REVIEW

ETIOLOGY AND RISK FACTORS FOR GASTRIC CANCER - A TARGETED REVIEW

Raluca-Ioana Dascălu[1], Iulia Ivanov[1], Florentina Mușat[1,2], Răzvan Vasile Stoian[1,2], Dan Nicolae Păduraru[1,2], Alexandra Bolocan[1,2], Octavian Andronic[1,2]

[1]"Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania
[2]Bucharest University Emergency Hospital, Bucharest, Romania

Corresponding author: Florentina Mușat
Email: flori.musat94@gmail.com

ABSTRACT

Adenocarcinomas represent approximately 95% of stomach cancers. Although its incidence has been steadily declining for the past decades, gastric cancer remains one of the most common malignancies and a leading cause of cancer death. About 1/12 cancer deaths is attributed to this disease, and more than one million new cases are diagnosed worldwide each year. In Europe, the average 5-year survival rate is 26%, probably due to the unavailability of a screening program, as the number of cases is considered insufficient. In contrast, in Japan and Korea, where the large number of new cases imposed a screening program on each person at the age of 50, the 5-year survival rate is considerably higher. Among the most relevant risk factors should be mentioned H. Pylori infection, chronic gastritis, achlorhydria, gastric adenomatous polyps or pernicious anemia. Besides, gastric cancer is most common in older men and there is a marked regional variability, thought to be attributable to genetics or environmental factors, especially diet. Prevention focused on a careful and healthier diet and lifestyle is the most promising strategy for increasing the survival rate and reducing mortality. Constant improvement in diagnostic methods and therapeutic management have led to a better quality of life and a steady increase in the survival rate of patients with gastric cancer.

KEYWORDS: *gastric cancer, risk factors, H. pylori infection, genetic factors, hereditary, diet, environmental factors*

INTRODUCTION

Gastric cancer is a major public health problem worldwide, being one of the most common and deadly cancers. Although its incidence has been steadily declining for the past decades, this neoplasm is the fifth most common malignancy after lung, breast, colorectal and prostate cancers, and the third leading cause of cancer death after lung and colorectal cancer (approximately 770,000 deaths) [1] [2]. It is found about twice as often among men than women, being diagnosed mainly between the ages of 60 and 80. Moreover, in Romania, gastric cancer represents the second digestive cancer after the colorectal cancer and the fifth in terms of neoplastic mortality, according to GLOBOCAN statistics.

Adenocarcinomas represent approximately 95% of stomach cancers [3]. In Europe and all around the world, there is a significant geographical variation regarding the incidence of this neoplasm, a variation which is based mainly on socio-economic status, different exposure to environmental factors, diet, genetic factors, and the prevalence of H. pylori infection.

Hence, the highest incidence is in East Asia, South America, Central and Eastern Europe [4]. The 5-year survival rate is considerably higher in Japan and Korea as a result of a screening program on each person at the age of 50, whereas in Europe, the average 5-year survival rate is 26%, probably due to the unavailability of a screening program, as the number of cases is considered insufficient [5][6].

The aim of this article is to highlight the most significant risk factors liable for the onset of gastric cancer.

MATERIAL AND METHOD

This study is based on the evaluation of the literature using the following advanced search formula: (GASTRIC AND ("CANCER" OR "NEOPLASIA") AND ("RISK FACTORS" OR "ETIOLOGY")), in Scopus, Web of Science and PubMed databases.

RESULTS AND DISCUSSION

Although the incidence has been steadily declining for the past 50 years, gastric cancer is one of the most common and fatal cancers in the world, especially among older men. About 1 in 12 cancer deaths is attributed to this disease and more than one million new cases are diagnosed annually worldwide. Also, the cumulative risk of developing gastric cancer from birth by the age of 74 is 1.87% in men and 0.79% in women [2].

Low socio-economic status is associated with a higher prevalence of the disease. In addition, age is an important factor related to the risk of developing this cancer, as the incidence increases considerably after the age of 60, according to GLOBOCAN 2018 statistics [2].

