ROLE OF HEREDITY, ENDOGENOUS AND EXOGENOUS FACTORS IN GASTRIC CANCER

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Gastric cancer (GC) usually has an unfavorable prognosis: the five-year survival rate is 20–30% in most world regions. Timely diagnosis and prevention of risk factors may reduce mortality from GC. This review discusses the meta-analyses of 40 endogenous and exogenous factors associated with GC. GC is significantly associated with family history; dietary preferences (increased consumption of roast and smoked red meat, hot foods, pickles, salt (over 5–6 g/day), nitrates (over 20 mg/L drinking water); lifestyle (smoking, opium use, strong alcohol, beer, stress); some diseases including gastroesophageal reflux disease, diabetes mellitus, obesity, and autoimmune disorders; infections (*Helicobacter pylori*, human papillomavirus, Epstein-Barr virus); ionizing radiation, and professional hazards. Data suggesting associations between the risk of GC and the consumption of coffee, tea, high-fat foods, simple carbohydrates, folic acid, sleep duration, and blood cholesterol turned out to be conflicting due to the inconsistencies of the results between cohort and case-control studies. About 3% of all gastric cancers are linked to hereditary syndromes associated with pathogenic variants of *CDH1*, *STK11*, *SMAD4*, *BMPR1A*, *TP53*, *MYH*, *APC*, *PTEN*, *ATM*, *BRCA1*, and some other genes.

Keywords: gastric cancer, risk factors, polymorphism, hereditary syndrome, occupational hazards

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ВКЛАД НАСЛЕДСТВЕННОСТИ И СОВОКУПНОСТИ ЭНДОГЕННЫХ И ЭКЗОГЕННЫХ ФАКТОРОВ РИСКА В РАЗВИТИЕ РАКА ЖЕЛУДКА

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Прогноз рака желудка (РЖ) обычно неблагоприятен: пятилетняя выживаемость в большинстве регионов составляет 20–30%. Выявление злокачественного новообразования на ранних стадиях, так же как и своевременное исключение факторов риска, помогут снизить смертность от РЖ. В обзоре обсуждаются данные публикаций по мета-анализу 40 эндогенных и экзогенных факторов, связанных с РЖ. Статистически значимый риск РЖ был ассоциирован с семейным анамнезом; некоторыми диетическими особенностями (высокое потребление жареного и копченого красного мяса, горячей пищи, маринованных продуктов, поваренной соли (свыше 5–6 г/сут.), нитратов (свыше 20 мг/л питьевой воды); стилем жизни (табакокурение, потребление опиума, крепкого алкоголя и пива, стресс); такими заболеваниями, как гастроэзофагеальная рефлюксная болезнь, сахарный диабет, ожирение, аутоиммунные нарушения; инфекциями (*Helicobacter pylori*, вирус папиломы человека, вирус Эпштейна–Барр); ионизирующим излучением; профессиональными вредностями. Данные о связи риска РЖ с потреблением кофе, чая, пищи с высоким содержанием жиров и быстроусваиваемых углеводов, фолиевой кислоты, продолжительностью сна, содержанием холестерина крови оказались противоречивыми, вследствие отсутствия согласованности результатов когортных исследований и «случай–контроль». Около 3% всех случаев РЖ обусловлены наследственными синдромами, ассоциированными с патогенными вариантами генов *CDH1*, *STK11*, *SMAD4*, *BMPR1A*, *TP53*, *MYH*, *APC*, *PTEN*, *ATM*, *BRCA1* и др.

Ключевые слова: рак желудка, фактор риска, генетический полиморфизм, наследственный синдром, профессиональная вредность

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Gastric cancer (GC) is usually diagnosed in advanced stages. The neoplastic transformation of gastric mucosa has a complex nature shaped by the interplay of endogenous and exogenous factors, from genetic polymorphisms to lifestyle choices and occupational hazards. Early detection and elimination of modifiable high-risk factors reinforced by the promotion of behaviors that can lower the risk of GC is the mainstay of cancer prevention strategies. The leading high-risk factors for GC are male sex (men are twice as likely to develop GC than women), *Helicobacter pylori* (*H. pylori*) infection, family history of cancer and smoking.

Across continents, the highest incidence of GC is observed in East Asia, followed by Central and Eastern Europe, South America, Southern Europe, Northern Europe, Central Asia, North America, and Africa [1]. Within countries, differences in GC incidence are linked to the ethnic composition of the resident population, culture, climate, and regional geochemistry. Survival depends on the stage of the disease at diagnosis, its classification category and molecular subtype. GC usually has a poor prognosis: the 5-year survival rate varies from 20% to 30% in most world regions [2], except Japan, where it exceeds 70% for stages I and II [3]. The high survival rate observed in Japan may indicate the success of mass screening programs for early cancer detection *in situ* that can prevent invasive cancer.

Today, public health systems all over the world are making progress in treating *H. pylori*, one of the key factors predisposing to GC, and raising health awareness among the population. Owing to health education, the mortality from GC declines by 3% annually in many countries, including Russia [1].

This review discusses over 100 meta-analyses of cohort and case-control studies investigating associations of exogenous and endogenous factors with the risk of GC, mortality and morbidity from this disease. The literature search included articles published within the past 7 years, but significant findings from earlier publications relevant to the subject are

also mentioned in the review. In addition, the review addresses possible associations between GC and hereditary syndromes, genetic polymorphisms and occupational hazards. The majority of gastric malignancies are adenocarcinomas. Many meta-analyses differentiate between adenocarcinomas in the gastric cardia and non-cardia cancers. Therefore, unless otherwise specified, in this paper gastric cancer will refer to adenocarcinomas with specific localizations.

