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Review Article

Gastric Cancer: Environmental Risk Factors, Treatment, and Prevention

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Abstract

Gastric cancer is a heterogeneous, multifactorial, aggressive disease that has been and remains one of the most common causes of cancer-related deaths and a significant public health issue worldwide. Currently, gastric cancer shows decreasing trends in its incidence and mortality in some geographic areas; however, the disease still shows a poor prognosis and remains difficult to cure. The prognosis for gastric cancer patients depends on the stage at which the gastric cancer is detected, and complete excision of the cancer is the only proven curative option. Gastric cancer prevention remains a priority. Patients at higher risk should be screened for early detection and chemoprophylaxis. Surgical resection enhanced by standardized lymphadenectomy remains the gold standard in the treatment of gastric cancer. Systemic therapy improves long-term disease-free survival compared to surgical treatment alone. Palliative chemotherapy in patients with inoperable gastric cancer prolongs survival and improves the quality of life. Demographic, ecological, environmental, cultural, and genetic variables all contribute to the heterogeneity of gastric cancer; however, environmental risk factors play an important role throughout all the stages of the disease progression, management, and surveillance. In this review, we address the role of important environmental risk factors in the onset of gastric cancer and highlight the current treatment modalities and prevention measures.

Keywords: Diet, gastric cancer, prevention, prognosis, risk factors, treatment

Introduction

Gastric cancer is considered as one of the most common causes of cancer-related deaths and a significant public health issue despite decreasing trends in its incidence and mortality.[1-3] Evidence of studies indicates that gastric cancer incidence

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varies in different parts of the world.[3-5] Less than a century ago, gastric cancer was the most common cancer in the United States. Over the last decade, gastric cancer is mostly prevalent cancer in Eastern Asia, East Europe, and South America, whereas the lowest rates are reported in North America and most parts of Africa. As such, the annual age-standardized gastric cancer incidence rates per 100,000 in men are 65.9 in Korea versus 3.3 in Egypt.[6] According to Global Cancer Observatory (GLOBOCAN, 2018), gastric cancer is the third-leading cause of cancer death worldwide, following lung and colorectal cancer in overall mortality. Gastric cancer has the fifth highest incidence among cancers, with 5.7% of all new cases attributable to the disease. Over a million, new cases of gastric cancer are diagnosed worldwide annually.[5,6]

Evidence indicates that gastric cancer is also one of the most behaviorally influenced and thus preventable.[5-7] Gastric cancer may be subdivided into three distinct subtypes: proximal, diffuse, and distal gastric cancer based on the histopathologic and anatomic criteria. Each subtype is associated with a unique.[7] This uniqueness was facilitated by the multifactorial nature of gastric cancer, which shows a complex interplay between genetics as well as lifestyle and environmental factors.[5-7]

Although gastric cancer's etiology is a complex topic, the most important and well-studied risk factors are *Helicobacter pylori* infections and host genetic factors, such as a positive family history for gastric cancer and/or a pro-inflammatory genetic profile. As such, the most recent study conducted at the National Cancer Center in South Korea among 1676 persons with *H. pylori* infection who had a family history of gastric cancer in first-degree relatives reported that *H. pylori* eradication treatment reduced the risk of gastric cancer.[8-10] In addition, environment and nutrition are identified as the risk factors for gastric cancer, including diet, body mass index, smoking, bacterial infections, and a variety of occupational exposures, such as tin mining, metal processing, rubber manufacturing industries, or ionizing radiation lead to an increased risk of gastric cancer.[4,9-11]

Methods

The search of the literature was carried out using a combination of the following search terms: "gastric cancer," "risk factors," "prevention," "lifestyle," "treatment," "prognosis," "*H. pilory*," "diet," and "nutrition." The search for eligible articles was conducted through CINAHL, Medline/PubMed, Scopus, Cochrane, Emerald Insight, and Web of Science scientific databases.