Gastric cancer is a multifactorial disease, so the pathogenesis is based on a combination of environmental factors and a specific set of genetic changes. For example, it seems that the incidence of gastric cancer in relatives of immigrants from geographical areas with a high incidence of the disease decreases to that of the destination region [7]. Although the incidence of this neoplasm appears to be declining, its prevention focused on a healthy diet and lifestyle, anti-H. pylori therapy and screening for early detection should be a priority.

From an anatomical perspective, the risk factors incriminated in cardial gastric cancer differ from those incriminated in non-cardial gastric cancer. For example, although the pathogenesis of cardial tumors is not fully understood, they are usually associated with gastroesophageal reflux disease (GERD) and obesity, while non-cardial tumors are correlated with dietary factors (increased consumption of salty and smoked foods, low consumption of fresh vegetables and fruits), H. pylori infection or poor socio-economic status [5]. Moreover, it seems that Hispanics are more prone to non-cardial gastric cancer, and Caucasians to cardial cancer [7]. There are also risk factors common to both locations, such as family history, old age, male gender, radiation or smoking [7].

The risk factors involved in this neoplasm can be changeable or unchangeable, early detection being vital in both cases. Unchangeable factors include genetics (e.g., a rare mutation in the gene encoding a protein called cadherin E could cause diffuse hereditary gastric cancer with a bleak prognosis), family history of gastric cancer in first-degree relatives, age, gender (frequently among men, because, for reasons not fully elucidated yet, estrogen seems to have a protective role), blood group A, certain comorbidities (familial adenomatous polyposis, hereditary nonpolyposis colon cancer) or race [8]. According to the SEER, the risk of gastric cancer in the United States is highest in the Pacific islands, among Asians, blacks, followed by Hispanics and, with the lowest frequency, whites; the correlation between race and the incidence of gastric cancer seems to be mediated by effects related mainly to the environment, rather than by genetic variations [7]. Regarding changeable risk factors, H. pylori infection is the main etiological factor, given that it is the most common chronic infection, affecting half of the world's population. According to the World Health Organization (WHO), H. pylori has been classified as a class I carcinogen, responsible for both diffuse and intestinal gastric adenocarcinomas. This infection produces lesions that precede the malignant transformation, going through a number of precancerous stages, namely atrophic gastritis, dysplasia and intestinal metaplasia. Basically, H. pylori acts on gastric epithelial cells directly, by bacterial agents and indirectly, by causing

inflammation [7]. The magnitude of the increased risk of developing adenocarcinoma associated with H. pylori infection is influenced by the duration of infection, the genetic background of the host, the coexistence of other dietary or environmental risk factors and the bacterial strain, the strains possessing the babA2, cagA and vacA genes with a higher risk. However, there has been a decrease in the incidence of non-cardial gastric cancer, probably due to improved hygiene and extensive use of antibiotics [8]. The coexistence of other dietary or environmental risk factors and the bacterial strain, the strains possessing the babA2, cagA and vacA genes being at higher risk. However, there has been a decrease in the incidence of non-cardiac gastric cancer, probably due to improved hygiene and extensive use of antibiotics [7]. The coexistence of other dietary or environmental risk factors and the bacterial strain, the strains possessing the babA2, cagA and vacA genes being at higher risk. However, there has been a decrease in the incidence of non-cardiac gastric cancer, probably due to improved hygiene and extensive use of antibiotics [7].

Dietary factors are also implicated, especially in the ethiopathogenesis of gastric cancer. In this regard, with the increase in the consumption of fresh vegetables and the replacement of canned foods by salting and smoking with refrigerated ones, there has been a downward trend in the incidence of this disease in recent decades [9]. Consumption of large amounts of meat (especially saturated fat-rich red meat) and salty foods, rich in nitrates and polycyclic amines are associated with a high risk of developing adenocarcinoma. The salt causes inflammation by eroding the mucous barrier of the stomach, increases the expression of the H. pylori cagA gene, promotes the development of gastritis and potentiates the carcinogenic effects of known gastric carcinogens, such as N-methyl-N-nitro-N-nitrosoguanidine: thus, a diet rich in salty and pickled foods (for example, Japanese food) is correlated with high rates of gastric cancer [5]. Moreover, preserved meat is rich in N-nitroso compounds with mitogen and carcinogenic properties. Cooking techniques such as frying, grilling or baking also amplify the formation of N-nitroso compounds [7]. On the other hand, adhering to healthy diets such as the Mediterranean diet rich in fruits, vegetables, dairy and fresh fish, diets high in fiber, and diets with high antioxidant capacity (green tea, vitamin A, C, E supplements), is correlated with lower risk of developing gastric cancer. Moreover, it is important to know that low temperatures decrease microbial proliferation with decreasing nitrite production.