High-risk factors for GC

Diet

A study of dietary habits conducted in 191 patients with gastric cardia cancer, 190 patients with non-cardia cancer and 222 healthy controls established a statistically significant correlation between the risk of GC and dietary habits, including irregular meals, overeating and insufficient mastication: odds ratios (OR) were 4.2 (95% confidence interval (CI): 2.3–7.7), 4.7 (2.1–10.8) and 7 (1.3–5.3), respectively [4].

1. Meat consumption

A diet rich in meat (over 160 g/day) contributed to the cumulative risk of GC in the main group (obesity, high body mass index (BMI), consumption of hot tea and high-fat foods). First, the risk of GC was found to vary depending on the type of consumed meat. A direct (OR = 1.87 (95% CI: 1.01–3.47)) and negative (OR = 0.36 (95% CI: 0.19–0.68)) correlations were established between the risk of GC and the consumption of red and white meats, respectively. In the cited publication, beef, lamb, sausages, and hot-dogs were defined as red meat, whereas white meat referred to fish and poultry. Fish is rich in polyunsaturated fatty acids, therefore N-nitroso compounds are less likely to form as fish cooks; this prevents carcinogenesis [5]. Second, frying and charcoal grilling were associated with increased risk of GC due to the formation of carcinogens: OR 1.9 (95% CI: 1.0–3.6) and OR 1.8 (95% CI: 1.3–2.6), respectively [6]. Thus, excessive consumption of fried or grilled red meat that can potentially contain heterocyclic amines, N-nitroso compounds and polycyclic aromatic hydrocarbons is reliably linked to the risk of GC and increases the risk of colorectal cancer (CC) by 20–50% [7, 8]. Obviously, the risk of GC can be lowered by choosing a safer cooking technique and enriching the diet with nitrosation inhibitors, such as vitamins C, E, phenolic and other bioactive compounds extracted from fresh vegetables and fruits. For the European population, the lack of fresh vegetables and fruits in the diet is a significant factor promoting the risk of GC, similar to the consumption of smoked meat products (bacon, sausages and ham) [9]. Besides, excessive intake of cholesterol with animal source foods was correlated with the increased frequency of malignancies, including GC [10].

2. Excessive salt consumption

Although salt (sodium chloride) is important for normal metabolism, it has adverse systemic effects when ingested in excess. Sodium chloride stimulates secretion of gastric juice, thereby accelerating DNA synthesis and cell proliferation and leading to atrophic gastritis [9]. According to some researchers, the chronic form of this disorder may provoke GC. In other words, excessive salt consumption provokes GC. A meta-analysis of prospective cohort studies concluded that high and moderate salt intakes (as opposed to low intake of < 5 g/day) were significantly associated with elevated risk of GC: OR 1.68 (95% CI: 1.17–2.41) and OR 1.41 (1.03–1.93), respectively [11]. Another study conducted in 422 patients with GC and 649 community controls assessed the role of high-salt diet (corrected for the presence *H. pylori* infection, smoking status, tumor site and histological type) as an independent risk factor for GC. The study found that individuals who added salt at the table were at greater risk for GC (OR = 2.01 (95% CI: 1.16–3.46)) as early as within a year before the onset of cancer symptoms [12]. Two more systematic reviews provide convincing evidence that excessive salt consumption (> 5–6 g/day) is associated with elevated risk for GC [13, 14].

3. Pickles

Pickles are traditional components of many cuisines. They contain high amounts of preservatives, including salt, acetic and benzoic acid, diphenyls, and nitrates. Can pickles increase the risk of GC? Regular consumption of pickled vegetables in an East Asian population was associated with heightened risk of GC in comparison with the control group (no pickles in the diet). According to the meta-analysis, the cumulative OR was 1.52 (95% CI: 1.37–1.68); for case-control studies OR was 1.56 (95% CI: 1.39–1.75); for cohort studies, OR was 1.32 (95% CI: 1.10–1.59) [14]. Similarly, another publication reported a high risk of GC in individuals who included pickled vegetables in their diet (OR= 5.5 (1.4–19.5)) [15].

4. Nitrates

Nitrates accumulated in crops and drinking water (> 20 mg/L) negatively affect human health. Ingesting high amounts of nitrates was correlated with increased risk of GC and death from this disease [16].

5. Dietary fat

A study reported an association between GC and increased consumption of vegetable oil (OR = 4.5 (95% CI: 1.00–20.17); p = 0.03) and lard (OR = 1.4 (95% CI: 0.63–3.01) for the population of South-East Asia [17]. Perhaps, the specific effects of vegetable oils on carcinogenesis may be explained by their chemical composition. For example, the well-known Mediterranean diet, in which olive oil is the central ingredient, reduces the risk of some cancers. This effect is attributed to monounsaturated oleic acid, which inhibits the overexpression of the HER2 (*Her-2/neu*, *erbB-2*) oncogene; such inhibition is particularly important in breast cancer [18]. However, the intake of trans fats, including hydrogenated fish oil, is correlated with increased GC morbidity (p = 0.01) [19].

6. Regular coffee consumption

The effects of regular coffee consumption on the neoplastic transformation in the gastrointestinal tract are an interesting research object. The relative risk (RR) of GC was 0.94 (95% CI: 0.80–1.10) for individuals who drank 3–4 cups of coffee a day vs. RR = 0.93 (95% CI: 0.88–0.99) for those who drank 1–2 cups of coffee, in comparison with the control group (zero coffee consumption). After the correction by design, sex, duration of observation and population, a statistically significant difference was discovered between coffee consumption and diminished risk of GC (RR = 0.85 (95% CI: 0.77–0.95; case-control studies) [20]. However, the opposite results were generated by another analysis of subgroups stratified by sex, region and time, revealing increased risk for GC (RR = 1.36 (95% CI:

1.06–1.75)) [21]. Frequent, long-term coffee consumption is likely to be both a risk factor and an anti-risk factor for GC.

