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Modifiable and Non-Modifiable Factors Associated with Gastric Cancer

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Abstract

Numerous studies have investigated the associations between dietary components, behavioral patterns, and susceptibility to gastric cancer (GC). Diet and lifestyle cover a spectrum of both protective and harmful factors associated with GC. Additionally, non-modifiable factors such as age, gender, blood type, family history, and genetic predispositions may influence GC development. This review aims to explore the interplay between modifiable and non-modifiable factors, along with dietary habits and lifestyle practices, in relation to GC risk and the potential underlying mechanisms. We have synthesized the primary findings of observational studies (case-control and cohort), systematic reviews, and meta-analyses pertaining to preventive and deleterious factors affecting the incidence of gastric cancer. A literature search was conducted on Google Scholar, MEDLINE (PubMed), ScienceDirect, and Scopus for articles published in English from 2001 to 2024. The main search terms included body weight and body fat; diet; fruits and vegetables; meats and processed meats; fried and fast foods; milk and dairy products; salty foods; food and dietary patterns; fat and sweets intake; alcohol consumption; smoking; physical activity; age; sex; family history; blood type; genetics; and medication, and the risk of gastric cancer. Unhealthy dietary patterns, consumption of fried and fast foods, salty foods, alcohol, and smoking have been associated with an increased risk of GC. Non-modifiable factors such as advanced age, male sex, family history, genetics, and blood type A were linked to an elevated risk of GC. Conversely, physical activity and high consumption of fresh fruits and vegetables may prevent GC occurrence due to the presence of antioxidants, fiber, and polyphenols. While many studies have demonstrated that dietary patterns loaded with red and processed meats were associated with a high

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risk of GC, others have yielded inconclusive results. Controversial findings regarding the relationship between body weight and body fat, medications, milk and dairy products, and fat and sweets consumption with the risk of GC were also observed. Adequate diet modification and addressing preventable factors may play a pivotal role in reducing the incidence of gastric cancer.

Introduction

Gastric cancer (GC) is one of the most rapidly lethal malignancies. It has been the fifth most frequent type of cancer worldwide and the second-leading cause of cancer-related death, responsible for over 1,089,103 new cases and an estimated 769 000 deaths in 2020.[1] While there has been a decline in gastric cancer incidence in certain regions, it remains a significant clinical challenge due to late detection in the majority of cases, limited predictive capabilities, and few treatment options available.[2] The prevalence of gastric cancer in Asian countries and Middle East varies greatly by regions, most prevalent being in Eastern Asia. In Japan, it is projected to be 12 times greater than in India and Iran, and seven times more common than in Iraq.[3] Gastric cancer develops when malignant cells start to grow out of control in the lining of the stomach.[4] Many factors may play a role in the development of gastric cancer. Age, gender, blood type, family history and genetic factors may contribute to the development of gastric cancer, but they are neither modifiable nor preventable.[5] Nutritional factors, body weight, body fat, and behavioral habits like cigarette smoking and alcohol consumption, along with Helicobacter pylori infection, are all recognized contributors to the onset of gastric cancer.[5 6] However, these factors are largely modifiable and preventable. Moreover, physical activity may play a role in the prevention of gastric cancer.

Diet is an important modifiable risk factor for gastric cancer. Various epidemiological studies observed an association between some nutritional exposures and dietary components with gastric cancer. High intake of processed meat, fat, sugar, salty and fried food and dairy products has been associated with a higher risk of gastric cancer.[7 8] The consumption of unhealthy processed food and low consumption of fruits and vegetables may increase the risk of development of gastric cancer. Conversely, a diet high in vegetables and fruits and a variety of natural food may have a preventive effect. Therefore, conducting a comprehensive review of studies, including cross-sectional, case-control, and cohort studies, as well as systematic reviews and meta-analyses, on both non-modifiable and modifiable factors in GC is essential for obtaining a thorough understanding of the disease. Such a review encompasses genetic, demographic, lifestyle, and dietary factors, providing valuable insights for healthcare professionals. This comprehensive understanding aids in patient assessment and management by informing healthcare professionals about relevant risk factors. Moreover, it facilitates the development of effective preventive strategies and guides research priorities in the field. Additionally, the findings of this review can play an important role in patient education, empowering individuals to make informed decisions about their health and contributing to improved outcomes in the management of GC.

Methods

A PubMed, ScienceDirect, Google Scholar and Scopus search was performed for publications from February 1998 through April 2022. Our search included modifiable and non-modifiable risk factors that are associated with the risk of GC, of any type (adenocarcinoma, lymphoma, sarcoma, or carcinoid) and location (cardia or non-cardia).

Terms used in the search strategy included the exposures— body weight and body fat, diet, fruits and vegetables, meats and processed meats, fried and fast foods, milk and dairy products, salty foods, food and dietary patterns, fat and sweets intake, alcohol consumption, smoking, physical activity, age, sex, family history, blood type, genetics, medication —and the risk of gastric cancer.

Observational (cohort and case-control) studies, systematic reviews and meta-analysis addressing the association between gastric cancer and any of the above exposures were included.

We restricted our extensive search to studies related to the objective of the review and those published in English and reported on human subjects. All of the authors conducted the literature search independently. Table 1 shows the search strategy summary.

