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REVIEW ARTICLE

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Environmental and genetic risk factors for gastric cancer

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Abstract

Gastric cancer is a heterogeneous and prevalent disease. The traditional environmental exposures associated with an elevated risk of gastric cancer are less prevalent in the United States today. Genetic risks and risks associated with inflammation remain. Most cases are sporadic and familial clustering is observed in about 10% of the cases. Hereditary gastric cancer accounts for a very low percentage of cases. Here we review the genetic and environmental risk factors associated with the disease.

KEYWORDS
adenocarcinoma, diet, *H. pylori*, stomach

1 | INTRODUCTION

The incidence of gastric cancer has decreased worldwide since the 1970s, likely due to multiple factors including effective *H. pylori* treatment[1] and improved refrigeration.[2] Despite this progress, it continues to be a major global health concern, particularly in Eastern Asian countries, with over 1 million cases diagnosed in 2020.[3] Prognosis for the treatment of this disease remains poor, and it is currently the fourth most common cause of cancer mortality worldwide. In the United States, an estimated 26 560 new cases were diagnosed in 2021 with 11 180 patients dying from the disease, making it the 16th most diagnosed cancer and 17th leading cause of cancer death.[4] The traditional environmental exposures (dietary risks) associated with an elevated risk of gastric cancer are less prevalent in the United States today. Genetic risks and risks associated with inflammation of the stomach remain. Most cases are sporadic and familial clustering is observed in about 10% of cases.[5,6] Defining populations at the highest risk is important to the consideration of novel screening protocols. Here, we review genetic and environmental risk factors that contribute to the formation of gastric cancer.

2 | GENETIC RISK FACTORS AND FAMILIAL SYNDROMES

Gastric cancer risk is likely modulated by multiple factors. Genetic susceptibility may modify the effect of environmental and dietary exposures, resulting in the high variation of gastric cancer incidence seen around the world. Here, we review some genetic factors associated with this increased risk. We also review familial cancer syndromes that confer a higher risk of gastric cancer (summarized in Table 1).

2.1 | Age and sex

The risk of gastric cancer increases with age. Between 2014 and 2018, 2% of gastric cancer cases were in those less than 34 years in age, 38% of cases were in those between 35 and 64, and 60% occurred in those above the age of 65.[4] The median age of diagnosis in this timeframe was 68 years.[4] Risk with increased age is likely secondary to longer exposure to potential carcinogens, increased susceptibility to mucosal damage, delayed healing of the gastric

TABLE 1 Cumulative risk of developing gastric cancer in various genetic syndromes

Genetic syndromes	Lifetime risk	References
Hereditary diffuse gastric cancer	67%–70% for Male 56%–83% for Female	Hansford et al.[7]; National Comprehensive Cancer Network[8]
Hereditary nonpolyposis colorectal cancer		
MLH1	2%–11%	Barrow et al.[9]; Bonadona[10]; Capelle et al.[11]; Vasen et al.[12]
MSH2	0.2%–9%	Barrow et al.[9]; Bonadona[10]; Capelle et al.[11]; Vasen et al.[12]
MSH6	0%–10%	Barrow et al.[9]; Capelle et al.[11]; Moller et al.[13]
Familial adenomatous polyposis	0.6%–2%	National Comprehensive Cancer Network[8]; Syngal et al.[14]
Gastric adenocarcinoma and proximal polyposis of the stomach	12%–20%	Kim et al.[15]; Worthley et al.[16]; Setia et al.[17]; Foretova et al.[18]
MUTYH-associated polyposis	1%–5%	Vogt et al.[19]; Win et al.[20]
Juvenile polyposis syndrome	5%–21%	National Comprehensive Cancer Network[8]; Attard and Young[21]
Peutz–Jegher syndrome	29%	National Comprehensive Cancer Network[8]; Giardiello et al.[22]
Li–Fraumeni syndrome	2%–5%	Kim et al.[15]; Masciari et al.[23]

mucosa, increased incidence of mucosal cancer stem cell markers, increased prevalence of chronic active gastritis, intestinal metaplasia, and mucosal atrophy, especially in those infected with *H. Pylori*.[24–26]

Men are twice as likely as women to be affected by gastric cancer.[3,4] Studies evaluating sociodemographic characteristics, environmental factors, sex hormones, hormonal interventions, and smoking habits to explain the difference in incidence between men and women have been inconclusive.[27–29] However, the prevalence of *H. Pylori* infection appears to be higher in men and likely contributes to the higher incidence of gastric cancer seen in the gender.[30,31]

