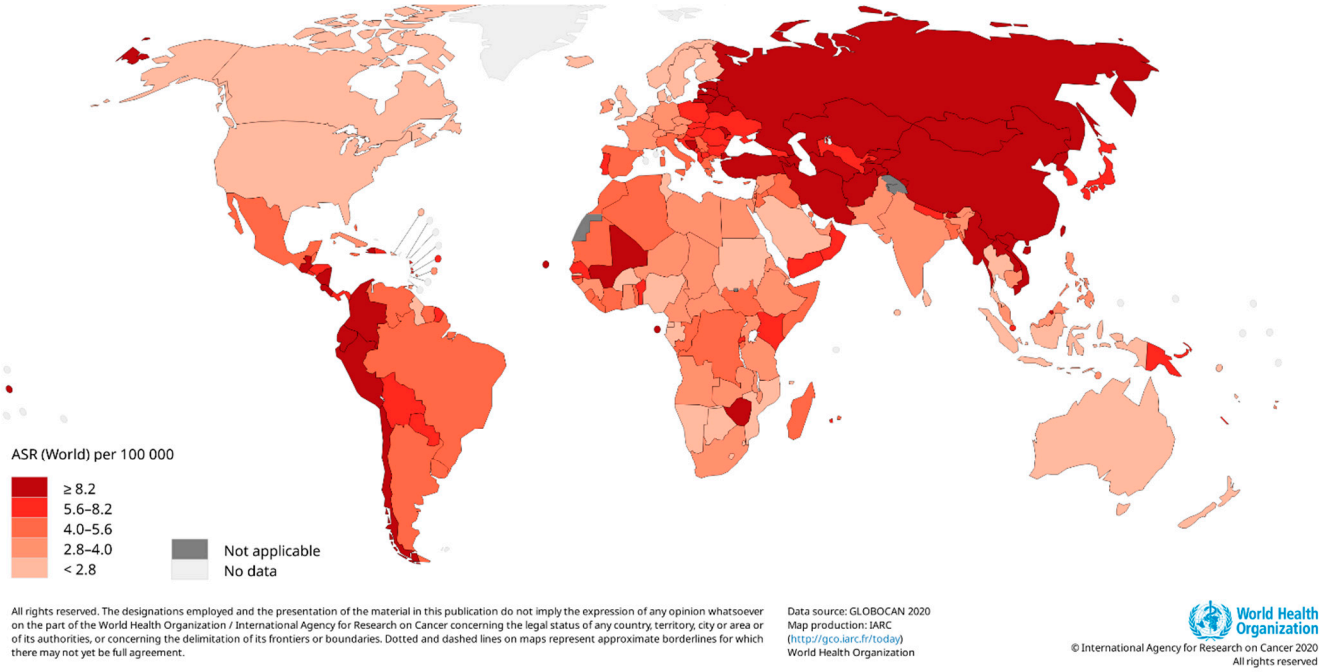

Figure 2. Estimated age-standardized global mortality rates of GC in 2020. Source: [9].

4. Etiology and Known Risk Factors of Gastric Cancer

While the development of GC is influenced by a variety of factors, more than 80% of cases have been linked to infection with the bacterium *Helicobacter pylori* (*H. pylori*). However, other factors, such as a family history, diet, lifestyle choices, genetics, socioeconomic status, and other environmental factors also contribute to the development of GC.