Table 1: Summary of Search Strategy

Items	Specification
Date of Search	October-December; 2023
Databases and other sources searched	Google Scholar; MEDLINE (PubMed); Scopus; and ScienceDirect
Search terms used	Body weight and body fat; Diet; Fruits and vegetables; Meats and processed meats; Fried and fast foods; Milk and dairy products; Salty foods; Food and dietary patterns; Fat and sweets intake; Alcohol consumption; Smoking; Physical activity; Age; sex; Family history; Blood type; Genetics; Medication —and the risk of gastric cancer.
Duration	2001 to 2024
Inclusion Criteria	- Studies from different designs; from cross-sectional, case-control, and cohort studies; as well as systematic reviews and meta-analysis. - Articles published in English language
Selection process	Each of the authors independently conducted the literature search.

Factors Associated with Gastric Cancer

Many factors that may lead or prevent cancer exist. It is divided into modifiable and non-modifiable factors. In this literature review we will shed the light on the most important modifiable and non-modifiable factors that are associated with GC.

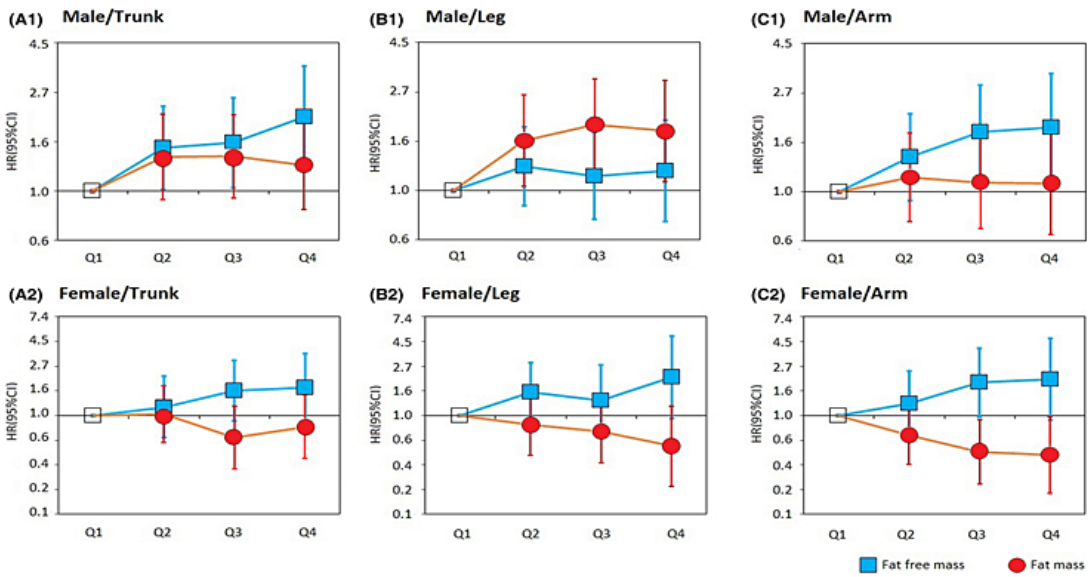

Fig. 1: The distribution of fat-free mass/fat mass[12]
(Abbreviations: RR, risk ratio; CI, confidence interval; Q1, Quarter 1; Q2, Quarter 2; Q3, Quadrant 3; Q4, Quadrant 4).

Modifiable Risk Factors Associated with Gastric Cancer:

Body Weight and Body Fat

Several studies show that there is an association between excess body weight and cancer prevalence.[7-9] Obesity has been linked to both cancer incidence and mortality in many epidemiological studies.[8] Although some studies have established a link between excess body weight and an increased risk of GC7, existing epidemiologic research on the link between high body weight and the risk of stomach cancer has shown controversial results.[10] It might be explained by the high levels of estrogen secreted by the adipose tissue. Exposure to estrogenic effects for prolonged periods of time may reduce the incidence of GC. Most studies show that there is an indistinct association between body fat and GC.[8 9] In fact, high adipocytes in the body and inflammatory cells that secrete adipokines and cytokines may promote tumor development and contribute to the development of GC. Gastroesophageal reflux disease (GERD), a risk factor for esophageal cancer and cardia gastric cancer (GC), may be caused directly by abdominal fat.[11] Furthermore, fat is metabolically active, producing a variety of metabolic products that circulate throughout the body such as insulin-like growth factor and leptin9. Both metabolites have been linked to cancer, possibly by inducing pro-growth modifications in the cell cycle, reduced cell death, and pro-neoplastic cellular changes. In most investigations, obesity was linked to a higher risk of stomach cancer9, especially in men and non-Asians. Being overweight and obese was linked to a higher risk of gastric cardia cancer (GCC)9. The link between total body fat and stomach cancer may vary between men and women.[12] For men, there is no sufficient evidence of an association, while in female participants, total body fat mass was associated with a reduced risk of stomach cancer[12] (Figure 1).