The inclusion criteria were English-language articles on the risk factors associated with gastric cancer in humans, study year (1990–2020), study type, and access to the full text of the studies. Based on the inclusion criteria checklist, as mentioned above, studies that did not meet this list were excluded. Considering the available data and literature, the authors present a summary of the main findings about the risk factors associated with gastric cancer. In this review, we address the role of important environmental risk factors in the onset of gastric cancer and highlight the current treatment modalities and prevention measures.

Gastric Carcinogenesis

Evidence in research shows that gastric cancer is a result of the interaction of many risk factors as well as protective factors, including genetic, environmental, unhealthy nutrition, exogenous chemicals, intragastric synthesis of carcinogens, infectious agents, host genetic, bacterial factors, as well as pathological conditions in the stomach (such as gastritis).[9-11] The understanding of gastric carcinogenesis and prevention is largely based on original articles published over the past three decades. One of the first publications was Correa's multistep model of gastric carcinogenesis, which presents a well-accepted general hypothesis.[12] In this hypothesis, a precancerous gastric process for the intestinal type is defined as a multistep and multifactorial process, with the following sequential stages: chronic gastritis, atrophy, intestinal metaplasia, and dysplasia.[12]

Helicobacter pylori

Since the discovery of *H. pylori* (1983), its close association with peptic ulcers and gastric cancer has

been documented in numerous studies. Although several prospective case–control studies have attempted to evaluate the link between *H. pylori* infection and gastric cancer development, results are inconsistent.[13-15] Based on the significant data from both control and cohort studies, *H. pylori* infection is causally associated with gastric cancer in the populations of Japan and China.[15] Most *H. pylori* infections are acquired during childhood and once established, usually persist for life unless treated. The prevalence of *H. pylori* infection in adults exceeds 50% in many industrialized countries. In 1994, the International Agency for Research on Cancer classified *H. pylori* as a Class I carcinogen and reconfirmed this classification in 2009.[16] Statistics from 2019 show that chronic infection with *H. pylori* is the leading cause of gastric cancer, accounting for approximately 89% of distal gastric cancer cases worldwide.[16]

H. pylori's identification as a risk factor for gastric carcinogenesis has stimulated extensive research on the mechanisms by which *H. pylori* induces carcinogenesis.[16-18] Furthermore, it has been considered that human gastric carcinogenesis is a multistep process whereby epithelial cells accumulate molecular alterations by genetic and epigenetic mechanisms involving oncogenes, tumor-suppressor genes, DNA repair genes, cell cycle regulators, and signaling molecules. Gastric cancer genetic basis studies, including host genetic susceptibility, have shed considerable light on the pathogenesis of this disease and have underscored the role of infection and chronic inflammation in gastric cancer. As such, gastric cancer is an infection-induced, inflammation-driven malignancy, developing after several decades among people with a genetic predisposition.[16-18] *H. pylori* is a genetically very diverse bacterium, and several genotypes have been associated with virulence and risk of gastric disease, including vacAs 1, vcAm 1, and cagA positive. CagA causes pathological changes that are closely associated with the development of gastritis, gastric ulcer, and gastric cancer. CagA-positive strains of *H. pylori* are more virulent, causing higher levels of inflammation of the gastric mucosa in gastritis and gastric cancer.[17,18]

The presence of *H. pylori* in the gastric mucosa can induce methylation of promoters containing CpG islands by activating DNA methyltransferase. Besides, the aberrant methylation of CpG islands is present along the multistep process of gastric carcinogenesis.[4,19] In their study, Kim *et al*. reported that *H. pylori* infection promotes gastric carcinogenesis by increasing endogenous DNA damage while decreasing repair activities and by inducing mutations in the mitochondrial and nuclear DNA.[20] Hence, it may be concluded that the aberrant DNA methylation and other molecular alterations observed in some genes induced by *H. pylori* infection are the significant risk factors for gastric carcinogenesis.[19,20]