7. Hot meals and hot drinks

A case-control study included 600 cases of esophageal squamous-cell carcinoma (ESCC), 599 cases of gastric cardia carcinoma (GCA), 316 cases of gastric non-cardia adenocarcinoma (GNCA) and 1,514 controls. The risk of cancer rose by 150–219% in patients who had hot foods every day in comparison with those who rarely or never had their meals hot [22]. Another risk factor for GC was hot tea ($p < 0.05$) [23].

8. High intake of simple carbohydrates

Food products with a high glycemic index (GI) can increase the risk of cancer as they modulate the levels of insulin-like growth factor 1 (IGF1) associated with diabetes. High-carb diets were shown to be strongly associated with heightened risk of colon cancer and diabetes, but did not contribute to the incidence of GC [24].

Lifestyle

1. Alcohol and smoking

Regular smoking is recognized as a significant risk factor for GC in men (RR = 1.62 (95% CI 1.50–1.75)) and women (RR = 1.20 (95% CI: 1.01–1.43)). The risk for this cancer increases from 1.3 (for occasional smokers) to 1.7 for those who smoked 30 cigarettes a day; the long history of smoking raises the risk of gastric cardia and non-cardia cancers: RR = 1.87 (95% CI: 1.31–2.67) and 1.60 (95% CI: 1.41–1.80), respectively [25], with OR = 1.9 (95% CI: 0.85–4.50) [17].

A few publications reported the overall negative effect of alcoholic beverages on the development of GC. The meta-analysis of 75 studies [26] revealed that alcohol consumption was considerably associated with the risk of gastric non-cardia (OR = 1.19 (95% CI: 1.01–1.40); $p = 0.033$) and cardia cancers (OR = 1.6 (95% CI: 0.98–1.39); $p = 0.087$). The relative risk of GC for heavy beer/wine drinkers, in comparison with those who drank little alcohol, was 1.13 (95% CI: 1.03–1.24; $p = 0.012$) and 0.99 (95% CI: 0.84–1.16; $p = 0.857$), respectively [26]. When adjusted for smoking, education and BMI, the risk of GC was 2.00 (95% CI: 1.04–3.82) for regular alcohol drinkers (2–7 times a week) vs. those who consumed alcoholic beverages only occasionally (a few times a year); the risk for GC was 1.90 (95% CI: 1.13–3.18) for individuals consuming ≥ 100.0 g ethanol a week. The odds ratio for death from GC for men who consumed ≥ 0.5 L vs. < 0.5 L of alcohol per occasion was 2.95 (95% CI: 1.30–6.68) [27]. High alcohol consumption (>60 g/day vs. 0.1–4.9 g/day) was associated with increased mortality from GC (1.65; 95% CI: 1.06–2.58). Beer consumption over ≥ 30 g of alcohol/day was associated with increased GC morbidity (1.75 (95% CI: 1.13–2.73)); however, there was no significant association with wine or liquor consumption [28].

Thus, the risk of GC was minimal or zero for individuals who consumed moderate amounts of wine. A possible explanation is that extractives contained in wine (like the polyphenolic compound resveratrol) exert a broad spectrum of favorable effects: antioxidant, anti-inflammatory and anti-carcinogenic [29].

2. Opium consumption

A 4-year-long prospective cohort study was carried out in 50,045 participants, of whom 17% were long-term opium users with an average history of opium smoking or ingestion of 12.7 years. The study found that the risk of death from gastrointestinal cancer (GIC) was 1.55 (95% CI: 1.24–1.93) for all subjects. During the observation period, 387 people died of GIC; cancer-associated mortality in the group of opium users was 2.21 times higher (95% CI: 1.57–3.31) and also dose-dependent [30]. Other authors report an association between opium use and elevated risk of cardia and non-cardia adenocarcinomas (OR = 3.1 (95% CI: 1.9–5.1)). Similar to the previous cited study, they point to the dose-dependent effect (OR = 4.5 (95% CI: 2.3–8.5)) [31].

3. Sleep duration

The meta-analysis of 25 articles (a total of 1,550,524 participants and 86,201 GC cases) revealed that neither short nor long sleep duration (relative to the baseline value of 7 h) was associated with increased risk of cancer [32]. A prospective cohort study, which recruited 173,327 men and 123,858 women aged 51–72 years, reported a significant risk of death from GC in men (1.29 (95% CI: 1.05–1.59); $p = 0.03$) who normally slept 5–6 h vs. 7–8 h a day. By contrast, women who normally shad 5 h of sleep per day were at reduced risk of death from GC (0.76 (0.24–2.41)). It should be noted that the average weighted risk of other cancers did not significantly correlate with variations in sleep duration relative to the control group [33]; these findings were consistent with the results of other studies [34].

4. Chronic stress

There is a known psychosomatic link between the level of stress and gastritis (or gastric/duodenal ulcers) [35]; these conditions, together with co-existing inflammation, can predispose to neoplasms [36]. Stress aggravates gastric cancers; the underlying molecular mechanism of this phenomenon was studied in [37]. According the study, the expression of the β_2-adrenergic receptor (ADRB2) was elevated in gastric tumors and positively correlated with their size, stage and spread to lymph nodes. Induced by the stress hormone, the activation of the ADRB2 signaling pathway played the key role in the progression of cancer and metastasis. This suggests that GC progression may be regulated by the drugs for β_2 blockade (propranolol) as an adjunct to existing therapies [37].