A recent study shows an association between lean and fat mass distribution and GC risk.[12] The analyses were segmented by age (37–49, 50–59, or ≥75 years) and further adjusted for various factors including ethnicity, smoking status, alcohol consumption, polygamy index, physical activity, fruit and vegetable consumption, diabetes, height, NSAID use, and family history of cancer. Additionally, adjustments were made for lean mass and fat mass, with mutual adjustments for each other.[12] The authors observed that lean body mass, especially located in the arms and torso in women, was associated with an increased risk of GC12. However, total and arm fat mass were associated with a reduced risk of stomach cancer in women.[12] For both sexes, lean arm mass is probably the best predictor of stomach cancer risk.[12] These results indicate that lean and fat mass may play different roles in GC development in men and women.[12]

Diet and GC

Fruits and Vegetables and GC

Several studies investigated the association between the consumption of fruits and vegetables and the risk of GC.[13-18] Schwingshackl *et al*. (2017) conducted a systematic review and meta-analysis study, and reported that high adherence to the Mediterranean diet has a positive effect on overall cancer risk in primary prevention.[17] Mediterranean diet mainly consists of high content of fruits, vegetables, and whole grains.[17] As a result, the phytic acid, resistant starch, and soluble fiber found in the stated food groups are capable of binding and neutralizing potentially carcinogenic compounds in foods which may protect from GC development (RR observational: 0.82, 95% CI 0.75 to 0.88; I2 = 73%, n = 11 studies; RR cohort: 0.86, 95% CI 0.80 to 0.92, I2 = 28%, n = 6 studies; RR case-control: 0.71, 95% CI 0.57 to 0.88, I2 = 88%, n = 5 studies).[17] Moreover, Cover *et al*. (2013) demonstrated that high consumption of fruits and non-starchy vegetables protects against stomach cancer.[14] In women, flavonoids have been associated with a 20% reduction in the risk of developing GC.[14] The protective effect of fruits and vegetables against the development of stomach cancer was associated to the high amounts of antioxidants.[14] Furthermore, Farmanfarma *et al*. (2020) found that citrus fruits, fresh fruits, and garlic intake were associated with a lower risk of stomach cancer.[15] Fruits are high in antioxidants, fibers, vitamins, and minerals that can prevent cancer development or progression.[15] Some vegetables, such as onions, had a little preventive effect against this malignancy when consumed less than twice a week (OR=1.28; 0.73–2.23).[15] The reason is unclear; however, it could be from the soil's contents.[15] Bae *et al*. (2016) reported that citrus fruit consumption significantly reduces the risk of stomach cancer, particularly cardiac gastric cancer (CGC) (p-value=0.002).[13] Consuming 100 g of citrus fruit per day decreased CGC risk by 40%

(RR, 0.603; 95% CI, 0.439 to 0.827).[13] Similarly, Wang *et al*. (2014) showed that fruit intake had a strong protective impact on GC risk, however not for vegetable consumption (fruit: SRR= 0.95, 95% CI: 0.91–0.99; vegetable: SRR = 0.96, 95% CI: 0.91–1.01).[18] Nemati *et al*. (2012) reported that a lack of fresh fruits and vegetables consumption was a risk factor for stomach cancer.[16] In fact, high consumption of fruits, particularly citrus fruits are associated with a lower risk of stomach cancer due to its antioxidant activity.[16] This study indicates that citrus fruit reduced the risk of developing GC more than other fruits due to high levels of ascorbic acid and beta-carotene.[16]

