

## Review Article



# Risk Factors of Gastric Cancer and Lifestyle Modification for Prevention

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### Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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## ABSTRACT

Gastric cancer has been consistently decreasing worldwide, whereas cardia gastric cancer is on the rise. This indicates that the exposure rates to epidemiological causes are changing. In this study, we aim to review the risk factors for gastric cancer with respect to cardia and non-cardia types. One of the most significant risk factors for gastric cancer is *Helicobacter pylori* infection. *H. pylori* infection is known as a risk factor for non-cardia gastric cancer, and there have been results indicating that *H. pylori* infection is not associated with cardia gastric cancer. However, in the East Asian region, there is epidemiological evidence suggesting that *H. pylori* infection might be a risk factor for cardia gastric cancer. Smoking and alcohol consumption are known risk factors for gastric cancer, regardless of anatomical location. Obesity is considered a factor in the development of cardia gastric cancer. However, further research is needed to understand the specific relationship with non-cardia gastric cancer. The consumption of high-salt and processed meat is more distinctly associated with non-cardia gastric cancer than in cardia gastric cancer. In addition to these factors, exposure to chemicals and radiation are considered risk factors for gastric cancer. Primary prevention of gastric cancer involves eliminating or avoiding risk factors such as *H. pylori* eradication and adopting a healthy lifestyle, including quitting smoking, reducing alcohol consumption, maintaining a healthy weight, and having a low-salt diet.

**Keywords:** Stomach neoplasms; Risk factors; Life style

## INTRODUCTION

Over the past 50 years, gastric cancer has been steadily decreasing worldwide, but it remains the fifth most common cancer type. In 2020, over a million people worldwide were diagnosed with gastric cancer, accounting for 5.6% of all cancer cases [1]. The cumulative lifetime risk of developing gastric cancer from birth to age 74 is 1.87% for males and 0.79% for females [1]. Gastric cancer incidence rates show significant regional and economic disparities, with higher rates in East Asia, Central and Eastern Europe, and developed countries. In East Asia, the age-standardized incidence rate of gastric cancer per 100,000 population is 32.5 for males, compared to 5.4 for North American males and 4.5 for Middle African males. In countries with a high Human Development Index, the incidence rate of gastric cancer is 18.9 cases per 100,000 people. In contrast, in countries with a medium to low Human

Development Index, it is 7.2 cases per 100,000 people [1]. Additionally, there is an existing disparity in the incidence of gastric cancer between men and women, with men having a rate 2.4 times higher than in women [1].

While gastric cancer was the leading cause of cancer-related deaths until the mid-1990s, it currently ranks as the third most common cause of cancer-related deaths. More than 760,000 people have died from gastric cancer. Gastric cancer accounts for approximately 7.7% of all cancer-related deaths, and the cumulative risk of dying from gastric cancer by age 74 is 1.29% for males and 0.55% for females. Similar to incidence rates, death rates are higher in males and are more pronounced in regions such as East Asia and Central and Eastern Europe.

The regional disparities, gender differences, and temporal changes observed in the epidemiology of gastric cancer indicate the presence of risk factors for gastric cancer and disparities among these risk factors. Research on risk factors for gastric cancer has been actively conducted, and organizations like the International Agency for Research on Cancer (IARC) and the World Cancer Research Fund International (WCRF) continuously update the levels of evidence for gastric cancer risk factors (Table 1) [2]. In this study, we aimed to examine the risk factors for gastric cancer, making a distinction between cardia and non-cardia gastric cancer.

## RISK FACTORS FOR GASTRIC CANCER

The risk factors for gastric cancer include family history, infection, smoking, alcohol consumption, obesity, dietary factors, and more. The strengths of the association between risk factors and whether it is cardia or non-cardia gastric cancer were summarized in Table 2.

### Family history

Family history is one of the most significant risk factors for gastric cancer. However, most gastric cancers occur sporadically, with only 10% showing familial aggregation and less than 3% being inherited in a Mendelian genetic pattern [14]. Hereditary diffuse gastric cancer, a representative form of familial gastric cancer, is caused by mutations in the cadherin-1 gene through an autosomal dominant inheritance [15].