4.1. Helicobacter Pylori

The International Agency for Research on Cancer has classified *H. pylori* as a class I carcinogen based on the evidence that its infection raises the risk of GC [13]. *H. pylori* is a Gram-negative bacterium that colonizes the human stomach, and can cause peptic ulcers and GC, among other gastrointestinal diseases. It spreads from one person to another through either the oral–oral or fecal–oral route [14], and about half of the world's population is chronically colonized with this bacterium [15]. *H. pylori* can bind to the surface of gastric epithelium cells through various adhesion factors, including *Bab*A, *Sab*A, *Oip*A, and *Alp*A/B, which can lead to chronic gastritis and eventually GC [16]. Epidemiological studies have shown that between 2% and 3% of people infected with *H. pylori* will develop gastric adenocarcinoma, and 0.1% will develop mucosa-associated lymphoid tissue (MALT) lymphoma, respectively. Chronic gastritis caused by *H. pylori* usually does not manifest any symptoms. However, when the infection first starts, it can cause acute gastritis with hypochlorhydria, which can cause stomach pain, nausea, and vomiting as a result. Over 20% of *H. pylori* strains adhere to the surface of the gastric epithelium cells, where they are protected from the low pH of the stomach by the mucus layer.

The cytotoxin-associated gene A (CagA), vacuolating cytotoxin A (VacA), and outer membrane proteins are all virulence factors of *H. pylori* that have been linked to the development of GC [17]. *Cag*A is a protein that is injected into gastric epithelial cells by a type IV secretion system (T4SS) encoded by the cag pathogenicity island (*cag*PAI) [18]. Once inside the cell, *Cag*A undergoes tyrosine phosphorylation, and interacts with various signaling pathways, leading to an abnormal cell growth and division [19]. *Vac*A is a pore-forming toxin that induces the vacuolation and apoptosis of gastric epithelial cells [20]. In addition to *Cag*A and *Vac*A, other *H. pylori* virulence factors, such as OMPs, have been shown to contribute to gastric carcinogenesis by promoting chronic inflammation, oxidative stress, and DNA damage [21].

The precise mechanisms by which *H. pylori* infection leads to GC are still not fully understood, but it is believed to involve a complex interplay between the bacterial and host factors, including genetic susceptibility, environmental factors, and the immune response. It is important to note that not all *H. pylori*-infected individuals develop GC, and other factors, such as diet and lifestyle, may also play a role in disease progression. Effective strategies for the prevention and treatment of *H. pylori*-associated GC include antibiotic therapy to eradicate the bacterium, as well as dietary and lifestyle modifications to reduce the risk of developing precancerous lesions in the stomach and eventual disease development [22]. However, treatment is not always successful, and there is a risk of antibiotic resistance [23]. Screening for *H. pylori* infection is not currently recommended for the general population, but it may be considered for people who have a family history of GC or other risk factors. Endoscopic examination and biopsy are the most reliable methods for diagnosing *H. pylori* infection and assessing the risk of GC [24].

4.2. Other Risk Factors and Susceptible Population

Besides *H. pylori* infection, another microbe that has been linked to GC development is the Epstein–Barr virus (EBV) [25]. Although EBV is a common infectious agent, transforming EBV proteins have been found to be expressed in the tumor cells with the EBV genome present. Although only around 10% of GCs are EBV-positive, it is unclear as to whether EBV plays a distinct role in the development of GC [25]. Studies have shown that EBV-positive gastric carcinomas differ based on patient characteristics, such as sex, age, and anatomic subsite, with a decrease in its prevalence observed among males with increasing age [26]. EBV-positive GC has distinct clinical and pathological characteristics. It typically occurs in the proximal stomach and presents as lumps or ulcers with lymphocyte infiltration. This type of GC has a lower rate of lymph node metastasis and a greater ease of invasion into the submucosa. Despite being diagnosed in its advanced stages, patients with EBV-positive GC have a better prognosis and a higher median survival duration of 8.5 years, as compared to 5.3 years for EBV-negative patients, respectively. Therefore, the prognosis and effective treatment rate for patients with positive EBV are more favorable, indicating the need for further research in this area [27].