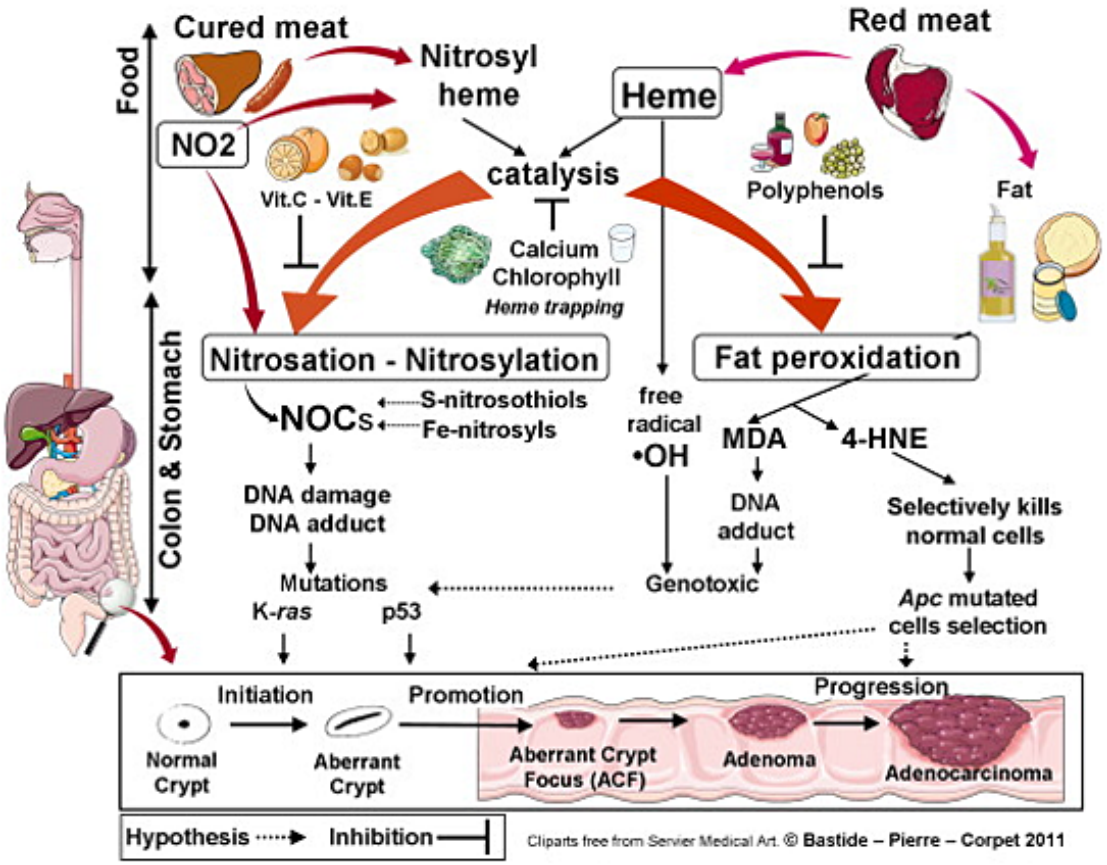

Fig. 2: The catalytic effect of heme iron on fat peroxidation and N-nitrosation, as well as their inhibition through dietary interventions.[27]

Meats and Processed Meats and GC

In the meta-analysis study conducted by Kim *et al*. (2019), a distinct correlation was observed between elevated consumption of red and processed meats and a heightened risk of gastric cancer.[19] Red and processed meat were linked to a 41% and 51% higher risk of GC, respectively (RR, 1.41; 95% CI, 1.21–1.66; RR, 1.57; 95% CI, 1.37–1.81).[19] Also, Tayyem *et al*. (2023) found that patients who consumed cooked red meat (veal and lamb) were more likely to develop GC.[20] In addition, Zhao (2017) stated that the dietary guidelines should be updated due to the relationship between red and processed meat consumption and GC risk.[21] Moreover, a study that was conducted in Iran by Farmanfarma *et al*. (2020) reported that there is a significant link between processed red meat intake and the risk of developing stomach cancer.[15] Furthermore, Huang *et al*. (2021) found that red meat consumption increased the risk of GC by 11%-51%, with every 100 grams/day raising the overall cancer mortality.[22] Besides, every 50 gram/day increase in processed meat consumption was linked positively to GC by 8%-72%.[22] These findings

might be explained by the high concentrations of nitrite present in processed meat that interact with secondary amines and N-alkylamides to form Carcinogenic N-nitroso compounds (NOCs), which is a mixture of nitrosamines and nitrosamides.[22] O6-Alkylguanines couple with thymine instead of cytosine, which causes changes in DNA base pairs, forming carcinogens due to the metabolism of nitrosamines.[22] Likewise, Collatuzzo *et al*. (2022) indicated a positive correlation between GC and total red meat intake.[23] This correlation had an HR of GC equal to 1.41.[23] Overall red meat consumption was associated with an 8% and 9% increase in GC risk.[23] Similarly, a significant increase was observed with the consumption of red meat and it was reported that red meat and processed meat consumption cause GC.[24] However, according to Poorolajal *et al*. (2020), the intake of red meat had no significant impact on stomach cancer (p=0.080), and the overall OR was 1.31 (95% CI, 0.87 to 1.96) when eating red meat ≥4 times/week vs. <4times/week.[25] In addition, Wilunda *et al*. (2022) demonstrated that consumption of all meats, red meats, and processed meats was not associated with GC.[26] In fact, meats heme iron promotes the endogenous formation of (NOCs), which is a risk factor for GC. It affects high levels of nitrogen residues in the gastrointestinal tract, which contributes to the formation of DNA adducts. Another reason is high temperatures used to cook red and processed meats, which creates a significant amount of carcinogens including polycyclic aromatic hydrocarbons, heterocyclic amines, and N-nitroso compounds.[15 19 21]

Nitrosation and fat peroxidation are catalyzed by heme iron.[27] The end products are N-nitroso compounds (NOCs), malondialdehyde (MDA), and 4-hydroxy-nonenal (4-HNE).[27] Through these pathways, red and cured meat promotes cancer.[27] Calcium carbonate or chlorophyll can be used to trap heme iron and inhibit its catalytic activity.[27] Vitamin C and E inhibit endogenous NOC formation.[27] Moreover, certain polyphenols may inhibit fat peroxidation and-or nitrosation.[27]