Genetic factors

Research is increasingly looking at the role of host/human genetics in *H. pylori*-associated gastrointestinal duodenal disease.[21-24] Several single nucleotide polymorphisms in genes encoding a variety of inflammatory mediators have apparent functional relevance since they influence cytokine bio-availability or expression levels. This includes interleukin (IL)-1 β, potent pro-inflammatory cytokine and inhibitor of gastric acid secretion. Thus, expression of IL-1B-511T and IL-1RN *2 has been associated with a significant increase in the risk of gastric cancer. While the L-C-T haplotype, including the wild-type IL-1RNL and IL-1B-511C alleles, has been more often associated with the control group than with gastric cancer cases.[21,22]

Major risk factors for gastric cancer include age, *H. pylori*, and Epstein-Barr virus infection, race, gender, obesity, GERD, tobacco, alcohol, and family history. In addition to nongenetic risk factors, about 10%–20% of gastric cancer patients show familial aggregation of the disease, of which 2%–5% has been classified as hereditary.[21-24] Three major familial gastric cancer syndromes have been described in existing data, including hereditary diffuse gastric cancer (HDGC), familial intestinal cancer, and gastric adenocarcinoma and proximal gastric polyposis of the stomach. The risk of developing gastric cancer is high in families with these syndromes, but until recently, only HDGC has been genetically explained. Thus, only one

gene, E-cadherin (CDH1), has been associated with hereditary gastric cancer, and 40% of HDGC cases carry CDH1 mutations. However, recent advances in high-throughput DNA analysis identified the several regions of the genome associated with an increased risk of gastric cancer.[21-24]

Thus, there is evidence for a causal role for PALB2 (gene for breast and pancreatic cancer) and other genes involved in homologous recombination DNA repair in gastric cancer risk. Gastric cancer has also been reported in cancer syndromes such as lynch syndrome, Li-Fraumeni syndrome, juvenile polyposis syndrome, Peitz-Jeghers syndrome, and hereditary breast and ovarian cancer syndrome.[23,24]

Dietary factors

Before the discovery of *H. pylori* (1983), epidemiological studies already suggested the critical role of lifestyle in the etiology of gastric cancer. Probably, the best-established associations are the links between cancer risk and diets that contain excessive salt intake and low consumption of fresh fruits and vegetables.[25] Studies conducted in 2013 reported that the incidence of gastric cancer has decreased over the past few decades in most European countries, which is thought to reflect mainly lifestyle and environmental changes such as smoking cessation and *H. pylori* eradication.[25] Thus, factors other than *H. pylori* have been implicated in the incidence of gastric cancer. Daily consumption high-salt foods significantly increase the risk of gastric cancer. Processed meat was found to significantly increase the risk of noncardia gastric cancer, while obesity was associated with a higher risk of stomach cardia cancer.[7,25]

The acute effects of concentrated salt liquids lead to mucosal damage, and its repair is associated with inflammatory changes in the human stomach.[11,12] In China, Kneller *et al*. studied the relationship between the mortality rate from gastric cancer and the results of a study on diet, lifestyle, and biochemical markers. The authors found a significant positive association between the consumption of salted vegetables and eggs and the mortality rate from stomach cancer.[26]