Along with dietary factors, other risk factors related to lifestyle are smoking, alcohol consumption, work, obesity (associated with cardiac gastric cancer) and the level of physical activity. Tobacco is responsible for the development of cardial gastric cancer, with smokers having a 1.5 times higher risk of disease than non-smokers [7]. According to the World Cancer Research Fund / American Institute for Cancer Research (WCRF / AICR), it is estimated that 11% of cases worldwide and 17% of those in Europe are attributed to smoking. Professions with a high risk of developing this neoplasm are those that involve exposure to dust, particles at high temperatures, nitrogen oxides, radiation, certain metals (e.g. chemical industry, coal, metals, rubber, etc.) [5]. At the same time, poor socio-economic status and a low level of education correlate with an increased risk of developing stomach cancer and a low survival rate, probably due to the increased risk of H. pylori infection and limited access to fresh food [5], [9].

The genetic involvement in the initiation and progression of gastric cancer is considerable. The vast majority (90%) of gastric neoplasms develop sporadically, while <15% are hereditary forms, with familial aggregation [10]. Sporadic forms are marked by a wide range of influences, such as microsatellite instability (found in up to 50% of sporadic gastric cancers), chromosomal abnormalities (amplifications, deletions, translocations, loss of heterozygosity), changes in microRNA profile, protooncogene action, mutation of tumor suppressor genes, and inactivation of cell adhesion molecules. Thus, one of the most common mutations occurs in the p53 gene, and abnormalities of the FHIT, p16, p27 genes and the TFF1 and RUNX3 gastric tumor suppressor genes are also common [11], [12]. Moreover, it can sometimes be noted to amplify the expression of growth factors, such as HGF / SF (hepatocyte growth factor), VEGF, c-met, AIB-1, EGF or β-catenin [13]. Another example of chromosomal aberration associated

with gastric cancer is the amplification of the HER2 gene (also known as ERBB2), which is responsible for overexpression of the HER-2 receptor (a transmembrane tyrosine kinase); recorded in approximately 20% of cases, this gene is involved in the control of cell proliferation and migration, being a prognostic factor and a target for molecular therapy. Furthermore, the uninucleotide polymorphism (SNP) of the IL1 gene (encoding IL-1α, IL-1β - potent inhibitor of gastric secretion and IL-1RN - natural receptor antagonist) associate an increased risk of developing premalignant gastric atrophy and hypochloridia in response to H. pylori infection [10]. Polymorphism of the TNF-α, IL-10, IL-17 and TLR4 genes are also involved in increasing the risk of non-cardial gastric cancer [7].