Fried and Fast Foods and Gc

A study conducted by Guo *et al*. (2018) in China demonstrated that fried food consumption is linked to stomach cancer and pre-cancerous lesions.[28] Fried food consumption was found to be a risk factor for GC (OR=1.89, 95% CI: 1.57-2.28; OR=1.91, 95% CI: 1.66-2.20).[28] Another study conducted in China found that fast-food patterns have been linked to increase gastric cancer risk.[29] In addition, Koszucka *et al*. (2020) demonstrated that acrylamide is a carcinogenic compound that is formed during heat-induced processes, such as frying, and causes mitochondrial dysfunction.[30] Moreover, Li *et al*. (2022) showed that GC and pre-cancerous lesions were independently associated with frequent consumption of fried foods.[31] Furthermore, Duan *et al*. (2021) reported that there was an independent risk for GC associated with both irregular meals and eating fast food (OR = 1.71, 95% CI: 1.62-1.91 for irregular meals, and OR = 1.83, 95% CI: 1.71-2.01 for fast food).[32] Ghaffari *et al*. (2019) reported that one of the risk factors that leads to GC is consuming fried food.[33] Additionally, Sun *et al*. (2019) found that the consumption of fried foods is associated with a significant risk of GC as it lowers the levels of vascular endothelial growth factor (Z=1.740, P=0.006) and increases tumor necrosis factor –α levels (P<0.05).[34] The mucous membrane of the upper digestive tract could be damaged by eating fried foods and fast food, which may lead to GC.[34] On the other side, fat may induce inflammatory events in diabetes by activating the Toll-like receptor 4 (TLR4) pathway in dendritic cells and Th17, which could result in chronically inflamed tissues producing high levels of IL-15.[34] Thus, serum IL-15 levels were higher in GC patients that consume large amounts of fried foods.[34] Similarly, Vahid and Davoodi (2021) showed that the risk of GC increased as it is associated with excessive consumption of fried foods at high temperatures and the frequent use of oil when cooking.[24] According to a meta-analysis study, fried food intake is positively correlated with gastric cancer risk.[35] The body converts nitrate to nitrite during metabolic processes, and nitrite has been linked to cancer development.[35] Therefore, a high nitrate intake can increase gastric cancer risk.[35] Nitrate content in foods is modulated by the cooking process.[35] In an additional study evaluating the risk of nitrate in vegetables, the cooking methods applied to raw vegetables resulted in a reduction of nitrate content, ranging from 4.094% to 59%. Notably, the boiling process exhibited the most substantial decrease, ranging from 47% to 59%36.[37] In contrast, frying vegetables increases nitrate content (12.46–29.93%).[36 37] It has been shown that frying oil is four-fold more likely to cause digestive cancers if it is reused more than four times.[35] Depending

on the temperature and duration of cooking, the harmful components of frying oil can have different impacts.[35] However, Aljumaily *et al*. (2023) showed that sautéed or fried vegetables cooked in olive oil can protect against gastric cancer in the second and third tertiles (AOR = .55 (.31-.97) and AOR = .53 (.32-.87)).[38] In fact, virgin olive oil consumption has been linked to protection against cancer due to its high content of polyphenols38. Polyphenols are natural substances found in olive oil that have antioxidant, anti-cancer, and anti-inflammatory properties38. Therefore, it protects against oxidative damage and helps regulate the immune system.[38] Additionally, individuals with the highest intake of olive oil have been found to have a 23% lower risk of gastric cancer.[39] Overall, limiting fried food consumption can help to avoid stomach cancer and pre-cancerous lesions, but using virgin olive oil as a substitute to sautéed or fried vegetables can protect against the development of gastric cancer.

Salty Foods and GC

According to the World Cancer Research Fund/ American Institute for Cancer Research (WCRF/ AICR), salt is one of the most major risk factors for stomach cancer.[40] Fang *et al*. (2015) demonstrated that excessive salt consumption has been linked to an increased risk of stomach cancer in earlier research.[41] According to estimates, more than 6 grams of salt per day was linked to 24% of stomach cancer incidences in the UK (31% in males and 12% in women).[4] According to the meta-analysis that was conducted by D'Elia *et al*. (2012), people who consume high amounts of salt have a greater risk of stomach cancer than those who consume less salt.[43] Furthermore, a Korean cohort research found that people who consumed more salty meals had a higher risk of stomach cancer (Kim *et al*., 2010).[4] Moreover, Ge *et al*. (2012) found that a high salt diet raised the incidence of s2tomach cancer by 22%.[45] Umesawa *et al*. (2016) reported that even after controlling for sodium consumption, there was a significant link between salty food choices and the risk of stomach cancer by approximately 30%.[46]Several epidemiological studies have found a link between salty pickle consumption and the incidence of stomach cancer.[46] However, in this study there was no link.[46] Furthermore, Kim *et al*. (2022) found a significant correlation between salty food and GC, and high sodium consumption can contribute to gastritis and mucosal irritation by damaging the mucosal barrier (relative risk = 1.68, 95% CI = 1.17–2.41).[47] Wu *et al*. (2021) showed an increase in GC risk associated with high and moderate salt intakes.[48] There is a high probability (RR: 1.25; 95%CI: 1.10-1.41); P = 0.001) or moderate probability (RR: 1.20; 95%CI: 1.04-1.38; P = 0.012).[48] Additionally, Vahid and Davoodi (2021) demonstrated that higher risk of GC was associated with salt consumption. In the presence of *H. pylori* infection, salt may have synergistic effects, including strengthening cytotoxin-associated gene A(CagA) expression, increasing mucus viscosity, inducing epithelial damage, increasing inflammatory responses, and causing hypergastrinemia.[24] Likewise, Yang *et al*. (2020) reported that GC may be increased by high salt intake, particularly in the presence of *H. pylori* infection and atrophic gastritis.[49] In summary, excessive salt intake amplifies gastric carcinogens like N-methyl-N-nitro-N-nitrosoguanidine and can act as a stimulant to the gastric mucosa, leading to atrophic gastritis, accelerated DNA synthesis, and increased cell proliferation.