Furthermore, studies have been conducted to evaluate the association of nitrates, nitrites, and N-nitroso compounds with gastric cancer. Salt ingestion has been shown to enhance gastritis and carcinogenic effects of known gastric carcinogens such as N-methyl-N-nitro-N-nitrosoguanidine.[26-28] Those societies whose diets are rich in salty and canned foods, such as the Japanese, report higher levels of gastric cancer. Furthermore, canned meat, vegetables and fish rich in N-nitroso compounds cause a similar effect in the body. Red meat fed with the grain is especially rich in saturated fats and contains few protective fats, such as omega-3, which contributes to its inflammatory processes and thus, increases the risk of gastric cancer.[26-28] Several case-control studies in Europe, Asia, and North America have continually reported that consuming fresh fruits and vegetables protect against gastric cancer, reducing the risk by about 40% with the consumption of fruits and 30% with vegetables.[29,30] Populations at high risk of developing gastric cancer were shown to consume food rich in starch and low protein and are not prone to eat fresh fruits and vegetables. Hence, diets with both high starch and low protein can promote acid-catalyzed nitrosation in the stomach and cause mechanical damage to the gastric mucosa.[29-31] According to a report by the World Cancer Research Fund/American Institute for Cancer Research (WCRF, 2018) on dietary factors and cancer prevention stated that nonstarchy vegetables and fruits probably protect against gastric cancer.[31] Data from experimental and animal studies indicate several potential mechanisms by which Vitamin C may affect gastric carcinogenesis. Vitamin C reduces gastric mucosal oxidative stress and DNA damage, and gastric inflammation by scavenging reactive oxygen species. It inhibits gastric nitrosation reaction for the formation of N-nitroso compounds by reducing nitrous acid to nitric oxide and producing dehydro-ascorbic acid in the stomach; it enhances host immunologic functions; it has a direct effect on *H. pylori* growth and virulence, and it inhibits gastric cell proliferation and induces apoptosis.[30-32]

Lifestyle factors

Additional risk factors for developing gastric cancer are drinking alcohol and smoking tobacco. In 2008, a meta-analysis of 42 studies showed that

smokers increased the risk of stomach cancer by about 1.53 times and was higher in men than in women. According to the WCRF, an estimated 11% of stomach cancer cases in the world and 17% of cases in Europe were related to smoking.[7,16,25] Furthermore, the European Prospective Investigation into Cancer and Nutrition project found a significant association between the intensity and duration of cigarette smoking and gastric cancer risk.[33] In Japan, a population-based prospective study of the combined influence of cigarette smoking and *H. pylori* infection indicated that approximately 28.4% of gastric cancers are related to cigarette smoking.[34] The relative risk for gastric cancer increases with rising frequency and amount of alcohol consumed. Those who tend to drink alcohol at least once a week have three times higher risk for gastric cancer than nondrinkers.[35]

The association between cigarette smoking and gastric cancer has been investigated in a number of epidemiologic studies, including both case-control and cohort studies, but the results are inconsistent.[35,36] However, recently new studies have confirmed the direct correlation between the consumption of alcohol and tobacco and the risk of gastric cancer. Smoking was associated with a risk of stomach cancer for both former smokers and current smokers, with current smokers posing a higher risk than former smokers. In Japan, approximately 28.4% of gastric cancers are related to cigarette smoking, according to data from the Hisayama Study, a population-based prospective study of the combined influence of cigarette smoking and *H. pylori* infection and confirmed that cigarette smoking is significantly associated with increased risk of gastric cancer independent of *H. pylori* infection.[35,36]

Prevention and high-quality treatment can dramatically improve the poor prognosis of gastric cancer. A key factor in designing prevention strategies is the distinction of the general population and individuals into high, intermediate, and low-risk categories for developing gastric cancer.[35-37]

Prevention and Treatment

In all populations and countries, gastric cancer is uniformly rare in adults aged <50 years. Gastric cancer incidence rates increase with increasing age and reach a plateau between 55 and 80 years. On average, the incidence rates for gastric cancer are 2-fold to 3-fold higher for men than women. Several countries, including Venezuela, Chile, Korea, China, and Japan, have implemented various screening programs.[38] Gastric cancer prevention has focused on screening and surveillance as well as *H. pylori* screening and eradication. The potential effectiveness of a gastric cancer prevention program that includes *H. pylori* screening and treatment is dependent upon a patient's level of cancer risk at the time *H. pylori* is eradicated (e.g., considering the 2-fold higher risk of developing gastric cancer between the most-and the least-virulent strains) and the screening modality used. Under various assumptions about both effectiveness and costs, population-based screening for *H. pylori* and eradication of the infection has been shown to be cost-effective.[16-18,38]