**Table 1.** Risk factors of gastric cancer according to evidence levels

	Carcinogenic agents with sufficient evidence in humans	Carcinogenic agents with limited evidence in humans
IARC	<ul style="list-style-type: none"> <li>· <i>Helicobacter pylori</i></li> <li>· Rubber manufacturing industry</li> <li>· Tobacco smoking</li> <li>· X- and gamma-radiation</li> </ul>	<ul style="list-style-type: none"> <li>· Art glass, glass containers, and pressed ware (manufacture of)</li> <li>· Asbestos (all forms)</li> <li>· Epstein-Barr virus</li> <li>· Lead compounds, inorganic</li> <li>· Nitrate or nitrite (ingested) under conditions that result in endogenous nitrosation</li> <li>· Opium consumption</li> <li>· Pickled vegetables (traditional Asian)</li> <li>· Chinese-style Salted fish</li> <li>· Processed meat (consumption of)</li> </ul>
	Established or strong evidence	Limited suggestive evidence
WCRF/AICR	<ul style="list-style-type: none"> <li>· Smoking</li> <li>· <i>Helicobacter pylori</i> infection</li> <li>· Industrial chemical exposure</li> <li>· Body fatness (cardia)</li> <li>· Alcoholic drinks</li> <li>· Foods preserved by salting</li> </ul>	<ul style="list-style-type: none"> <li>· Processed meat (non-cardia)</li> <li>· Grilled (broiled) or barbecued (charbroiled) meat and fish</li> <li>· Low fruit intake</li> <li>· Citrus fruit (cardia risk decreasing)</li> </ul>

IARC = International Agency for Research on Cancer; WCRF = World Cancer Research Fund International; AICR = American Institute for Cancer Research.

**Table 2.** Associated risk factors with gastric cancer and RRs of the recent meta-analysis or pooled analysis

Factors associated with gastric cancer	Recent meta-analysis, RR (95% CI)		
	Overall	Cardia	Non-cardia
Family history [3]	1.84 (1.64–2.04)	1.38 (0.96–1.77)	1.82 (1.59–2.05)
<i>Helicobacter pylori</i> infection [4-6]	2.56 (2.18–3.00)	1.08 (0.83–1.40)	2.81 (2.14–3.68)
East Asia	2.83 (2.36–3.39)	2.86 (2.26–3.63)	4.36 (3.54–5.37)
West	2.12 (1.70–2.63)	0.80 (0.61–1.05)	4.03 (2.59–6.27)
<i>Helicobacter pylori</i> eradication [7]	0.54 (0.40–0.72)		
Cigarette smoking [6,8]	1.61 (1.49–1.75)	1.56 (1.18–2.08)	1.43 (1.02–2.00)
Alcohol drinking [9,10]			
Never vs. ever drinking	1.20 (1.12–1.27)	1.18 (1.03–1.35)	0.93 (0.76–1.13)
Never vs. heavy drinking	1.36 (1.12–1.27)	1.61 (1.11–2.34)	1.28 (1.13–1.45)
Obesity [11]	1.22 (1.07–1.39)	1.32 (0.80–2.16)	1.18 (0.73–1.92)
High salt intake [12]	1.24 (1.01–1.51)	1.25 (0.80–1.95)	1.46 (1.21–1.76)
Processed meat [13]	1.23 (1.06–1.43)	1.34 (0.97–1.84)	1.24 (1.03–1.49)

RR = relative risk; CI = confidence interval.

The risk of developing gastric cancer is known to be two or three times higher in individuals with a family history compared to those without [3,16]. Recent meta-analyses showed that the association between family history and gastric cancer appeared to be stronger for non-cardia (odds ratio [OR], 1.82; 95% confidence interval [CI], 1.59–2.05) than for cardia gastric cancer (OR, 1.38; 95% CI, 0.98–1.77) [3]. Despite a higher prevalence of family history among patients with gastric cancer in Asian regions compared to those in Western regions, the frequency of hereditary diffuse gastric cancer is low. This suggests that in regions with a high incidence of gastric cancer, environmental factors might play a larger role in familial gastric cancer compared to genetic factors.