Pharmacotherapy

1. Nonsteroidal anti-inflammatory drugs and aspirin

This class of drugs includes selective cyclooxygenase-2 (COX-2) inhibitors that, according to some studies, reduce the risk of GC and hold potential for chemoprevention [38]. Still, many aspects of their use, such as optimal dosing and therapy duration, remain understudied. Perhaps, the inhibitory effect of NAIDs on carcinogenesis stems from their ability to induce apoptosis of epithelial cells and regulate angiogenesis via COX-2-dependent and COX-2-independent signaling pathways [39]. A population case-control study enrolled individuals aged 30-79 years with esophageal adenocarcinoma ($n = 293$), esophageal squamous-cell carcinoma ($n = 221$), gastric non-cardia cancer ($n = 368$) and gastric cardia cancer ($n = 261$). The control group comprised 695 participants. Prolonged aspirin therapy over the course of 2 to 5 years reduced the risk of such cancers: OR = 0.37 (95% CI: 0.24–0.58), 0.49 (95% CI: 0.28–0.87), 0.46 (95% CI: 0.31–0.68), respectively, in comparison with the

control group (no aspirin), except cardia cancer (OR = 0.80 (95% CI: 0.54–1.19)) [40].

2. Statins

The association between blood cholesterol levels and the risk of GC is debatable. Statins inhibit endogenous cholesterol synthesis and are traditionally used to treat metabolic disorders; in addition, they can exert anticancer activity [41]. The meta-analysis of 26 randomized control and 8 observational studies of over 7,000 GC cases demonstrated that statins reduced the risk of GC by an average of 30% (RR = 0.73 (95% CI: 0.58–0.93)) [42].

Chronic diseases

1. Gastroesophageal reflux disease

Many studies have established a significant association between GERD and the risk of gastric cardia cancer [43, 44]. In most studies, GERD was associated with a 2- to 5-fold increase in GC morbidity. At the same time, some studies reported the lack of or the negative association between GERD and non-cardia gastric cancer [43–45].

2. Metabolic syndrome

Disrupted metabolism may be an additional risk factor for different cancer types and affect the overall survival of cancer patients. A retrospective study analyzed the clinical and histological data of 808 patients with GC and a history of metabolic syndrome (MS). The control group consisted of 1,146 individuals. Main group patients had high blood levels of triglycerides ($p = 0.007$), lower levels of high-density lipoproteins (HDL) ($p < 0.001$), a higher frequency of hypertension disease ($p < 0.001$) and diabetes (OR = 1.86 (95% CI: 1.39–2.48)). MS was associated with poorly differentiated gastric carcinoma and late progression to advanced stages according to the TNM classification [46].

Type 2 diabetes mellitus is the most common endocrine disorder characterized by hyperglycemia due to deficient insulin secretion and impaired metabolism. A few clinical studies investigated a causal link between diabetes and cancer. At least two studies showed that patients with diabetes mellitus were at greater risk for hepatic, pancreatic, gastric, colon, renal and breast cancers [47, 48]. According to a prospective cohort study, there was an association between early GC onset and hyperglycemia ($p = 0.000$; OR = 1.066), insulin resistance ($p = 0.024$; OR = 1.084), glycated hemoglobin (HbA1c) levels ($p = 0.004$; OR = 3.225), and low total blood cholesterol ($p = 0.005$; OR = 1.015). Besides, there was no significant association between the risk of early GC onset and the levels of the insulin-stimulated hormone adiponectin in the blood [49]. Hyperglycemia (glucose concentrations ≥ 5.3 mmol/L) contributed to the risk of GC associated with *H. pylori* infection [50]. It was discovered that HbA1c concentrations ≥ 6.0% (42 mmol/L) adjusted for sex, age and *H. pylori* seropositivity were a statistically significant factor predisposing to GC [50]. Likewise, an association was confirmed between the poor survival of GC patients ((1.73 (95% CI: 1.08–2.79) and the risk of death from gastric cardia cancer (3.40 (95% CI: 1.45–7.97)) in the setting of type 2 diabetes mellitus. HbA1C concentrations ≥ 6.0% (42 mmol/L) were the endogenous marker of increased mortality from GC (1.68 (95% CI: 1.07–2.63)) [51].

There is no firm association established between the levels of blood cholesterol and the risk of GC because the data generated by case-control vs. cohort studies are conflicting [52]. Nevertheless, high cholesterol should not be ignored if a patient is exposed to other risk factors for GC. The multivariate analysis of variance suggested a statistically significant association between the risk of gastric dysplasia (corrected to age and sex) and the levels of glucose of 100–125 mg/100 ml (RR = 2.261; 95% CI: 1.147–4.457); total cholesterol ≥ 240 mg/200 ml (RR = 6.299; 95% CI: 1.277–31.076); LDL of 130–159 mg/100 ml (RR = 0.250; 95% CI: 0.069–0.903), and MS (RR = 2.177; 95% CI: 1.082–4.379) [53].

3. Obesity

Recently, obesity has become a public health priority due to the growing incidence of cancers reliably associated with this condition. Globally, obesity-associated malignancies account for 11.9% of cancers in men and 13.1% of cancers in women. There is evidence that excess body weight may increase the risk of 13 different cancers, including endometrial, esophageal, renal, pancreatic, hepatocellular, gastric cardia, colorectal, ovarian, thyroid, bladder, and postmenopausal breast cancers meningiomas and multiple myelomas [54]. It is emphasized that abdominal obesity is a significant risk factor for GC [52, 55–57]. After adjustment for age, alcohol consumption, smoking, family history and total blood cholesterol, BMI from 27.5 to 29.9 was associated with the risk of grade 3 gastric dysplasia in men (OR = 1.87; 95% CI: = 1.24–2.81) and women (OR = 2.72; 95% CI: 1.44–5.16). For men with BMI from 27.5 to 29.9, the risk of developing gastric cardia dysplasia was OR = 1.78 (95% CI: 1.02–3.10); for BMI ≥ 30.0 OR was 2.54 (95% CI: 1.27–5.08); for women with BMI of 27.5–29.9 OR was 2.88 (95% CI: 1.27–6.55) and for women with BMI ≥ 30.0 OR was 2.77 (95% CI: 1.36–5.64) [52]. The analysis of 2,130 cancer cases from the sample of 913,182 patients showed that obesity increased the risk of gastroesophageal cancer and GC by 49–68% and 33–48%, respectively [57].