The gut microbiome, which varies between individuals, has been found to differ even more significantly in its composition among GC patients compared to healthy individuals. Several studies on this topic have been conducted in Asian populations, where GC is more common. One study of 276 Asian patients identified specific bacteria that were deregulated in GC patients, including *Bacteroides uniformis* and *Sphingobium yanoikuyae* [28]. *Bacteroides uniformis* is a bacterium that degrades the isoflavone compound genistein, which has been associated with a decreased cancer incidence, particularly in breast and prostate cancer. The downregulation of malignancies associated with genistein ingestion may be correlated with a high soy consumption in Asian countries [29]. *Sphingobium yanoikuyae* is a Gram-negative bacterium that degrades pollutants, such as those found in cigarettes, and its downregulation was also observed in GC patients [30]. Other bacterium, such as *Streptococcus anginosus*, *Peptostreptococcus stomatis*, *Parvimonas micra*, *Slackia exigua*, and *Dialister pneumosintes*, were all found to have been enriched in GC patients [28]. These bacteria have various functions and associations with the disease, such as *S. anginosus'* role in glucose and lactose metabolism relied upon by the GC cells [31], *P. stomatis* and *S. exigua's* production of the end products of fermentation that cause cellular injury and induce GC development [32], *Parvimonas micra's* association with septic arthritis and colon carcinoma [33], and *Dialister pneumosintes'* presence in brain abscesses and its association with endodontic pathogens [34].

People with a family history of GC are three times more likely to get the disease than those without a family history. Even though only 10% of GCs are caused by a family history, hereditary diffuse GC (HDGC) caused by changes to the cadherin 1 gene (CDH1) is the most well-known familial subtype [35]. Asia has a higher rate of familial GC than Europe

and North America, but environmental factors may be more important to consider than changes in genes causing familial GC in these areas [36].

People with blood group A have a relatively higher risk of developing GC compared to those with other blood types. Aird et al. in 1953 were the first to write about the link between group A blood and GC [37]. Since then, many studies, including a few meta-analyses performed more recently, have confirmed what they originally found. Those with group A blood are 1.11–1.21 times more likely to get stomach cancer than those with other blood types [38–41]. Several possible reasons have been given for this link, such as changes in gastric secretory function, intracellular adhesion receptors, membrane signaling, immune surveillance, an inflammatory response to *H. pylori* and cancerous cells, and an increased risk of pernicious anemia [42].

Socioeconomic status (SES) is a significant risk factor for GC. Typically, SES is determined through a combination of income, education, and occupation. Individuals with a lower SES have been shown to have a higher risk of developing GC, as well as a poorer prognosis [43]. Recent research using the Surveillance, Epidemiology, and End Results (SEER) database has revealed a 30% increase in GC incidence with a decreasing neighborhood SES [44]. By using SES to identify at high-risk populations, targeted screening programs for GC could be implemented. However, only a few studies have investigated individual-level SES variables as a means of identifying the individuals at a greater risk for GC [45].

Extensive research has established a clear link between dietary factors and the likelihood of developing GC. According to the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR), fruits and vegetables provide protection against GC, while broiled and charbroiled animal meats, and salt-preserved and smoked foods are likely to increase the risk of GC [46]. The carcinogens present in food may interact with the gastric epithelial cells, leading to changes in gene expression. Studies have indicated that a high intake of sodium chloride can be detrimental to the gastric mucosa and trigger cell death, followed by regenerative cell proliferation in animal models [47]. N-nitroso compounds have been identified as endogenous or dietary factors that significantly increase the risk of gastrointestinal cancer, especially non-cardia GCs [48].

Environmental factors play a significant role in the development of GC, as identified in a study by Yang et al., 2020 [49]. Risk factors include the water type, water pollution, water hardness, soil type, soil pollution, soil element content, climate change, air pollution, radiation, altitude, latitude, topography, and lithology. Most of these factors have an adverse impact on GC. This study also found that the leading environmental factors that affect GC incidence and mortality vary by region. Additionally, the same environmental factors may have different effects on GC in different regions, and some different environmental factors may exhibit similar effects on GC in essence. Moreover, different environmental factors often interact to form combined or synergistic effects on GC.