### Infection

The most significant contributing risk factor for gastric cancer is *Helicobacter pylori* infection. *H. pylori* is a gram-negative bacteria classified as a Group 1 carcinogen by the World Health Organization (WHO) [17]. Direct and indirect pathways link the infection to gastric cancer development. *H. pylori* can directly affect gastric epithelial cells through protein modification and gene mutations and indirectly by inducing inflammatory reactions in the gastric mucosa, promoting gastric cancer development [18,19].

*H. pylori* infection increases the risk of gastric cancer by 2.9 times, and in cases of patients diagnosed with *H. pylori* infection and having gastric cancer for at least 10 years, the risk of developing gastric cancer can increase up to 5.9 times.

Approximately 44% of the global population is infected with *H. pylori*, and the infection prevalence increases with age [20]. Asian regions have higher infection rates, reporting 35% in high-income countries and 51% in low-income countries. Despite 80%–90% of non-cardia gastric cancer cases being associated with *H. pylori* infection, gastric cancer only occurs in 2% of all infected individuals. A correlation exists between gastric cancer incidence rates and *H. pylori* infection prevalence. However, this correlation is not seen in regions like Africa and South Asia, where infection rates are high; however, gastric cancer rates are low [21]. This discrepancy might be attributed to factors such as the presence of toxins such as CagA, VacA, Omp, and Hp0305 [22]. Even in individuals infected with *H. pylori* carrying the CagA toxin, those who test positive for *H. pylori* markers such as Omp and HP0305 have a threefold increased risk of gastric cancer compared to those who test negative [23].

While there is strong evidence supporting the role of *H. pylori* infection as a risk factor for non-cardia gastric cancer, the evidence is less clear for cardia gastric cancer. Studies even suggest that *H. pylori* infection might lower the risk of cardia gastric cancer [24]. *H. pylori* infection is known to reduce acid secretion in the cardia, decreasing inflammation and potentially lowering the risk of cardia gastric cancer [24]. Globally, *H. pylori* infection rates are declining, which is associated with a decrease in non-cardia gastric cancer cases. However, cardia gastric cancer rates are increasing. According to recent meta-analyses, *H. pylori* infection was associated with an increased risk of non-cardia gastric cancer, regardless of the region [4,25]. However, when considering cardia gastric cancer, the association was statistically significant in East Asia with a relative risk of 2.86; however, it was not statistically significant in Western regions, where the relative risk was 0.80 [4].

Epstein-Barr virus is another infection factor associated with gastric cancer, apart from *H. pylori*. The infection rate of Epstein-Barr virus in patients with gastric cancer is around 10%, and individuals infected with Epstein-Barr virus have a higher risk of developing gastric cancer compared to those without the infection [25]. However, the exact role of the Epstein-Barr virus in gastric cancer development is not yet fully understood.

### Smoking

Smoking is a significant risk factor for gastric cancer. Tobacco contains over 7,000 toxic chemicals, including carcinogens. These toxic and carcinogenic substances can directly damage DNA, leading to abnormalities in the growth and function of gastric epithelial cells and ultimately causing cancer [26].

Globally, smoking contributes to about 11% of gastric cancer cases, with the contribution being around 17% in Europe. Individuals with a history of smoking have a 1.5 to 2.5 times increased risk of developing gastric cancer compared to that in non-smokers [8]. A dose-response relationship has been observed between smoking and gastric cancer risk, where longer smoking duration, an earlier age of smoking initiation, and higher daily cigarette consumption are associated with increased risk of gastric cancer development [27]. Smoking was significantly associated with an increased risk of both cardia gastric cancer and non-cardia gastric cancer. Additionally, it raised the risk of cardia gastric cancer by 1.56 times and non-cardia gastric cancer by 1.43 times [8]. The risk of gastric cancer associated with smoking is evident with cigarette smoking and with the use of smokeless tobacco products like chewing tobacco.