Milk and Dairy Products and GC

Wang *et al*. (2018) has found a strong relation between dairy consumption and the risk of stomach cancer.[50] Qin *et al*. (2004) stated that oestrogen found in milk may have a role in the development of prostate cancer, but it may also protect against stomach cancer.[51] However, in the study that was conducted by Sun *et al*. (2014), the intake of dairy products was linked to a non-significant increase in the incidence of stomach cancer.[52] Furthermore, Tayyem *et al*. (2022) documented an association between a high-dairy diet and a reduced risk of gastric cancer mortality specifically among males.[53] The multivariate hazard ratios were 0.82 (95% CI: 0.61–1.10), 0.74 (95% CI: 0.54–1.01), and 0.72 (95% CI: 0.52–0.99).[53] On the other hand, an Italian study found that a diet high in dairy products is associated with a higher risk of GC (OR, 2.13; 95% CI, 1.34–3.40).[54] Moreover, Kwak *et al*. (2021) showed that dairy products have some components that could potentially increase the risk of GC and other components that could decrease it (e.g., calcium, potassium, magnesium, riboflavin, vitamin B12, and insulin-like growth factor I).[55] There was a positive association between dairy product consumption and lower GC risk (RR=0.76; 95% CI, 0.64-0.91).[55] The result found was explained by the

fact that dairy products may alleviate symptoms such as indigestion.[55] In addition, Gunathilake *et al*. (2021) found a significant positive correlation between a high dairy pattern score and a low microbial dysbiosis index with a lower risk of GC in females (OR = 0.23; 95% CI: 0.07-0.76; p-interaction = 0.018).[56] In response to metabolic imbalances and microbial dysbiosis, probiotic-containing dairy products reduce the levels of several cancer-related biomarkers and increase IFN-γ production resulting in anticancer effects.[56] As a result, a dairy product such as fermented milk should be consumed daily to decrease the risk of GC56. Controversially, Asfari *et al*. (2022) demonstrated that intake of dairy products was associated with GC development (OR=2.28).[57] Cows are exposed to several carcinogens in feedstuffs such as bracken fern, which could lead to GC development. In addition, cows' milk is contaminated with pesticides that are shown to be carcinogenic or tumour promoters.

Food and Dietary Patterns and GC

Nemati *et al*. (2012) showed that dietary habits and *H. pylori* infection were the two most important factors linked to stomach cancer.[16] Regular consumption of vegetables and fruits, especially citrus fruits, was found to lower the incidence of stomach cancer.[15] Unsaturated fat consumption has also been demonstrated to protect against the development of stomach cancer.[16] Drinking hot tea was linked to a nearly twice increase in the incidence of stomach cancer.[16] A study con[16] ucted by Abnet *el al*. (2015) showed that eating habits that included more fruits and vegetables, were linked to a lower risk of stomac *el al*. h cancer and gastric adenocarcinoma (OR, 0.63).[58] The same study demonstrated that diet high in meat and nitrates was strongly linked to a greater incidence of stomach adenocarcinomas (OR, 2.40).[58] Moreover, Kim *et al*. (2021) conducted a study including two dietary patterns: westernized and prudent patterns.[59] The westernized pattern consists of a high amount of meat and other animal items, and the prudent pattern contains a high amount of vegetables and fruits.[59] The prudent pattern was found to lower the incidence of GC.[59] As a result, adherence to a healthy dietary pattern, which is characterized by high consumption of fruits and vegetables, is beneficial in lowering the incidence of GC.[59]

Fat and Sweets Intake and GC

There are controversial findings about the association between dietary fat intake and GC. Several studies have found that high intake of total fat was positively correlated with GC.[7 8 60] Despite the fact that many case-control studies have indicated that a high dietary fat intake may increase the risk of stomach cancer8, other studies showed an inverse effect of dietary fat on GC.[7] Since cholesterol is ingested in conjunction with other substances such as salt, nitrates, multivitamins, minerals, and high-quality protein, the interplay of multiple nutrients precludes us from fully comprehending cholesterol's particular effect. Total fat, saturated fat, and cholesterol intake were all found to be substantially linked to the risk of stomach cancer, with ORs of 1.58 (95 percent CI 1.13–2.20), 1.86 (95 percent CI 1.37–2.52), and 1.75 (95 percent CI 1.36–2.25) for the highest quartile against the lowest quartile, respectively.[60] In addition, it was reported that long-term high sugar or carbohydrate intake could lead to chronic hyperinsulinemia.[61-63] In fact, hyperglycemia may cause insulin release and consecutively lead to a hyperinsulinemia.[64] The risk of developing cancer will increase through insulin signaling pathway.[64] Moreover, foods or beverages high in sugar content are low in fiber and micronutrients that help with digestion.[65] Refined sugar causes acute fluctuations in blood sugar levels, which may lead to oxidative stress and modulate carcinogenic pathways.[63 66-68]

Alcohol Consumption and GC

The association between alcohol consumption and the risk of GC has been proved by many studies.[69-73] Dong and Thrift (2017) stated that consumption of alcohol is a known high-risk factor GC69. Moreover, Li *et al*. (2021) explains that alcohol consumption has been linked to an increased risk of stomach cancer.[70] In addition, Ma *et al*. (2017) indicated that the findings of a meta-analysis back up the theory that drinking alcohol raises the risk of GC.[71] Moreover, Moy *et al*. (2010) found that alcohol consumption may have independent impacts on the development of GC in this high-risk population.[72] However, the apparent link between alcohol consumption, particularly hard liquor, and the incidence of stomach cancer may be due to nitrosamines found in alcoholic beverages.[72] A meta-analysis shows that there is no link between moderate alcohol consumption and the risk of GC.[73]