The impact of smoking and alcohol intake has been identified as a risk factor for GC development. Studies have shown that smokers have an 80% increased risk of developing GC, and particularly of those who are non-drinkers. Heavy drinkers also exhibit a higher risk of GC, with the risk estimated to be 80% among smokers [50]. Additionally, in the European prospective nutrition cohort study, heavy alcohol intake at the baseline was found to be positively correlated with GC risk. Intestinal non-cardia carcinoma has been linked with heavy alcohol consumption. A Korean population study exploring the ALDH2 genotype found that current/ex-drinkers among the ALDH2*1/2 carriers had a higher likelihood of developing GC compared to never/rare drinkers. This study highlights the association between alcohol consumption and GC development in patients with ALDH2 polymorphisms and the ALDH21/*2 genotype [51].

Occupation has been recognized as a potential risk factor for gastric cancer, although it has been considered to have a lesser impact compared with dietary and other environmental exposures. Nonetheless, occupational factors can interact with non-occupational factors during the crucial stages of gastric cancer development [52]. Epidemiological studies have

highlighted certain occupational exposures that have been associated with an increased risk of stomach cancer, including exposure to dusts, nitrogen oxides, N-nitroso compounds, and ionizing radiation. Various occupational groups have shown excess risks, such as miners and quarrymen, farmers, fishermen, masonry and concrete workers, machine operators, nurses, food industry workers, cooks, launderers, and dry cleaners [53]. These findings suggest that occupational exposures may contribute to the overall risk of gastric cancer. Further research is needed to better understand the specific mechanisms and interactions between these occupational factors and other risk factors in the development of gastric cancer [54].

5. Pathogenesis and Hallmarks of Gastric Cancer

GC is a type of malignant tumor that arises from the area between the junction of the esophagus and the pylorus. Adenocarcinomas, which are tumors that arise from glandular cells, are the most common type of GC, accounting for about 95% of cases. Other types, such as adenosquamous, squamous, and undifferentiated carcinomas, are rare [55]. The World Health Organization and Lauren's classification system have identified two distinct types of GC based on their clinical and epidemiological features: intestinal and diffuse. The well-differentiated intestinal-type is more common in men, older people in high-risk regions, and African Americans. It typically forms gland-like structures that often ulcerate. On the other hand, the poorly differentiated diffuse-type is more prevalent in women and younger patients and is characterized by the thickening and infiltration of the stomach wall, giving it a "leather bottle appearance" without the formation of a distinct mass. Mixed gastric carcinomas that contain both intestinal and diffuse components are also present [56,57].

Developing invasive gastric carcinoma is a slow process that happens as precancerous lesions get worse over time. This includes a series of sequential histopathological changes in the gastric mucosa, beginning with atrophic gastritis and the loss of the parietal cell mass, followed by intestinal metaplasia, dysplasia, and finally carcinoma. This metaplasia/dysplasia/carcinoma sequence is more important for the type of GC that arises from the intestines. This type of cancer is caused by a series of genetic changes that are similar to those observed in colorectal cancer. Environmental factors, such as *H. pylori* infection, obesity, and dietary habits influence the development of GC, particularly the intestinal-type. The diffuse-type GC, however, has been associated more with the genetic susceptibility indicated by the blood group A, and is the major histological type observed across endemic areas [58].

The hallmarks of GC are similar to those of other types of cancer, and has been detailed in the original and revised papers of Hanahan and Weinberg [59,60]. These hallmarks include sustained proliferative signaling, and the ability of cancer cells to proliferate uncontrollably even in the absence of external growth signals. GC cells also evade growth suppressors, bypassing normal cellular mechanisms that would usually inhibit their growth, allowing them to continue to divide and multiply. In addition, GC cells are capable of resisting cell death, evading programmed cell death (apoptosis) that would usually eliminate abnormal cells from the body. GC cells can also enable replicative immortality, which allows them to divide indefinitely, thereby avoiding senescence (cellular aging) and becoming immortal. They can also induce angiogenesis, stimulating the formation of new blood vessels to supply nutrients and oxygen to the tumor. Furthermore, GC cells are capable of activating invasion and metastasis, meaning they can invade the surrounding tissues and spread to other parts of the body [59,60].

