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Risk factors of the gastric cancer – the short review

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Summary:

Introduction and purpose: Gastric cancer (GC) is one of the most frequent malignancies around the world. There were nearly 1 million new cases in 2018. Gastric malignancies have heterogeneous etiopathogenesis. Lifestyle, socioeconomic status, blood group A, medical condition, Helicobacter Pylori infection, family history, genetic polymorphism, diet, demographic characteristics, occupational exposure, ionizing radiation are considered as predisposing factors.

Objective: The purpose of our study is to review a currently available data on PubMed about risk factors of gastric cancer to consider better understanding of gastric cancer etiology.

A brief description of the state of knowledge: Current studies suggest that red meat, pickled vegetable or alcohol consumption, low socioeconomic status, cigarette smoking, blood group A and Helicobacter Pylori infection increase risk of GC. Decreased risk of gastric cancer is observed in case of white meat consumption, statin and non-steroidal anti-inflammatory drugs

intake. It seems that family history and other genetic predispositions may have a crucial role in gastric cancer development.

Conclusions: Variety of environmental, genetic and medical factors are considered with an increased risk of gastric cancer. The awareness of its existence facilitates pathogenesis of gastric malignancies and enables the implementation of proper diagnostic procedures, screening programs and prophylaxis.

Key words: gastric cancer; risk factors; review

1. Introduction:

Gastric cancer (GC) is one of the most frequent malignancies around the world. There were nearly 1 million new cases in 2018 and it is in the 5th place among occurring cancer in both sexes worldwide. GC death rate is estimated for 800 000 deaths per year [1-3]. Due to better surveillance, detection and treatment, for the last 50 years, its morbidity is constantly decreasing, but this is mainly dependent on social status of the geographical region. In Poland, GC is still the leading cause of cancer related deaths [4] and the majority of cases is recognized in advanced stage, thus, treatment outcomes are still unsatisfactory. It should be noted that there are differences in incidence of gastric cancer around the world; thus, certain controversies are constantly raised [2].

Histologically, adenocarcinoma constitutes the vast majority of gastric cancer in contrast to squamous gastric cancer. According to Lauren's classification, cancer of the stomach contains 3 histological types: intestinal, diffuse and mixed [5]. The clinicopathological appearance reveals evaluating of prognostic factors [5,6]. Evidence-based science suggests that histological type of stomach malignancies may have heterogeneous etiology.

Gastric cancer has nonhomogeneous etiopathogenesis, what sheds light on GC risk factors, including: lifestyle, socioeconomic status, blood group A, medical condition, Helicobacter Pylori infection, family history, genetic polymorphism, diet, demographic characteristics, occupational exposure and ionizing radiation [7-42]. This multifactorial disease is constantly diagnosed in late stage; thus, variable strategies should be elaborated to consider appropriate prevention.

Objective: The purpose of our study is to review currently available data on PubMed about risk factors of gastric cancer to consider better understanding of gastric cancer etiology.

2. State of knowledge:

Cancer of the stomach is considered the most frequent type of upper gastrointestinal malignancies. Its burden is increasing in the world due to variable predisposing factors [7]. The identification of appropriate risk factors seems to be a key for early diagnosis and disease management.

2.1 Family history and genetic susceptibility

Family history is considered with a shared exposure to carcinogens, familial aggregation of the disease and genetic predispositions. Current studies show that approximately 10 % of GC reveal familial aggregation, but ca. 2–5% can be classified as hereditary cases [8-10]. Oliviera et al. [10] indicated that Mendelian inheritance pattern has association in less than 3 % of all gastric cancer cases and it constitutes 3 main hereditary syndromes, including: gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS), hereditary diffuse gastric cancer (HDGC), and familial intestinal gastric cancer (FIGC). Since 1998, when HDGC was first described in Maori families, the role of CDH1 gene in heredity of diffuse gastric cancer was established [10,11]. Gastric malignancies are also reported in genetic syndromes such as: Hereditary Breast and Ovarian Cancer Syndrome, Lynch Syndrome, Li-Fraumeni Syndrome, Juvenile Polyposis Syndrome [10]. Evidence-based knowledge reported that the prevalence of GC in case of familiar genetic susceptibility increased the risk of cancer of the stomach [7]. The identification of cases with family history should be highlighted, due to a necessity of early diagnosis involving regular endoscopy. Kwak et al. [12] reported that the onset of the GC is nearly 10 years earlier in patients with genetic susceptibility, than in cases without family history. There is a reason why members of families with familial aggregation should undergo early screening diagnosis.