4. Autoimmune disorders

Autoimmune disorders may be regarded as an alternative etiological factor for chronic inflammation of gastric mucosa, promoting the risk of carcinogenesis. A systematic review of 52 observational studies discovered an association of some autoimmune diseases with the risk of GC (OR = 1.37; 95% CI: 1.24–1.52) [58]. Specifically, a significant link was established between GC and the following disorders: dermatomyositis (OR = 3.69; 95% CI: 1.74–7.79), pernicious anemia (OR = 2.84; 95% CI: 2.30–3.50), Addison's disease (OR = 2.11; 95% CI: 1.26–3.53), dermatitis herpetiformis (OR = 1.74; 95% CI: 1.02–2.97), IgG4-related disease (OR = 1.69; 95% CI: 1.00–2.87), primary biliary cholangitis (OR = 1.64; 95% CI: 1.13–2.37), type 1 diabetes mellitus (OR = 1.41; 95% CI: 1.20–1.67), systemic lupus erythematosus (OR = 1.37; 95% CI: 1.01–1.84) and Graves' disease (OR = 1.27; 95% CI: 1.06–1.52) [58].

Infection

1. Helicobacter pylori

Corrected for other risk factors, *Helicobacter pylori* infection has a critical role in the etiology and early onset of GC [59]. Patients seropositive for *H. pylori* and prone to excessive salt consumption were at a 10 times higher cumulative risk for GC than the control group (no antibodies to *H. pylori* and low-salt diet). *H. pylori* infection was shown to aggravate GC prognosis

in patients with a family history of cancer and smokers [60]. Interesting observations were described in a study that reported an association between the Lewis antigen system and the risk of GC [61]. The frequency of the Lea^+b^- phenotype was higher in patients with GC and *H. pylori* infection; the risk of GC was 3.15 times higher in the carriers of this phenotype than in those with the Lea^-b^+ phenotype [61]. Another meta-analysis that summarized the data generated by 22 studies demonstrated that patients who had undergone *H. pylori* eradication therapy were at lower risk for GC than those who had not (0.53; 95% CI: 0.44–0.64). Eradication of *H. pylori* ensured a stable therapeutic effect for asymptomatic infected individuals (0.62; 95% CI: 0.49–0.79) and patients who had undergone the endoscopic resection of GC (0.46; 95% CI: 0.35–0.60) [62].

2. Human papillomavirus

There are causal links between human papillomavirus (HPV) infection and GC. The meta-analysis of 30 studies (1,917 cases and 576 controls) found that the prevalence of HPV among the patients with GC was 28.0% (95% CI: 23.2–32.7; $p < 0.001$) and established an association between the infection and the risk of GC (OR = 7.388; 95% CI: 3.876–14.082; $p = 0.004$). According to the analysis of 15 case-control studies, HPV 16 was diagnosed in patients with GC 3 times more often than HPV 18. The researchers concluded that HPV may play a role in the pathogenesis of GC; more solid evidence can be obtained by isolating HPV from precancerous cells of gastric dysplasia lesions or and adenomas [63].

3. Epstein–Barr virus

About 90% of the population are infected with the Epstein–Barr virus (EBV). The virus was isolated from a variety of tumors, including nasopharyngeal and gastric cancers, Burkitt, Hodgkin and non-Hodgkin lymphomas. Today EBV infection is thought to be a potential risk factor for cancer. A correlation was established between the seropositivity for EBV and the nasopharyngeal cancer/Hodgkin lymphoma [64]. However, only 7–10% of gastric tumors were associated with EBV [64]; according to the authors of the analysis, this might be due to small sample sizes. For example, seropositivity for EBV was not associated with elevated risk of GC in the main and control groups that comprised 185 and 200 cases, respectively. High antibody titers for the Epstein–Barr nuclear antigen were associated with longer survival in patients with cardia cancer [65]. In another retrospective study (54 individuals with gastric adenocarcinomas), the risk of cancer in patients seropositive for IgA against the viral capsid protein and IgG against the early antigen R-component was 4 and 2 times higher, respectively, than in the control group. Antibody titers against EBV were significantly higher in patients who were later diagnosed with EBV-associated GC than in those with GC not associated with EBV infection [66].

These findings suggest that the failure of the immune system to control EBV infection may increase the risk of malignancies in the long term [66]. According to the published study of the associations between GC and a coinfection with 3 pathogens (*H. pylori*, HPV and EBV) [67], the GC specimens contained the nucleic acids of *H. pylori*, EBV and HPV in 87, 20 and 3% of cases, respectively. *H. pylori* was mainly represented by the $cagA^+$ (*H. pylori* - $cagA^+$) strain. The cagA gene encodes the virulence factor, which is essentially an oncogenic protein capable of causing hyperplasia of the gastric epithelium and polyposis. A coinfection with *H. pylori-*$cagA^+$ and EBV was correlated with advanced stages of GC, and the presence of EBV infection was correlated with distant metastasis [67]. Consequently, measures for *H. pylori* and EBP prevention help to ward off GC and especially its aggressive forms.

Ionizing radiation

The literature analysis shows that the association between the risk of GC and ionizing radiation doses remains understudied. Exposure to both natural or man-made sources of radiation (accidents at nuclear power stations) can cause multiple damage to human genes and induce shifts in the global gene expression [68].