Of the forms with familial aggregation, <3% are correlated with hereditary cancer syndromes, such as diffuse hereditary gastric cancer, juvenile polyposis, familial adenomatous polyposis (PAF), Peutz-Jeghers syndrome, or hereditary nonpolyposis colon cancer [7], [10]. Hereditary diffuse gastric cancer is among the most common, being an autosomal dominant condition often associated with mutation of the CDH1 gene encoding the E-cadherin protein of epithelial cell adhesion; the penetration of gene mutations is high, with average age of diagnosis being 38 years [9], [10], [14]. PAF is an autosomal dominant colorectal cancer syndrome caused by mutations in the APC gene, with a 100% risk of developing colorectal cancer by the age of 35-40 and a high risk of malignancy, including gastric cancer [5], [7]. Among patients with PAF, the risk of gastric cancer is 10 times higher than the general population, and the prevalence of gastric adenomas is 35-100% [7]. Hereditary nonpolyposis colon cancer (Lynch syndrome) is associated with a high risk of intestinal gastric cancer (it has an 11% risk of associating a localization in the stomach [15]). Lynch Syndrome arises from an altered DNA repair mediated by a mutation in DNA repair genes, such as MSH2 or MLH1, which in turn increases the rate of mutation in oncogenic and tumor suppressor genes, leading to the initiation and progression of cancer [9], [10]. Li Fraumeni syndrome (caused by mutations in the TP53 gene, a tumor suppressor gene with a role in regulating cell growth and division), Cowden syndrome (autosomal dominant disease characterized by the appearance of multiple benign tumors called hamartomas) and Peutz-Jeghers syndrome (SPJ) (autosomal dominant disease characterized by the appearance of hamartomatous intestinal polyps in association with mucocutaneous cancer melanocytic macules) are other examples of hereditary syndrome correlated with other malignancies, including gastric cancer [10], [16], [17]. Recent studies have also reported gastric adenocarcinoma and proximal stomach polyposis (AGPPS) as a syndrome predisposing to inherited cancer [9]. This syndrome, whose underlying genetic background is still unclear, is characterized by autosomal dominant transmission of fundic gland polyposis, with areas of intestinal dysplasia or gastric adenocarcinoma limited to the proximal stomach and no evidence of colorectal and duodenal polyposis or other cancer syndromes of hereditary gastrointestinal cancer [18].

Moreover, there are premalignant conditions responsible for the appearance of gastric neoplasm, including: chronic atrophic gastritis, intestinal metaplasia, gastric dysplasia, gastroesophageal reflux disease (GERD), gastric ulcer, gastric polyps, and previous surgery (gastrectomy). Chronic atrophic gastritis is an early change in the development of stomach cancer, with an annual rate of progression of 0.5-1% [19], the risk of neoplastic transformation being proportional to the extent of atrophy. Multifocal atrophic gastritis from H. pylori infection is the most common form and often associates metaplasia; fundic and corporeal atrophic gastritis is autoimmune in nature, with a lower neoplastic risk than the multifocal form [7]. Intestinal metaplasia consists in replacing the foveolar and glandular gastric epithelium in the oxyntic and antral mucosa with an intestinal epithelium, being characterized by the presence of goblet cells and depending on the type of mucin secreted; intestinal metaplasia is classified into 3 categories [20]. Thus, type II or III metaplasia is associated with a 20-fold increase in the risk of gastric cancer, and in patients with intestinal metaplasia type III, early gastric cancer occurs in 42% of cases [7]. GERD is a risk factor for the development of cancer at the intersection of the esophagus and stomach by the appearance of the Barrett's esophagus [23]. The most

common gastric polyps are hyperplastic and adenomatous; malignant transformation of hyperplastic polyps is very rare, while adenomatous polyps occur in 10% of cases, with a risk of neoplastic transformation of 40-45% [23] [7]. All polyps >1 cm in size and all adenomatous polyps should be resected and endoscopic surveillance is recommended 1 year after adenoma polypectomy. Also, previous gastric resections (especially Billroth type II) performed for benign pathologies may be responsible for the appearance of gastric abutment cancer after a period of 10-20 years after the procedure, most likely due to achlorhydria or bile components (by reflux or following the digestive circuit made by anastomosis) [23]. Last but not least, in the development of gastric neoplasm, pernicious anemia (the consequence of chronic autoimmune atrophic gastritis) has been incriminated, associating a 6.9% risk of developing gastric cancer [5], Ménétrier disease (a rare condition with a risk of 15% conversion to gastric cancer) or Epstein-Barr virus (EBV) infection. Studies suggest that approximately 5-10% of gastric cancers are associated with EBV infection, occurring twice as frequently in men [5].

CONCLUSION

Remarkable development in diagnostic methods and therapeutic management, which are constantly being adapted and advanced, have led to an improvement in the quality of life and a steady increase in the survival rate of patients with gastric cancer. Nevertheless, prevention focused on a careful and healthier diet and lifestyle is the most promising strategy for increasing the survival rate and reducing mortality. This effective approach can be well noticed in countries with the highest risk and incidence, which have imposed an adequate program of screening (Japan vs. European countries).

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