In addition to the established hallmarks of GC, there are emerging hallmarks that contribute to the development and progression of the disease. One such hallmark is the ability of GC cells to avoid immune destruction by evading their detection and destruction through immune cells [59,60]. This allows the cancer cells to continue to grow and spread throughout the body. Another emerging hallmark of GC is genome instability and mutation. GC cells can accumulate genetic mutations and chromosomal abnormalities over time,

which can lead to further changes in cell behavior and proliferation. This can make the cancer more aggressive and resistant to treatment, and can also contribute to the development of drug resistance [59,60].

6. Treatment and Prevention of Gastric Cancer

Surgical resection is a crucial strategy for treating GC, ideally when the tumor is sensitive to chemotherapy. Endoscopic resection and minimally invasive techniques have had a significant impact on treatment. Endoscopic mucosal resection and endoscopic submucosal dissection are the standard treatments for the differentiated types of GC without ulcerative findings [61]. Laparoscopic and robotic-assisted gastrectomies provide positive outcomes with lower postoperative complication rates [62]. Conversion therapy has been used for unresectable or marginally resectable GCs, particularly in stage IV cases [63]. Comprehensive surgical resection with lymphadenectomy D2 is the primary treatment strategy for curing GC, with chemotherapy continuation being crucial after resection. D2 lymphadenectomy involves the removal of a more extensive range of lymph nodes compared to D1 lymphadenectomy. Various reconstruction methods can be used following subtotal gastrectomy [64].

Adjuvant chemotherapy has been studied extensively for the treatment of GC, with inconsistent outcomes due to the heterogeneity of the study cohorts, varying surgical precision, and chemotherapy regimens [65,66]. However, meta-analyses have shown that postoperative adjuvant chemotherapy based on fluorouracil regimens can significantly reduce the mortality rate of GC patients, and also improve overall survival and disease-free survival [67]. Other studies have also demonstrated the efficacy of adjuvant therapy following D2 gastrectomy and the use of neoadjuvant chemotherapy in cases of limited metastatic GCs [68]. The genotype of GC is also an important factor to consider when applying neoadjuvant chemotherapy.

Neoadjuvant chemotherapy has become increasingly important in treating gastric cancer. Studies have shown that neoadjuvant chemotherapy prior to surgery can significantly improve the survival outcomes for patients with gastric, gastroesophageal junction, and lower esophageal adenocarcinoma, respectively [69]. Perioperative chemotherapy with epirubicin, cisplatin, and fluorouracil (ECF) or 5FU/cisplatin have all been shown to be effective in reducing the tumor size and stage, and improving the progression-free and overall survival [70]. Neo-adjuvant chemoradiation therapy is also effective, and has similar outcomes to neoadjuvant chemotherapy [71].

Targeted therapy for GC includes drugs that target specific molecules involved in the growth and spread of cancer cells. Trastuzumab targets HER2, ramucirumab targets VEGFR2 [72], cetuximab targets EGFR [73], and dovitinib and AZD4547 target FGFR2 [74], respectively. Clinical trials have shown that these targeted therapies can improve the overall survival in some patients with advanced GC. However, some studies have not shown positive results, such as the use of the mTOR inhibitor everolimus and the AKT inhibitor MK-2206. The effectiveness of targeted therapy depends on the molecular characteristics of the tumor and its response to the drug [75].

Imaging strategies for GC include computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) [76]. CT is commonly used for local tumor invasion and detecting lymph node metastases [77]. It is the first staging modality due to its broad availability and accuracy. MRI is beneficial for differentiating between tumor tissue and fibrosis, and in detecting liver metastases and peritoneal seeding [78]. PET is not ideal for T-stage evaluation, but can be useful in detecting distant metastases and the preoperative chemotherapy response [79].