Some secondary tumors can be provoked by radiation therapy for the abdomen. The cumulative coefficient of primary GC incidence in the studied group (22,269 subjects) was 1.45% 30 years after the diagnosis. Individuals who received radiation therapy for testicular cancer were at a 6-times higher risk of developing GC (OR = 5.9; 95% CI: 1.7–20.7). The risk grew with the total dose approaching 50 Gy ($p < 0.001$), OR = 20.5 (3.7–114.3) in comparison with the total dose of <10 Gy. Thus, the highest risk of developing secondary cancers was observed for the total radiation dose of >30 Gray [69]. It should be noted that in its latent state, EBV associated with GC expresses a very small number of genes. However, exposure to ionizing radiation leads to the NF-κB-mediated activation of the lytic form of the virus, whose persistence is an additional risk factor for GC [70].

Occupational hazards

Exogenous factors predisposing to GC include social factors and occupational hazards. For example, an association was discovered between the heightened risk of GC quantitatively expressed as the relative indexes of inequality and a few social factors [71], such as low educational status (2.97 (95% CI: 1.92–4.58)), job (4.33 (95% CI: 2.57–7.29)), socioeconomic status (SES) (2.64 (95% CI: 1.05–6.63)), and income (1.25 (95% CI: 0.93–1.68)). Differences in GC incidence between social groups were more pronounced in another study [72] showing that the risk of GC decreased from 22.7% to 2% ($p < 0.001$), from 12% to 0.5% ($p < 0.001$) and from 6.5% to 0.1% ($p < 0.001$) in the groups with low, moderate and high SES. A significant correlation was observed between low SES and GC incidence and mortality [73]. According to the meta-analysis of 25 studies (9,773 GC cases and 24,373 controls), the risk of GC decreased in groups with a high educational status: OR and the relative index of inequality were 0.60 (95% CI: 0.44–0.84) and 0.45 (95% CI: 0.29–0.69), respectively [73].

Stratification of occupational hazards in a Swedish population revealed an almost two-fold difference in the risk of GC between different socio-economic groups [74]. Individuals involved in manual labor (miners, quarry workers, fishermen, construction workers, packers, loaders, warehouse workers, clerical workers, nurses and postmen) were at higher risk for GC [74]. Standardized incidence ratios of gastric cardia cancer were significantly increased for male gardeners, transport workers, chemical industry workers and bricklayers. Cement and mineral dusts were the main occupational risk factor for GC [74].

In a Spanish population, the risk of developing GC was statistically significant for male cooks (OR = 8.02), wood processing plant operators (OR = 8.13), food and related product machine operators (OR = 5.40), miners and quarry workers (OR = 4.22; 95% CI: 0.80–22.14)) [75]. The risk of GC was also significant for men and women involved in plant

cultivation and exposed to pesticides (OR = 10.39; 95% CI: 2.51–43.02), as well as for those involved in manufacturing and exposed to asbestos (OR = 3.71; 95% CI: 1.40–9.83) and wood dust (OR = 3.05) [75].

Cr(VI) is an established carcinogen provoking lung cancer. The meta-analysis of 56 cohort and 74 case-control studies sought to test the hypothesis about the association between the risk of GC and occupationally inhaled chromium in chrome plating and leather workers and those exposed to Portland cement [76]. The cumulative relative risk was 1.27 (95% CI: 1.18–1.38); in comparison with other studies reporting the increased risk for lung cancer, RR for GC was 1.41 (95% CI: 1.18–1.69) [76]. On the whole, these results allow identifying Cr(VI) as a risk factor for GC.

Genetic factors for GC: hereditary cancer syndromes and genetic polymorphism

1. Hereditary GC syndromes and family history

The family history of GC is another factor that augments the risk of the disease 1.5–3.5 fold if at least one first-degree relative has GC [77]. Although GC is mostly sporadic, familial aggregation is observed in about 10% of cases and 1–3% of cases are associated with cancer syndromes [78, 79]. According to a study, the incidence of GC was higher in individuals whose relatives had a history of early-onset GC (before 50 years) [80, 81]. The frequency of GC was higher among patients whose first-degree relatives had GC (OR = 2.7; 95% CI: 1.7–4.3). If two or more relatives had GC, OR rose to 9.6 (95% CI: 1.2–73.4) [82]. The incidence of GC was also higher in patients whose first/second degree relatives had a history of malignancies including GC, breast or lung cancer, gynecological and hematologic cancers, as shown by the long-term observations of the main group (n = 44; 54.5%, $p < 0.01$) and the control group (n = 44; 11.4%, $p < 0.01$) [79]. It is reported that GC-associated mortality was higher in patients with a family history of *H. pylori* and GC (OR = 8.2; 95% CI: 2.2–30.4) than in the control group (no family history of *H. pylori* and GC). At the same time, non-cardia cancer was the most common malignancy in the sample [83].

The most significant hereditary cancer syndrome manifested as GC is hereditary diffuse gastric cancer (HDGC). This syndrome is associated with pathogenic variants of the *CDH1* gene, which encodes the cell adhesion protein E-cadherin. A study conducted in 75 families found that the cumulative risk of GC was 70% and 56% for female and male carriers of the pathogenic *CDH1* variants, respectively, by the age of 80 years [84]. An earlier study involving 13 families produced the opposite results: the cumulative risk of GC was 67% for men and 83% for women [85]. It should be noted that the cited study included 3 Maori and one Pakistani families. Thus, ethic differences should be accounted for when estimating the cumulative risk of HDGC. Besides, both publications show that female carriers of the pathogenic *CDH1* alleles are at increased risk for lobular breast cancer (cumulative risk of 39–42% by age of 80 years). Importantly, the pathogenic CDH1 variants are detected in only 40% of patients with clinical signs of HDGC. Genetic causes of this disease in other patients are obscure [86].