2.2 Genetic polymorphism

Mutations and polymorphism are components, which are responsible for many incidents of human cancers. Nevertheless, no specific mutations have been known to predispose for each type of cancer. In the study of Yousefi et al. [7] the review of many publications was performed. The role of certain gene polymorphism was underlined in oncogenesis of gastric malignancies. Correlations between GC and cytokines gene polymorphisms (such as the IL1RNVNTR), polymorphism of CYP19A1 or genetic polymorphisms of CYPE1, NAT2 M1, NAT2 phenotype and XRCC1 have been identified as significantly associated with GC occurrence.

2.3 Diet

It is interesting to note that in industrial and developing countries the number of GC cases has declined for years. In the research of Jarosz et al. [13] this phenomenon was pointed

out; thus, the association between countries economic development within changes in dietary pattern is most probably related. Afflated results of earlier studies [14,15], Jarosz research team [13] analyzed dietary preference of Polish society in an association with mortality and morbidity of gastric cancer. A very significant correlation was found between decrease in gastric cancer incidence rates and increase in vitamin C consumption, which was related to growing consumption of fruits and vegetables. Similar correlation with availability of refrigerators in habitations is observed. A decrease of this rate resulted from reduction in salt consumption as well.

Research about "Risk Factors of Gastric Cancer in High-Risk Region of China" performed by Chen et al [16] shows that dietary habits, including: omission of breakfast, consumption of pickled vegetables 30 years ago, overeating significantly increase risk of GC. Their results suggest that individuals with low socioeconomic status and skipped breakfast or consumed pickled vegetables 30 years ago had 10-fold and 6-fold higher risk of GC respectively in comparison to a control group of patients, who used to eat breakfast regularly and live in high socioeconomic status. Current studies indicate possible carcinogenic ingredients of long-term pickled vegetables, including: mycotoxins and N-nitroso compounds, which are responsible for the injury of gastric mucosa [16,17].

The next issue under discussion in our review was meat consumption. Current studies indicate that high intake of red meat or processed meat was significantly related with higher risk of GC (41% and 57% increased risk, respectively), but a consumption of white meat may reduce GC risk for about 20 %. [18]

2.4 Socioeconomic status

Socioeconomic status is one of factors that may determine gastric carcinoma incidence. Study on the population of Xianyou County of China, where incidence of stomach cancer is high, may support this claim. The data show that current low socioeconomic status increases the risk of gastric cancer 2,56 times while low socioeconomic status 10 years before increases it 2,89 times. It can be suspected that dietary habits, smoking, family disharmony and lower level of education - that are other risk factors may be associated with socioeconomic status [16].

The study of Kim et al. [19] underlined that lower socioeconomic status may be a negative prognostic factor for gastric cancer. The lowest income group of patients are less likely to receive endoscopic mucosal resection (EMR), which is an effective treatment procedure for noninvasive gastric cancer. The probable cause of this phenomenon is delayed cancer detection. While all citizens of South Korea have national health insurance, the higher income groups of patients have more time and opportunities for screening procedures.

The study of Gupta et al. [20] from the USA shows that lowering of socioeconomic status is related to an increase of gastric cancer risk. Non-cardia cancer type incidence is higher among ethnic minorities and is correlated with socioeconomic status. It is hypothesized

that the most well-established risk factor of gastric carcinoma - H. pylori infection may be responsible for the differences. These problems shall be elaborated in more detail further on.

2.5 Lifestyle

Smoking and alcohol consumption are the main lifestyle risk factors which may determine gastric cancer. The evidence for smoking as a risk factor is unequivocal. In the EPIC study [21,22] there was observed that during a 11.4 years follow up of patients that never smoking or quitting over 10 years previously was associated with a reduced risk of developing gastric cancer. Other studies show that the risk of gastric cancer, expanding both: cardia and non-cardia region, rises with the number of smoked cigarettes, especially in case of consumption approximately 30 cigarettes per day [23]. Current studies show that smoking influences devastating and non-reversible effects on the gastric tissue which increases the risk of carcinogenesis [7]. Furthermore, a strong relationship between alcohol intake and gastric cancer was demonstrated in a systematic review by Yusefi et al. [7]. This association was reported only in heavy alcohol consumption (≥ 4 drinks per day). It should be noted that people who consume over 50g alcohol per day were at 24% higher risk of gastric cancer compared to other people (who do not consume alcohol or consume less). The possible mechanism of relationship of alcohol consumption and higher risk of GC may be inflammatory stimulation, which could lead to the response of toxic ethanol metabolites.

Interestly, high level of stress, depression or anxiety disorder may increase the risk of gastric cancer [24].

2.6 Medical condition

Medical condition and treatment are the effective factors in the incidence of gastric cancer. In the study of Yousefi et al. [7] the review of many publications was achieved. It should be noted that, gastric ulcers, chronic atrophic gastritis, intestinal metaplasia, history of gastrectomy and stomach surgery were associated with an increased risk of gastric cancer.