The strong causal link between *H. pylori* and gastric cancer presents a unique opportunity for considering antibiotic eradication treatment as a chemo preventive strategy against a neoplastic disease. Current evidence suggests that, in a subpopulation of the treated subjects, *H. pylori* eradication prevents the progression of preneoplastic lesions.[9] As was shown in a randomized trial involving first-degree relatives of gastric cancer patients, the risk of gastric cancer was 55% lower among those who received *H. pylori* eradication treatment than among those who received a placebo during a median follow-up of 9.2 years. Whereas the risk of gastric cancer was 73% lower among persons in whom *H. pylori* eradication was achieved than among those in whom infection was persistent.[10,38,39] A meta-analysis of six randomized trials, including healthy, asymptomatic participants with *H. pylori* infection, reported that the risk of gastric cancer was approximately 34% lower among those who received treatment than among those in the control groups.[10,38,39]

Diet and nutritional chemoprevention is the ideal strategies proposed for the prevention of gastric cancer, considering the role of diet in the etiology of the disease. The chemoprevention approach involves using specific natural or synthetic chemical agents

to reverse, suppress, or prevent premalignancy from progressing to invasive cancer.[28,39] It is essential to test the chemo preventive efficacy of a putative agent in gastric carcinogenesis in an animal model before embarking on clinical trials.[38,39]

Gastric cancer remains difficult to cure. Prognosis depends on the stage at which it is detected, and complete surgical resection remains the only curative modality for early-stage gastric cancer. Early gastric cancer may be treated with surgery, usually followed by chemotherapy or combined chemo-and radiotherapy. Although surgery, including gastrectomy in combination with systemic lymph node dissection, is the current treatment of choice for gastric cancer, laparoscopy-assisted distal gastrectomy (LADG) is widely accepted surgery for early gastric cancer in recent years. The practice of LADG for early stage of gastric cancer is considered a first-line additional therapy after endoscopic resection in Japan.[40]

In some cases where surgical resect ability is doubtful in the initial presentation, neo-adjuvant chemotherapy is preferred. Several trials proved the survival benefit from combined modality therapy.[37-40] Surgical resection with regional lymphadenectomy is the treatment of choice for patients with stage II gastric cancer. According to the new American Joint Committee on Cancer 7th ed.ition, tumor-nodal-metastasis staging classification, gastric cancer Stage II is an intermediate stage between Stage I and Stage III. However, preoperative and intraoperative staging to confirm Stage II disease is complicated. The degree of surgical resection depends on the histopathological outcome. A multidisciplinary method for the planning of gastric cancer treatment is necessary. The multidisciplinary team should include at least a surgeon, pathologist, gastroenterologist, medical, and radiation oncologists. The treatment depends on the stage of the disease.[19,37-40]

Conclusions

Based on the present evidence, gastric cancer of the intestinal types is likely related to environmental exposure as well as lifestyle of people.[25,31] Gastric mucosal damage and atrophic gastritis can be caused by either *H. pylori* infection and/or by a diet lacking fresh fruits and vegetables, and consumption of highly salted or poorly preserved foods. Subsequently, antioxidants and salt play an essential role in the more advanced stages of gastric carcinogenesis. Gastric cancer prevention remains a priority. However, patients at higher risk should be screened for early detection and chemoprophylaxis. Surgical resection enhanced by standardized lymphadenectomy remains the gold standard in the treatment of gastric cancer. Systemic therapy improves long-term disease-free survival compared to surgical treatment alone. Palliative chemotherapy in patients with inoperable gastric cancer prolongs survival and improves the quality of life.[19,37-40]

Many of these studies may not have considered sufficiently confounding factors that are typically hampering epidemiological studies, particularly those dealing with environmental factors such as dietary patterns or occupational exposures using retrospective data. In the future, well-designed prospective studies or intervention trials are needed to form a more accurate perception of the correlation between the environmental factors and gastric cancer development.

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Authors' contributions

All authors contributed to the conception, development, and revision of the manuscript and approval of its final version.

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Conflicts of interest

There are no conflicts of interest.

Compliance with ethical principles

Not applicable.

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