Another hereditary cancer syndrome contributing to the risk of GC is the Peutz–Jeghers syndrome. It is characterized by the development of gastrointestinal hamartomatous polyps. Its distinctive feature is the presence of melanin spots on the lips, buccal mucosa and other parts of the body. The disease is manifested as gastrointestinal tumors, including GC. The affected women are at increased risk for breast cancer. The disease is caused by the pathogenic variants of the *STK11* gene [87]. According to some estimates, the cumulative risk of GC in patients with the Peutz–Jeghers syndrome aged 15 to 64 years is 29% [88].

Another syndrome that significantly increases the risk of GC is juvenile polyposis. This condition is caused by the pathogenic mutations in the *SMAD4* or *BMPR1A* genes. As a rule, juvenile polyposis affects children but can also arise at older age. The cumulative risk of GC is 21% for patients afflicted with this syndrome [89].

Among other hereditary cancer syndromes that aggravate the risk of GC are Lynch syndrome, Li–Fraumeni syndrome, familial adenomatous polyposis, MYH-associated polyposis, gastric adenocarcinoma and proximal polyposis of the stomach [86]. There is evidence that patients with ataxia-telangiectasia, Bloom syndrome, Cowden syndrome, and xeroderma pigmentosum are at increased risk for GC [89].

Another condition worth mentioning is the syndrome of hereditary breast and ovarian cancers associated with mutations in the *BRCA1* and *BRCA2* genes. Carriers of the pathogenic *BRCA1/BRCA2* alleles are at increased risk for GC [90, 91]. Although this risk is only slightly increased, the syndrome is very common and therefore its association with GC may be clinically significant.

In addition to the listed hereditary cancer syndromes (see Table), the risk of GC is elevated in patients with inherited primary immunodeficiency [92]. Recently, the incidence of GC among such patients has started to decline; this might be tied to the spread of *H. pylori* eradication therapy [93].

2. Genetic polymorphism

It is not only the pathogenic variants of nucleotide sequences associated with cancer syndromes that contribute to the risk of developing GC, but also non-pathogenic populational polymorphisms. According to one of the largest research studies of twins conducted in Sweden, Denmark and Finland, the contribution of genes to GC is much greater than to other nosologies. The risk of GC for a male monozygotic twin of a twin with GC was 9.9 times higher than for a male monozygotic twin of a twin without GC. Concordance for GC in male monozygotic twins was 0.08, i.e. there is an 8% probability of GC in one of the twins if the other already has GC [94].

According to a 2019 meta-analysis that covered 186 studies, the strongest associations were observed for 9 variants of 9 genes: *APE1* rs1760944, *DNMT1* rs16999593, *ERCC5* rs751402, *GSTT1* 0/0 genotype, *MDM2* rs2278744, *PPARG* rs1801282, *TLR4* rs4986790, *IL-17F* rs763780 and *CASP8* rs3834129. The metanalysis included a total of 61 gene variants [95]. The strongest association with GC was shown for the G allele of the *APE1* gene (rs1760944): OR was 1.77 [95]. The existing data on the associations between genetic polymorphisms and GC are not clinically relevant and cannot be used to elaborate screening recommendations. So, it is more reasonable to focus on the family history while estimating the risk of GC.

Factors reducing the risk of GC

Fruits and vegetables

By and large, diets enriched in fruits and vegetables (especially fresh) were negatively correlated with the risk of GC [4, 9]. Regular intake of fruits and vegetables reduced the risk of GC by

Table. Hereditary cancer syndromes associated with increased risk of GC

Syndrome	Genes	GC risk	Inheritance pattern	Reference
Hereditary diffuse GC	*CDH1*	56–83%	Autosomal-dominant	[84, 85]
Peutz–Jeghers syndrome	*STK11*	29%	Autosomal-dominant	[86]
Juvenile polyposis	*SMAD4, BMPR1A*	21%	Autosomal-dominant	[86]
Lynch syndrome	*MLH1, MSH2, MSH6, PMS2, EPCAM*	1–13%	Autosomal-dominant	[86]
Li–Fraumeni syndrome	*TP53*	2,8%	Autosomal-dominant	[86]
Familial adenomatous polyposis	*APC*	1–2%	Autosomal-dominant	[86]
Hereditary breast and ovarian cancers	*BCRA1, BRCA2*	Increased	Autosomal-dominant	[86]
MYH-associated polyposis	*MYH*	Increased	Autosomal- recessive	[86]
Gastric adenocarcinoma and proximal polyposis	Pathogenic variant of *APC* promoter	Increased	Autosomal-dominant	[86]
Ataxia-telangiectasia	*ATM*	Likely increased	Autosomal- recessive	[89]
Bloom syndrome	*BLM*	Likely increased	Autosomal- recessive	[89]
Cowden syndrome	*PTEN*	Likely increased	Autosomal-dominant	[89]
Xeroderma pigmentosum	*DDB2, ERCC1, ERCC2, ERCC3, ERCC4, ERCC5, POLH, XPA, XPC*	Likely increased	Autosomal- recessive	[113]

48–70% and 46–68%, respectively [22], which was consistent with the findings of another research study (OR = 0.3; 95% CI: 0.1–1.0) [6]. By contrast, low intake of fruits and vegetables promoted the risk of GC (OR = 1.2; 95% CI: 0.74–1.96) [17]. Onions and garlic had a protective effect on the gastrointestinal tract and reduced the risk of GC [96]. A negative association was established between the risk of GC and consumption (often vs never) of garlic stalks (OR = 0.30; 95% CI: 0.12–0.77). In another study, increased consumption of allium vegetables (onions, garlic, leeks, shallots, garlic stalks, Chinese chives, Welsh onions) reduced the risk of GC (OR = 0.54; 95% CI: 0.43–0.65) [97]. The meta-analysis of 18 studies showed that the relative risks of developing colorectal cancer and GC were 0.69 (95% CI: 0.55–0.89) and 0.53 (95% CI: 0.31–0.92), respectively, in the main group (garlic consumption > 28.8 g/week) in comparison with the control group (3.5 g/week) [98].