Current studies show that obesity and GERD (gastroesophageal reflux disease) are important risk factors for gastric cardia adenocarcinoma development [22,25]. They observed that the risk of GC increases simultaneously to body mass index. However, no increased risk has been found for non-cardia gastric cancer [22]. Several studies have reported statistically significant association between GERD and cardia GC, with increased risks of 2-4 folds [25].

Caroline et al. [21] summarized current knowledge about pharmacological interventions of statin and non-steroidal anti-inflammatory drugs on gastric cancer incidence. Statin and aspirin or celecoxib use were associated with a reduced risk of gastric cancer.

2.7 The blood type

Relationship between ABO blood groups and stomach carcinoma has been discussed since 1953 [26]. Majority of the studies agree that blood type A is a risk factor for gastric cancer. The results of Shanghai Cohort Study [27] suggest that people with blood type A are

20% more likely to get gastrointestinal tract carcinoma than other groups. The same study shows that people with blood type B are at the lowest risk of developing cancer, especially located in the stomach or urinary bladder. The study on Taiwanese population shows that blood type A is associated with 38% higher risk of gastric cancer compared to type O. Moreover, the mortality was also elevated by 38% in group A compared to group O [28]. Other studies suggest that not only group A is associated with higher risk of gastric carcinoma, but also group AB. Compared to group O, stomach cancer risk was 19% higher in group A and 9% higher in group AB. The difference between groups B and O was insignificant [29]. There are some possible explanations for this regularity. Current studies suggest that blood type A may result in higher proneness for H. pylori infection [30]. Other explanations include lower production of acid in the stomach in blood type A individuals and a variety of physiological differences between blood groups [29].

2.8 Helicobacter Pylori

Helicobacter pylori is the most common cause of infection-related cancers, because of its worldwide popularity [31]. Circa half of the population is infected and H. pylori is especially common in developing countries. The prevalence of infection increases rapidly during childhood, because of its horizontal transmission via multiple routes [32]. Most cases are asymptomatic. The presence of H. pylori was associated with atrophic gastritis, intestinal metaplasia, dysplasia and gastric cancer especially glandular and diffuse type, but not cardia cancer [31 - 33]. The bacterium significantly increases the risk of chronic active gastritis, which leads to: peptic ulcer disease, gastric adenocarcinoma and mucosa-associated lymphoid tissue lymphoma [31]. The bacterial strains contained genes of CagA protein or VacA, which may lead to carcinogenesis. [34] CagA in its non-phosphorylated form targets the E-cadherin and causes disruption of cell-junctions, loss of cell polarity, pro-inflammatory and mitogenic effects [35]. Helicobacter pylori VacA is a channel-forming toxin and contributes inflammation processes [34]. Virulence factors cause stronger inflammation and atrophy processes of gastric mucosa, which initiate mucosal injury, dysplasia and cancerogenesis [36].

High expression of IL-1 beta polymorphisms in H. pylori-infected patients increases risk for gastric atrophy and distal gastric adenocarcinoma, because of a more intensive inflammation process. Current studies suspect that IL-1 plays a crucial role in the development of gastric cancer [37].

Co-existence of H. pylori and some commensal bacteria, such as: ASF361 Lactobacillus murinus or ASF519 Bacteroides species, leads to more intensive inflammation. Lack of commensal flora reduces the risk of gastritis and delays intraepithelial neoplasia [38].

The study of Gupta et al. [20] suggests applying prevention against these bacteria in populations with lower socioeconomic status to reduce incidence of gastric carcinoma [20]. Early eradication of H. pylori is thought to be more effective in preventing dysplasia or gastric cancer, because of inhibiting the progression of precancerous lesions with molecular alterations. Every case should be discussed individually - people with polymorphisms

associated with high levels of IL-1 beta expression and colonized by CagA strains may be most beneficial after eradication treatment, which could result in minimizing cancer risk [31].

2.9 Ionizing radiation

Impact of ionizing radiation may be observed in patients after radiotherapy. Decades after exposure, solid tumor occurrence increases. The younger the person is during exposition, the greater is the risk of gastric cancer development [40]. A significant association of stomach carcinoma existence was connected with absorbed dose of gamma rays - especially greater than 30 Gy, which was spotted after abdominal radiation [41]. Significant risk was also caused by having radiotherapy or chemotherapy containing a high-dose procarbazine together [42].

3. Conclusions:

Variety of environmental, genetic and medical factors are associated with an increased risk of gastric cancer. The awareness of its existence facilitates pathogenesis of gastric malignancies and enables the implementation of proper diagnostic procedures, screening programs and prophylaxis. A reduction in the burden of gastric cancer may be achieved by reduction of red meat consumption, quitting smoking cigarettes and abstaining from alcohol abuse. Appropriate prophylactic operation and early screening diagnosis in patients with genetic predisposition enable to prevent from occurrence of advanced stage gastric cancer cases and decrease mortality and morbidity due to carcinoma of the stomach.

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