2.2 | Blood type A

The relationship between group A blood and gastric cancer was first described by Aird et al. in 1953.[32] Since then, many studies, including several recent meta-analyses, have confirmed their findings that those with group A blood carry a higher relative risk (1.11–1.21) of gastric cancer compared with other blood types.[33–36] There have been several proposed mechanisms behind this association, including alterations in gastric secretory function, intracellular adhesion receptors, membrane signaling, immune surveillance, inflammatory response to *H. Pylori* and malignant cells, and increased susceptibility to pernicious anemia.[37–39]

2.3 | Hereditary diffuse gastric cancer

Hereditary diffuse gastric cancer (HDGC) is an autosomal dominant genetic pre-disposition syndrome characterized by early onset diffuse gastric cancer affecting multiple generations, and lobular breast cancer. Forty percent of HDGC families have germline mutations in *CDH1* and over 100 different pathogenic germline mutations have been reported.[7] Guilford et al.[40] first identified *CDH1* as the responsible gene for early onset diffuse gastric cancer in a study of several Māori families with the disease. Human *CDH1* is located at chromosome 16q22 and encodes for E-cadherin, a transmembrane protein with five tandemly repeated extracellular domains and a cytoplasmic domain that connects to the actin cytoskeleton through a complex with α-, β- and γ-catenin. This cell adhesion molecule is important for establishing cell polarity and maintaining normal tissue morphology and cellular differentiation.[41] Downregulation of E-cadherin expression often correlates with strong invasive potential and poor prognosis of human carcinomas. In a recent study of 183 patients with HDGC who underwent *CDH1* testing, the cumulative incidence of gastric cancer was found to be 70% in males and 56% in females.[7]

Up to 60% of families meeting clinical criteria for HDGC do not have a detectable *CDH1* mutation.[7] In 2013, Majewski et al.[42] identified a germline mutation in *CTNNA1*, resulting in loss of α-E-catenin expression. Since then, four additional families with HDGC have been shown to express the mutation.[7,43] Not much is currently known regarding the penetrance of *CTNNA1* variants. However, there is evidence suggesting that it carries a similar risk of diffuse gastric cancer as *CDH1* mutations.[44] The International Gastric Cancer Linkage Consortium (IGCLC) guidelines now recommend genetic testing for *CTNNA1* mutations, in addition to *CDH1* mutations, in those meeting genetic testing criteria for HDGC.[45] However, the incidence of *CTNNA1* mutation in *CDH1*-negative HDGC-like disease remains low and most of the genetic susceptibility remains unknown with further research needed to characterize additional mutations leading to increased susceptibility.

2.4 | Hereditary nonpolyposis colorectal cancer (HNPCC)

HNPCC, also known as Lynch syndrome, is an autosomal dominant disorder, affecting DNA mismatch repair genes. It is characterized by a mutation in 1 of 4 DNA mismatch repair genes: *MLH1*, *MSH2*, *MSH6*, and *PMS2*.[46] Affected patients have a significantly increased risk for colorectal and endometrial cancer, however mutations in *MLH1*, *MSH2*, and *MSH6* have been shown to increase lifetime risk of gastric cancer as well. *MLH1* mutations have been shown to confer a lifetime risk up to 10.9%, *MSH2* mutations confer a risk up to 9.0%, and *MSH6* mutations up to 10.4%.[8–13] Most gastric cancers in patients with HNPCC are intestinal-type and have the same natural history as sporadic intestinal-type gastric cancer.[47]

2.5 | Familial adenomatous polyposis (FAP)

FAP is an autosomal dominant disorder arising from a mutation in the *APC* tumor-suppressor gene. It is characterized by the formation of >100 synchronous colorectal adenomas and a near 100% risk of colon cancer. FAP also increases the risk of gastric polyps with rates ranging from 23% to 100%, and these polyps tend to be more numerous and occur at a younger age, although these are typically benign.[14] The risk of gastric cancer in those with FAP is comparable to the general population risk, however, in countries with a higher prevalence of gastric cancer, such as Japan and Korea, higher risk has been reported.[14,15,48]

2.6 | Gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS)