### Alcohol drinking

The carcinogenic mechanism of alcohol consumption is linked to acetaldehyde, a toxic metabolite of ethanol. Acetaldehyde disrupts DNA methylation and interacts with retinoid metabolism, inducing DNA lesions. These DNA lesions ultimately lead to cellular mutations, promoting the development of cancer. According to the IARC and the National Cancer Institute (NCI), meta-analyses have shown a correlation between a daily alcohol intake of 10 g and a 1.02-fold increased risk of gastric cancer. Additionally, nonlinear dose-response analyses have reported a high level of epidemiological evidence that consuming more than three drinks per day increases the risk of gastric cancer.

Compared to the never-alcohol-drinking group, the ever-alcohol-drinking group showed an association with the risk of cardia gastric cancer; however, no significant association was observed with non-cardia gastric cancer [9]. However, the heavy alcohol-drinking group had

a higher risk of both cardia and non-cardia gastric cancers compared to that in the never-alcohol-drinking group [10]. The toxic effects of acetaldehyde, along with the interaction between alcohol consumption and other factors, contribute to the increased risk of gastric cancer. Alcohol consumption is a modifiable risk factor, and reducing or eliminating alcohol consumption can help lower the risk of gastric cancer and other related health issues.

### Dietary factors

Research on the association between dietary factors and gastric cancer has been conducted in various population groups. Carcinogenic substances in foods can interact with gastric epithelial cells, inducing genetic changes in these cells.

According to the IARC and the NCI, salted foods commonly consumed in East Asia, such as pickled vegetables and salted fish, have been identified as strong risk factors for gastric cancer, with substantial evidence supporting their association [2]. Additionally, processed meat consumption, smoked meat intake, and insufficient fruit consumption have been assessed as limited evidence of risk factors for gastric cancer development [2].

Compared to fresh vegetables, pickled vegetables contain lower levels of micronutrients and higher levels of salt, and they can undergo fermentation during storage. Laboratory studies have shown that excessive salt intake can generate carcinogenic substances called N-nitrosamines, leading to damage to the gastric cell walls, inflammation, and atrophy, which increases the colonization of *H. pylori* [28,29]. Meta-analyses have reported that a high intake of pickled vegetables is associated with a 1.24-fold increased risk of gastric cancer compared to that in low intake. A dose-response meta-analysis indicated that an increase in pickled vegetable consumption by 40 g per day results in a 1.15-fold significant increase in gastric cancer risk [30]. Moreover, the highest salt-containing food consumption group showed a 1.24-fold increased risk of gastric cancer compared to that in the lowest consumption group [12].

Fruits are rich in antioxidants such as flavonoids and can mitigate damage and inflammation caused by *H. pylori*. According to a dose-response meta-analysis, consuming more fruits and vegetables was associated with a reduced risk of stomach cancer [31]. A 5% reduction in the risk of gastric cancer for each 100 g increase in daily fruit consumption and a 6% reduction in the risk of gastric cancer for each 200 g increase in the daily consumption of fruits and vegetables [31]. Reports from the IARC and the NCI published in 1997 considered vegetable and fruit consumption as “possibly” preventive factors for gastric cancer. However, the 2016 report downgraded their level of evidence to “limited” due to a lack of observed associations between vegetable fruit consumption and gastric cancer prevention in well-designed cohort studies involving large populations [2].

Processed meats contain high levels of salt, nitrite, and nitrate. Nitrites and nitrates in meats react with amino acids to form N-nitrosamines, known carcinogens [32]. Smoked meats produce N-nitrosamines. While a clear association between processed meat consumption and gastric cancer has not been established, there is a significant association with gastric cancer [13].

### Obesity

A state of low-grade chronic inflammation characterizes obesity. In this state of chronic inflammation, inflammatory factors such as tumor necrosis factor-alpha, interleukin-6,

and C-reactive protein are increased, promoting cancer development. Obesity increases certain hormones in the body, such as leptin and insulin, leading to dysregulation of cell proliferation and apoptosis, ultimately promoting the growth of cancer cells.