However, heavy alcohol consumption was linked to a higher risk.[73] A study found that alcohol intake raises the incidence of GC (odds ratio (OR) of 1.39) (Ma *et al*., 2017).[71] Tramacere *et al*. supported the relationship between the risk of stomach cancer and heavy alcohol consumption (four drinks per day).[73] Moreover, a study found that people that consume more than 50g of alcohol per day had a 24% higher chance of developing stomach cancer than others that did not drink alcohol or consumed less.[74] Alcohol can help to induce a cancer-stimulating mechanism involving a chronic inflammatory response to the toxic effects of ethanol metabolites[40] and stimulates cytokines secretion, thereby increasing nitrosamine intake.[40]

Smoking

Research showed the role of tobacco smoking in the development of stomach cancer. A study conducted in 2017 stated that smoking has been identified as a major risk factor for stomach cancer in previous research.[69] Additionally, a study demonstrated that male smokers have a 60% greater risk of GC, whereas female smokers have a 20% increased risk. Another study showed that among previous male smokers, a shorter time since quitting resulted in a higher risk, even after cigarette-years were taken into consideration. This builds on the evidence that there is a link between cigarette smoking and stomach cancer and it shows that smoking may be a risk factor for developing GC. Moreover, the link between cigarette smoking and the risk of stomach cancer is confirmed by the worldwide dataset. A study revealed that current smokers have a 25% higher risk of developing stomach cancer.[75] When compared to never smokers, the risk increased dramatically with cigarette smoking intensity and duration, reaching 32% for smokers who smoke more than 20 cigarettes per day and 33% for smokers who had smoked for more than 40 years.[76] In addition, Shah and Bentrem (2022) stated that cigarette smoking, like many other malignancies, is a risk factor for stomach cancer.[77] Smokers have a 1.5–1.8 times increased chance of developing stomach cancer than non-smokers.[77] There is ongoing study about the mechanisms underlying how smoking affects cancer in the stomach.[77] Cigarette smoke contains a range of carcinogenic components.[77] Possible mechanisms include DNA adduct production, stimulation of tumor angiogenesis, activation of nicotinic cholinergic receptors, and induction of cell proliferation.[77]

Physical Activity (PA)

Most of the researchers found a relationship between PA and GC. Abioy *et al*. (2015) stated that regular physical activity may lower the risk of stomach cancer.[78] McTiernan *et al*. (2019) showed strong evidence that physical activity lowers cancer risk.[79] Moreover, Singh *et al*. (2015) indicated that the incidence of overall and site-specific GC is lower among the most physically active persons than among the least physically active people.[80] In fact, it has been demonstrated that physical activity might reduce chronic inflammation by reducing interleukin-6 and tumour necrosis factor-α, partly through fat loss.[80] Additionally, Psaltopoulou *et al*. (2016) showed in their meta-analysis that physical activity can reduce the risk of stomach cancer, particularly in Asian populations.[81]Moreover, case-control study showed a relationship between GC and PA82. The study found that people with highest PA level were 78% less likely to have GC.[82]

Medication

There is an association between the intake of medication and the risk of developing GC. Seven randomized meta-analysis studies have found that treatment of *H. pylori* can reduce GC risk by 35%.[1] It has been reported that indirect effect of *H. pylori* on gastric epithelial cells through generating inflammation and direct action of the bacteria on epithelial cells are the two most common mechanisms. Results indicates *H. pylori* may directly regulate epithelial cell activity through bacterial compounds like cytotoxin-associated gene A (CagA). Treating *H. pylori* can reduce the likelihood of future gastric cancer incidence in healthy, asymptomatic individuals infected with the bacterium.[83] In preventing development of subsequent gastric cancer, *H. pylori* eradication therapy was superior to placebo or no treatment (RR = 0.66; 95% CI 0.46 to 0.95).[83] Studies have indicated that eradicating *H. pylori* can be advantageous in preventing the future development of GC.[8] In individuals with *H. pylori* infection who had a family history of gastric cancer among first-degree relatives, undergoing *H. pylori* eradication treatment decreased the risk of developing gastric cancer.[84]

Additional observational studies suggest that the use of non-steroidal anti-inflammatory drugs (NSAIDs) and statins may decrease the incidence of stomach cancer. Furthermore, individuals diagnosed with

type 2 diabetes who take metformin may have a reduced risk of gastric cancer. However, the use of sulfonylureas might be linked to an increased risk of gastric cancer.[85]