GAPPS is an autosomal-dominant disorder characterized by multiple (>100) fundic gland polyposis with areas of multifocal dysplasia. Recently discovered, the syndrome was first described by Worthey et al. in 2012 in three families from Australia, the USA, and Canada.[16] The gene mutations responsible were described by Li et al. in 2016 as various point mutations in Exon 1B of the *APC* gene.[49] Given its recent discovery, data concerning lifetime risk of gastric cancer is sparse, however, in the available literature, risks of 12%–20% have been described.[15–18]

2.7 | *MUTYH*-associated polyposis (MAP)

MAP is an autosomal recessive disorder caused by mutations in the base-excision repair gene *MUTYH*. MAP is characterized by multiple adenomas in the colon and rectum and typically becomes symptomatic between the fourth and seventh decade of life, with a cumulative lifetime risk of colon cancer approaching 100%. Patients affected with MAP have up to a 5% lifetime risk of gastric cancer.[19,20]

2.8 | Juvenile polyposis syndrome (JPS)

JPS is an autosomal dominant disorder caused by mutations in *BMPR1A* or *SMAD4* - tumor suppressor genes in the TGF-B signaling family that regulate cell growth inhibition and apoptosis.[14] JPS is characterized by multiple hamartomatous polyps throughout the GI tract. *SMAD4* mutations carry an increased risk of gastric polyposis and gastric cancer compared to *BMPR1A* mutations, with lifetime gastric cancer risk approaching 21%.[21]

2.9 | Peutz–Jegher syndrome (PJS)

PJS is an autosomal dominant disorder caused by mutations in the *STK11* gene, which encodes a threonine kinase that functions as a tumor suppressor.[50] Clinically, it is characterized by hamartomatous polyps in the GI tract and mucocutaneous pigmentation. Patients with PJS are at increased risk of a variety of common GI and non-GI tumors, with a lifetime gastric cancer risk of 29%.[22]

2.10 | Li–Fraumeni syndrome (LFS)

LFS is an autosomal dominant disorder caused by germline mutations in the *TP53* tumor promotor gene. Classically associated with sarcomas of the soft tissue and bone, adrenal cortical carcinomas, breast cancer, leukemia, and brain tumors, LFS is also associated with a broad range of other neoplasms. Patients affected by LFS carry a 2%–5% lifetime risk of being diagnosed with gastric cancer.[15,23]

3 | ENVIRONMENTAL FACTORS

Given the high variation in incidence seen around the world, environmental factors likely play a major role in modulating the risk of gastric cancer. Here, we review several environmental risk factors that affect gastric cancer risk. Table 2 provides a summary of these risk factors and their associated relative risk.

3.1 | Geographic variation

Gastric cancer incidence varies markedly across the globe with almost a 40-fold difference between the lowest and highest incidence countries. Incidence rates are highest in Eastern Asian and Eastern European countries, with lower rates in North American, North Europe, and Africa[3,65] (Figure 1). The reason behind geographical variations is likely multifactorial, with contributions from environmental, genetic, and infectious factors. Diet is an important factor in the development of gastric cancer, and variations in diet across the globe are likely a major contributor. Differences in *H. pylori* genotypes may also explain why certain populations with high rates of *H. pylori* infection experience increased incidence of

TABLE 2 Risk factors for gastric cancer

Factor	Relative risk (RR)	References
Male sex	1.95	Sung et al.[3]
Family history	1.5–3.5	La Vecchia et al.[6]; Yaghoobi et al.[51];Yaghoobi et al.[52]
H. Pylori infection	3.8–5.8	Vohlonen et al.[53]; Helicobacter, Cancer Collaborative Group[54]; Kikuchi et al.[55]
Smoking	1.53–1.84	Koizumi et al.[56]; Nishino et al.[57]; Ladeiras-Lopes et al.[58]; Nomura et al.[59]
Heavy alcohol intake	1.20–1.65	Wang et al.[60]; Tramacere et al.[61]; Duell et al.[62]; Rota et al.[63]
Blood group A	1.11–1.21	Yu et al.[33]; Wang et al.[34]; Edgren et al.[35]; Vasan et al.[36]
Moderate-high salt intake	1.41–1.68	D'Elia et al.[64]

gastric cancer, while other populations with similarly high infection rates do not.[66] Variations in cigarette and alcohol use likely contribute to a variable risk profile as well. Studies evaluating the risk of gastric cancer in migrants from high-incidence countries to low-incidence countries have found a decrease in cancer risk in successive generations, with the risk approaching the overall risk of the host country, further supporting the idea that environmental factors play a large role in carcinogenesis and contribute to the variation seen around the world.[67,68]