On a population level, the most important measures for preventing GC involve improving dietary habits and reducing the incidence of *H. pylori* infection, which is the primary cause of GC. Secondary prevention efforts should focus on early detection, which can be achieved through the use of available resources, including endoscopic methods, which are considered the gold standard. Consuming more fresh fruit and vegetables and limiting salt

and salt-preserved food intake could reduce the risk of GC. Fruit and vegetables contain beneficial nutrients, such as folate, carotenoids, vitamin C, and phytochemicals that may protect against GC [80]. Studies have shown that vegetable consumption can prevent the intestinal type of GC, while citrus fruit intake may protect against gastric cardia cancer. The International Agency for Research on Cancer also suggests that an increased consumption of fruit and vegetables can lower the risk of GC [81]. Lifestyle changes, such as increasing physical activity and limiting smoking can also reduce the risk of developing the disease.

H. pylori eradication is a potential approach for the prevention of GC. Studies have suggested that it causes a reduction in the incidence of GC in healthy, asymptomatic, infected Asian individuals. However, these results cannot be necessarily extrapolated to other populations [82]. Some trials have shown that the prophylactic eradication of *H. pylori* after the endoscopic resection of early GC should be used to prevent the development of metachronous gastric carcinoma [83]. Another randomized trial has shown that *H. pylori* treatment might decrease GC incidence by 30–40%, but there are still significant restrictions to the data [84].

The early detection of GC is important and requires support and the available health services. Various tests, including photofluorography and endoscopic examination, are recommended, and have shown a higher sensitivity and specificity than radiographic methods. In Japan, the five-year survival rate is better among the screen-detected cases than in the symptom-diagnosed patients [85]. Upper gastrointestinal endoscopy has been established as the gold standard for the diagnosis and treatment of early gastric carcinoma [86]. Studies have suggested that both screening methods can prevent the development of gastric carcinoma, and endoscopic screening can reduce the mortality by 30% [87].

7. Study Strengths and Limitations

The study has several strengths. Firstly, it offers a comprehensive examination by analyzing diverse data sources, including epidemiological studies, population-based surveys, and international databases. The presentation of the epidemiological evidence is clear and organized, facilitating a thorough understanding of the current trends and risk factor associations. Furthermore, this review emphasizes the future directions for research and preventive strategies, thereby contributing to the advancements that have been made in this field. However, this study had some limitations, such as variability in the study designs, publication bias, and heterogeneity in the observed populations. Awareness of these limitations ensures a balanced interpretation of the findings and acknowledges the potential impact on the generalizability and coverage of the recent developments in gastric cancer epidemiology.

8. Conclusions and Future Direction

Understanding the mechanisms by which *H. pylori* colonizes humans and mediates physiological, microbiologic, immune, and histologic features of the gut has significantly advanced the field of GC research. In particular, a recent study showed that a "stable colonization" of *H. pylori* in mice for 6 months led to an increase in the expression of "immune response genes" that lasted for a long time in the stomach and for a short time in the lungs [88]. This finding provided important insights into how *H. pylori* influences the host immune responses and the microbiota of not only the stomach, but also of the distal organs. The study indicates that *H. pylori* infection is associated with the emergence of the distinct structures of microbial populations in both the stomach and the intestines, which may contribute to the pathogenesis of GC [88]. This kind of knowledge could inform the development of novel preventive and therapeutic strategies for GC that target the microbiota and the immune system. It also underscores the importance of investigating the molecular mechanisms by which *H. pylori* influences the host immune system and microbiota to better understand the development of GC.

One gap in the understanding of GC biology is the incomplete knowledge of the molecular mechanisms underlying the initiation and progression of the disease. While it is known that long-term infection with *H. pylori* and other risk factors is associated with GC, the exact sequence of the genetic and epigenetic events that drive the transition from normal gastric mucosa to "preneoplastic lesions" and ultimately to invasive cancer remains unclear.

Gaining clarity on these mechanisms would potentially lead to the discovery of novel therapeutic targets. It could also help identify biomarkers for early detection and risk stratification, allowing for more effective screening and prevention strategies. Additionally, it could shed light on the interplay between environmental factors, such as diet and microbiota, and genetic susceptibility in the development of GC, ultimately leading to the development of personalized prevention and treatment approaches.

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