Non-Modifiable Risk Factors Associated with Gastric Cancer

Age

Many researches revealed that the impact of GC varies by age group.[86 87] Asaka *et al*. (2020) showed that preventing all cancers, not only GC, is extremely difficult in people over the age of,[80] implying that cancer preventive methods should be evaluated separately for people under the age of 80 and those above the age of 80.[86] Furthermore, studies found that participants with a higher age had a higher susceptibility for screening.[87] Screening acceptance rises with age, with the highest rate of screening reported among those aged.[50–59] As a result, age, education level, and household income are all factors that influence stomach cancer screening.[87] Moreover, Shah and Bentrem (2022) stated that with aging, the chance of stomach cancer rises.[77] Indeed, the increased risk of gastric cancer with age can be attributed to various factors. Prolonged exposure to potential carcinogens, along with heightened susceptibility to mucosal damage and delayed healing of gastric mucosa, are significant contributors. Additionally, older individuals may exhibit elevated levels of mucosal cancer stem cell markers, a greater prevalence of chronic active gastritis, intestinal metaplasia, and mucosal atrophy, particularly in those infected with *H. pylori*. These combined factors create a conducive environment for the development of gastric cancer as individuals age.[77]

Sex

The risk of GC is higher in men than women. Li *et al*. (2020) found that men had larger, more advanced, and higher-grade GC than women.[88] Furthermore, Rawla and Barsouk (2019) indicated that females have a significantly lower rate of GC than males.[89] It might be explained by the estrogen's preventive impact reducing the risk of stomach cancer in women.[89] In addition, Shah and Bentrem (2022) showed that GC affects men twice as frequently as it affects women.[77] Studies attempting to explain the difference in incidence between men and women have yielded conflicting results.[77] These studies looked at sociodemographic traits, environmental factors, sex hormones, hormonal therapies, and smoking habits.[77] However, men tend to have a higher prevalence of *H. pylori* infection, which presumably plays a role in the difference of stomach cancer incidence observed in both genders.[77]

Family History (FH)

Many research have confirmed the link between FH and the risk of GC.[90-92] Man *et al*. (2021) stated that family history of early-onset cancer is strongly associated with the development of GC, with an OR ranging from 1.77 to 3.27.[90] Elevated GC risk is connected to genetic backgroud characteristics such as IL-17 polymorphisms and cell proliferation-related genetic polymorphisms, which can explain part of the link between family history and an increased risk of GC.[90] Additionally, Yaghoobi *et al*. (2010) reported that a strong and constant risk factor for GC is a positive family history, but the molecular basis for the aggregation is mainly unknown.[9] In addition, Song *et al*. (2018) stated that specific subtype2s of GC are closely linked to a family history of GC.[91]

Genetics

Many studies showed that genetic risk factors play a big role in developing GC.[89 93 94] Rawla and Barsouk (2019) indicated that certain inherited gene mutations, such as the GSTM1-null phenotype or the CDH1 gene, have been linked to an increased risk of stomach cancer. Hereditary differentiated GC (HDGC) is an autosomal dominantly inherited disorder in which malignant cells proliferate beneath the stomach lining and metastasize as a result of the loss of one of the CDH1 gene's copies.[89] Additionally, Slavin *et al*. (2019) stated that many well-known genetic disorders carry a risk of GC94. These syndromes are frequently linked to a higher risk of non-gastric malignancies.[94] Furthermore, Lu *et al*. (2015) reported that the impact of DNA damage and repair in the development of stomach cancer cannot be overstated.[93] Additionally, Shah and Bentrem (2022) showed that there are many genetic syndromes affecting GC such as Hereditary diffuse GC, Hereditary nonpolyposis colorectal cancer, Familial adenomatous polyposis, Gastric adenocarcinoma and proximal polyposis of the stomach, MUTYH-associated polyposis, Juvenile polyposis syndrome, Peutz–Jegher syndrome and Li–Fraumeni syndrome.[77]

Blood Type

There is an association between the blood group A and the risk of GC. Zhang *et al*. (2014) indicate that blood group A is linked to a higher risk of cancer, while blood group O is linked to a lower risk of cancer.[95] Moreover, Goral (2016) stated that GC is more common in people with blood type A, but this is thought to be due to genes rather than blood type antigens.[96] In addition, Benbrahim *et al*. (2017) reported that people with blood group A had a 20% higher risk of stomach cancer than those with blood groups O, B, or AB.[97] Moreover, Shah and Bentrem (2022) demonstrated that compared to other blood types, group A blood carriers have a higher relative risk (1.11–1.21) of developing stomach cancer.[77] Multiple mechanisms have been proposed to explain this association, including alterations in gastric secretory function, intracellular adhesion receptors, membrane signaling, immune surveillance, inflammatory responses to *H. pylori* and cancer cells, and heightened susceptibility to pernicious anemia.[77]

Conclusion

In summary, this review showed that high consumption of fried and fast foods, salty foods and alcohol, smoking, advanced age, male sex, family history, genetics, and blood type A may increase the risk of GC; whereas physical activity, consumption of fruits and vegetables that are rich in antioxidants, fiber, and polyphenols might play a protective role against GC. Dietary patterns characterized by high consumption of red and processed meats was associated with an elevated risk of GC. Studies found controversial results related to body weight and body fat, medications, milk and dairy products, fat and sweets consumption with the risk of GC. Further research is needed to define the efficacy of diet and behavioral modifications in the prevention and treatment of gastric cancer as well as determine and clarify the underlying reasons behind gender differences in the relationship between dietary patterns and GC risk.

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Competing Interests

The authors declare that they have no any competing or conflict of interest.

Author Contributions

All authors contributed to writing this review, all approved the final version to be published.

Ethics Policies

This research did not request ethical approval.

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