3.2 | Salt intake

Diet is an important, modifiable risk factor for gastric cancer. The World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) and the World Health Organization/Food and Agricultural Organization (WHO/FAO) expert panel have both stated that salt is a probable cause of gastric cancer.[69,70] Early ecological studies first established the link between salt and gastric cancer. In a 1996 study evaluating 39 populations from 24 countries, Joossens et al. showed a link between urinary salt excretion and cancer.[71] Subsequent case-control and prospective cohort studies have confirmed the increased risk of gastric cancer with higher salt intake. A meta-analysis of prospective studies by D'Elia et al.[64] found a 40%–70% increased risk of cancer in those with high and moderate salt intake compared to low salt intake. In the same study, foods with high salt content, such as pickled foods, salted fish, and processed meat were all significantly associated with an increased risk of cancer.

There are several mechanisms via which salt may contribute to carcinogenesis. High salt concentration has been shown to disrupt the mucosal barrier of the stomach and lead to inflammation and atrophy. Experimental studies in mice and gerbils have shown increased rates of *H. Pylori* colonization with a high salt diet due to alternations in the protective mucin layer.[72,73] High salt intake has also been found to increase *CagA* expression, a potent virulence factor in *H. Pylori* and a known risk factor for gastric cancer development in those infected.[74] Studies also suggest that salt intake may enhance the effect of other carcinogens such as N-nitroso compounds.[75,76]

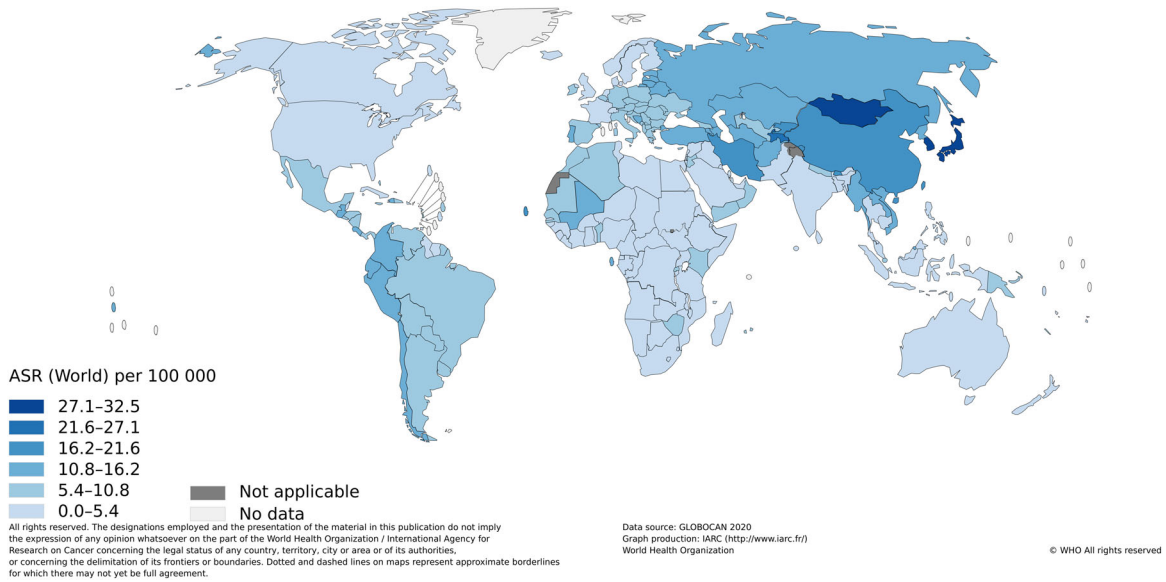

FIGURE 1 Global age-standardized incidence rates of gastric cancer. Copyright 2022 International Agency Research on Cancer (IARC). Reprinted with permission.