Dietary fiber intake

Dietary fiber is a food component that is poorly digested by the gastrointestinal tract of humans but can be fully digested by the intestinal microbiota. A systematic review [99] analyzed 21 publications, to find that the odds ratio of GC for high dietary fiber intake was 0.58 (95% CI: 0.49–0.67; $p < 0.001$). Moreover, inclusion of 10 g of dietary fiber in the diet was associated with a 44% reduction in the risk for GC [99].

Tea

Similar to coffee, regular tea consumption was also studied for the association with GC. Polyphenolic compounds contained in tea exert antioxidant activity and have a variety of anticancer effects: they inhibit nitrosation and stimulate apoptosis in carcinoma cell lines. About half of the of prospective cohort studies investigating the effect of regular tea consumption on GC did not find any associations between green tea consumption and GC, whereas the rest established a negative association [100].

Dietary carotenoids

Intake of α-, β-carotins, lycopene, and lutein was negatively correlated with the risk of GC: OR = 0.59 (95% CI: 0.37–0.92); 0.52 (95% CI: 0.46–0.59); 0.88 (95% CI: 0.55–1.41) and 0.85 (95% CI: 0.56–1.30), respectively. The RRs of GC at 95% CI were as follows: 0.72 (0.50–1.03), 0.79 (0.58–1.07), 0.80 (0.60–1.07) and 0.95 (0.77–1.18), respectively [101]. Thus, case-control studies established a negative correlation between the intake of dietary carotenoids and the risk of GC.

Vitamins

High vs. low vitamin intake was negatively associated with the risk of GC (RR: 0.78 (95% CI: 0.71–0.83)) [102]. However, if daily intake of vitamins was increased 4 times (9 studies), the risk of GC also increased slightly (OP = 1.20; 95% CI: 0.99–1.44) [102]. The analysis of dose-dependent effects of vitamin A (1.5 mg/day), vitamin C (100 mg/day) and vitamin E (10 mg/day) indicated a decline in the risk of GC by 29%, 26% and 24%, respectively [102]. Diets high in fruits (100 g/day) rich in vitamin C were negatively correlated with the risk of GC [9]. Interestingly, intake of food supplements containing garlic extracts, vitamins C, E and selenium was associated with reduced morbidity and mortality from GC although the associations were statistically insignificant. By contrast, vitamin therapy was significantly negatively correlated with mortality from esophageal cancer and GC (0.51; 95% CI: 0.30–0.87; $p = 0.014$) [103].

Vitamin D, the precursor of the steroid hormone calcitriol, regulates a number of metabolic and signaling pathways in the cells. Low blood levels of vitamin D were shown to correlate with cancer [104]. Spanish patients with GC had low blood concentrations of vitamin D, in comparison with the control group (no cancers and vitamin D deficiency): OR = 8.8 (95% CI: 5–22; $p < 0.0001$) [105]. Case-control studies conducted in the USA demonstrated that both deficiency (< 20 ng/L) and excess (20–29 ng/L) of vitamin D were far more common in patients ($n = 103$) with incomplete gastric metaplasia than in healthy individuals ($n = 216$) with vitamin D concentrations in the blood ranging from 30 to 100 ng/L; this factor might play a role in the development of gastric adenocarcinoma *in situ* [106]. Sufficient concentrations of vitamin D (over 20 ng/L) in the blood plasma of Korean adults were associated with high efficacy of *H. pylori* eradication therapy and low risk of GC (OR = 0.57; 95% CI: 0.32–1.00) [107].

The link between dietary folic acid (vitamin B9) and GC remains understudied. Studies in mice with induced gastric dysplasia demonstrate that dietary folic acid slows DNA

hypomethylation in the epithelial cells and stromal myofibroblasts of the stomach associated with worse survival [108]. Besides, folic acid exerts an inhibitory effect on inflammation [108]. Still, the efficacy of folic acid in preventing and treating gastric malignancies is yet to be proved in future research.

Exercise

Some systematic reviews indicate that regular exercise and sports are usually negatively correlated with the development and relapse of cancer. For example, exercise was associated with a 20–50% reduction in the risk of lung [109] and breast [110] cancers. The cited reviews discussed a few possible causes underlying this phenomenon: optimization of hormonal status, reduction of oxidative stress in tissue due to oxygen saturation and activation of immune mechanisms. Four studies demonstrated that exercise had a protective effect against gastric cardia cancer (OR = 0.80; 95% CI: 0.63–1.00), and 5 studies showed the same effect against non-cardia cancer (OR = 0.63; 95% CI: 0.52–0.76), regardless of sex, study quality, study design, and geographic location [111].

CONCLUSION

Based on the prevailing risk factors for GC described in the review, a few cancer prevention strategies can be singled out, including measures for reducing the risk of primary gastric malignancies, prediction of GC risk using genotyping panels of genetic markers and early detection. Obviously, by changing modifiable behaviors (quitting smoking, reducing salt consumption to <5 g/day according to WHO recommendations, enriching the diet with vegetables, fruits, dietary fibers and antioxidants) one can significantly reduce the risk of developing GC. Special attention should be paid to the detection and treatment of *H. pylori*, which is the primary infectious factor of GC. Eradication therapy for *H. pylori* in patients with diagnosed GC reduces the risk of metachronous recurrence by almost 50% [112].

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