According to the IARC and the American Cancer Society, being overweight or obese is a strong risk factor for distal esophageal cancer, supported by robust epidemiological evidence [2]. Quantitative meta-analyses have shown that every 5 kg/m<sup>2</sup> increase in body mass index (BMI) is associated with a 1.23-fold increased risk of distal esophageal cancer. However, this relationship has not been observed for cancer in other parts of the esophagus. Nonlinear dose-response meta-analyses have indicated that the risk of distal esophageal cancer significantly increases when BMI exceeds 26 kg/m<sup>2</sup> using a reference point of 21.7 kg/m<sup>2</sup>. In the meta-analysis, the association between obesity and gastric cancer was more pronounced in cardia gastric cancer compared to that in non-cardia gastric cancer [11,33].

### Chemical substances and radiation exposure

Dust, high-temperature processed particles, and metals like hexavalent chromium are associated with non-cardia gastric cancer. Occupations involving wood processing, food cooking equipment operation, rubber manufacturing, coal mining, and metal processing pose significant risks for cancer development. According to recent meta-analyses, asbestos exposure was associated with a standardized mortality ratio of 1.15 for gastric cancer, and workers exposed to talc had a 1.21-fold significantly increased risk of gastric cancer compared to that in unexposed workers [34,35]. Similarly, workers exposed to silica had a 1.25-fold significantly increased risk of gastric cancer compared to that in unexposed workers [36].

Radiation exposure, evaluated by the IARC's Monographs Program as a Group 1 carcinogen for gastric cancer, includes exposure to X-rays and gamma rays from ionizing radiation. A cohort study conducted on survivors exposed to radiation from the Hiroshima and Nagasaki atomic bombings showed an increased risk of gastric cancer among individuals with higher radiation exposure [37]. Furthermore, a study involving pediatric patients with cancer revealed that those without radiation exposure had a 2.4-fold standardized incidence ratio for gastrointestinal cancer compared to that in the general population, while patients with pediatric cancer with radiation exposure had a 4.6-fold standardized incidence ratio for gastrointestinal cancer compared to that in the general population, indicating an association between radiation exposure and gastrointestinal cancer [38].

## LIFESTYLE MODIFICATION FOR CANCER PREVENTION

Primary prevention aims to eliminate or avoid disease risk factors to prevent their occurrence. Therefore, primary prevention of gastric cancer involves improving lifestyle habits such as preventing and eradicating *H. pylori* infection, quitting smoking, reducing alcohol consumption, maintaining a healthy weight, and adopting a balanced diet.

Recent meta-analyses of prospective studies on the gastric cancer-preventive effects of *H. pylori* eradication showed that the group undergoing *H. pylori* eradication had a reduction of around 50% in the risk of gastric cancer compared to the group that did not undergo eradication [7,39,40]. Additionally, even asymptomatic individuals infected with *H. pylori* showed a significant reduction in gastric cancer risk after undergoing eradication [40].



The recognition of tobacco smoking as a health hazard gained significant traction after the release of the 1964 Surgeon General's report in the United States. The awareness of these health risks subsequently expanded globally, prompting many countries to implement anti-smoking campaigns and policies. Limiting alcohol consumption is recommended for cancer prevention by many health authorities and organizations. However, the recommended level of alcohol restriction may vary. The American Cancer Society recommends that people who do choose to drink alcohol should have no more than 1 drink per day for women or 2 drinks per day for men, although it is best not to drink alcohol [41]. The national cancer prevention guidelines of Korea recommend avoiding alcohol consumption for cancer prevention [42]. For reducing salt intake, the WHO recommends less than 5 g/day salt intake for adults to prevent non-communicable diseases, including gastric cancer [43].

The risk factors for gastric cancer vary by region, race, and era. The decreasing trend in non-cardia stomach cancer while an increasing trend in cardia stomach cancer suggests that the causal factors for gastric cancer differ between these 2 types. Moreover, it is essential to find epidemiological evidence for these risk factors and apply them in practice.

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