3.3 | Fruit and vegetables

Fruits and vegetables may have a protective effect against gastric cancer, possibly related to their antioxidant capacity. A meta-analysis by Riboli and Norat[77] found a pooled risk of 0.81 and 0.74 for each 100 g increase in vegetable and fruit, respectively.[77] However, when only more reliable prospective studies were considered, the benefit was no longer significant. Indeed, two large prospective studies also found minimal to no risk reduction with increased consumption of fruits and vegetables.[78,79]

3.4 | Smoking

Cigarette smoking has been implicated as a risk factor in many cancers, and gastric cancer is no exception. The risk of gastric cancer in smokers is 1.5–1.8 times higher compared to those that do not smoke.[56–59] The relationship appears to be dose-dependent, with a higher number of cigarettes per day and a longer duration of smoking conveying a higher risk; however, evidence of this effect has not been consistent in the literature.[59,80] Smoking cessation attenuates the risk, with a longer duration of cessation associated with an increased risk reduction.[59,80]

Cigarette smoke contains a variety of carcinogenic components, and the mechanism behind the effects of smoking on tumorigenesis in the stomach is an area of active research. Possible mechanisms include activation of nicotinic acetylcholine receipts, formation of DNA adducts, stimulation of tumor angiogenesis, and induction of cell proliferation.[81,82] Additionally, smoking is a risk factor for induction of chronic inflammation in the GI tract via alteration of mucosal cell proliferation, induction of immune dysfunction, and increased risk of bacterial or viral infection, which may further contribute to carcinogenesis.[81]

3.5 | Alcohol

Heavy alcohol intake increases the risk of gastric cancer by up to 65% when compared to low-moderate intake, specifically increasing the risk for noncardia cancer.[60–63] While the mechanism behind the increased risk is unclear, it is likely multifactorial. One mechanism may be the presence of *N*-nitrosodimethylamine (NDMA), a carcinogen, in certain alcoholic beverages, particularly beer.[62] Additionally, alcohol consumption results in the formation of acetaldehyde, a known carcinogen.[60] Ethanol may also directly damage the gastric mucosa, allowing other carcinogenic substances to penetrate into the mucosa and allowing tumorigenesis.[60] Finally, heavy alcohol consumption likely induces a chronic inflammatory state in the stomach, thus predisposing the organ to cancer.[61] Interestingly, some reports indicate that low to moderate alcohol consumption may have a protective effect against gastric cancer.[61,62] However, these findings are not consistent across all studies and may be a result of confounding. Possible mechanisms of the protective effect may be a possible bacteriocidic effect of ethanol on *H. Pylori* or favorable dietary patterns of light-moderate alcohol drinkers compared to non-drinkers and heavy drinkers. While there is good evidence that heavy drinking does increase the risk of gastric cancer, further studies are needed to understand the mechanisms at play.

3.6 | *H. pylori*

H. pylori is a spiral-shaped, gram-negative, microaerophilic bacterium thought to be transferred via oral-oral or fecal-oral transmission.[83,84] The pathogen was first described by Warren and Marshall in 1983 as the possible mechanism behind chronic active gastritis.[85] Since then, *H. Pylori* has been established as one of the primary risk factors for gastric cancer, accounting for up 89% of noncardia gastric cancer and 18% of cardia gastric cancer.[86] In 1994, the Internal Agency for Research on Cancer (IARC) an entity of the World Health Organization declared *H. Pylori* a class I carcinogen.[87]*H. Pylori* infection has been shown to increase the risk of gastric cancer three- to sixfold.[53–55] The mechanism behind how *H. Pylori* increases this risk is unclear, but two possible pathways have been considered: direct modulation of gastric mucosa through virulence factors such as *CagA* and *VacA*, and indirect action of *H. Pylori* on gastric epithelial cells. What is clear is that *H. pylori* infection induces a state of chronic active inflammation that can last decades. This chronic, active gastritis can subsequently promote gastric carcinogenesis, typically via the Correa model which suggests that chronic gastric inflammation leads to a cascade of mucosal atrophy, metaplasia, dysplasia, and eventually carcinoma.[88] Host genetic factors likely play a role as well – specific gene polymorphisms in genes encoding for tumor necrosis factor-α, interleukin (IL)-1, IL-8, and IL-10 have been associated with increased risk of gastric cancer in the setting of *H. Pylori* infection.[89]*H. Pylori* is a very common pathogen, infecting approximately half of the world's population, however, only a small percentage of that infected progress to gastric cancer, suggesting that progression is modulated by various elements including bacterial, environmental, and host genetic factors.

4 | CONCLUSION

Gastric cancer remains one of the most common causes of cancer mortality worldwide. Various modifiable and nonmodifiable factors modulate the risk of gastric cancer, and it is important to consider these risks when defining populations for novel screening methods. *H. Pylori*, diet, and smoking are important modifiable risk factors. Continued studies are needed to further delineate the genetic susceptibilities in those with a family history of the disease.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

NA.

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