Genetic and environmental risk factors for gastric cancer

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SUMMARY
Objective: this review aims to address the main aspects about the risk factors related to gastric cancer. Method: we performed a literature review in scientific journals, books and websites that discuss the subject: Scielo, pubmed, Virtual Health Library and National Cancer Institute, being searched 30 articles. Results: Note that the knowledge about the risk factors for Gastric Cancer are of great importance to preventing and combating the gastrointestinal carcinogenesis

Keywords: risk factors. Gastric Neoplasms.

1. INTRODUCTION

Gastric cancer is one of the most commons cancers, and is known as the second leading cause of cancer deaths worldwide. Every year, more than 930,000 new cases of gastric cancer have been diagnosed worldwide, followed by 700,000 deaths.

In Brazil, these tumors appear in third place in the incidence among men and in fifth place among women. In the country the estimated new cases of 20,390, being men and women 7,520 12,870.

In Pará, in 2014, the estimated new cases per 100000 inhabitants was of 450 men and, among women, of 240.
Bethlehem, the estimated new cases per 100000 inhabitants was 140 men and, among women, ³ 100.

The clinical picture of patients with gastric cancer often is characterized by weight loss in short time, local pain, dyspepsia, nausea, vomiting, flatulence, sensation of fullness that contribute to early worsening of the disease, hinder the proposed treatments and, consequently, promote worse prognóstico⁴. These symptoms can easily be confused with those of gastritis or ulcer gástrica⁵.

The survival rate in six months is strictly related to the diagnostic phase, and is about 65% in people diagnosed early and less than 15% in those diagnosed in advanced stages. Metastatic invasion occurs in 80%-90% of the paciente⁵.

The prognosis is set from the extent of tumor invasion, presence or absence of metástases⁶ and the involvement of lymph nodes, which is considered the most reliable indicator of prognosis in gástrico⁶ cancer⁷. The gastric carcinogenesis, as well as other organs is multi-step process that can clinically manifest as gastritis, gastric atrophy, intestinal metaplasia, Dysplasia, ulcerations and, finally, as a malignant neoplasm. These conditions tend to be sequential and occur over a period of many years, as a result of exposure to a variety of endogenous factors and exógenos⁶.

The fact that the incidence of this neoplasm differ substantially by geographic region, indicates that modifiable lifestyle factors, especially dietary factors, added to genetic factors, can influence the development of this doença⁷.

Based on this context, the present study aims to address the main aspects about the risk factors related to gastric cancer and contribute to the development of effective preventive measures to combat the appearance of gastric neoplasms.

2. METHODOLOGY

This work was conducted through a literature review in scientific journals, books and websites that discuss the subject under study: Scielo, pubmed, Virtual Health Library and National Cancer Institute. The inclusion criteria were based on the period of time between 2003 and 2014 and in English, Spanish and Portuguese.

3. LITERATURE REVIEW AND DISCUSSION

3.1 genetic factors

The Lauren classification for gastric cancer has been the most used in gastric adenocarcinoma, which is divided
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into intestinal and diffuse. Subsequently, the indeterminate type was included to describe a rare histology. There is evidence that the intestinal type is associated with intestinal metaplasia of gastric mucosa caused by exogenous factors and the diffuse type is more related to genômicas abnormalities. This fact may indicate tumor development paths for intestinal and diffuse adenocarcinoma of the stomach.

The gastric Carcinogenesis is a multifactorial process, in which genetic and environmental factors interact to enable multiple intracellular signals, leading to the uncontrolled growth and survival of cancer cells. The accumulation of genetic and molecular abnormalities modifies the expression of various kinds of genes whose function is important for regulating cell function.

The PAR-1 and PAR-2 are expressed in gastric cancer cells and its activation triggers amplify intracellular biochemical pathways that underpin the gastric carcinogenesis. There is also evidence that the expression of any PAR-1 or PAR-2 correlates with depth of invasion on the wall and metastatic spread and inversely with the overall survival of the patients.

In addition, the amplification of the epidermal growth factor receptor 2 (HER2) gene human and about HER2 protein expression is present in 15% -20% of patients with gastric cancer and gastresofágico junction. The degree of HER2 expression and amplification varies with the location of carcinoma, with highest expression in gastresofágico and proximal parts compared to the distal parts of the stomach. A large number of studies seem to indicate that the HER2 is a prognostic factor.

Among the most prevalent and common genetic alterations in gastric cancer are mutations in the TP53 gene CDH1 and CDH1. In addition to genetic mutations in CDH1 gene to induce hereditary diffuse gastric cancer (HDGC), epigenetic factors, such as the hipermetilação of DNA also contribute to the reduction of E-cadherin in gastric carcinogenesis.

In addition, the expression of E-cadherin may be mediated by infectious agents, such as h. pylori. As E-cadherin is vital in the process of signaling that modulate cell proliferation, survival, migration and invasion, deregulation of the E-cadherin leads to dysfunction of gastric epithelial cells and contributes to the development of cancer.

In gastric carcinogenesis, tumor suppressor genes P53, P73 are changing, Bcl-2 and APC. Genes that repair DNA damage are responsible for detect and repair changes to other genes and changes in its function triggers a gradual accumulation of mutations in addition, any uncontrolled expression of P16, p27 and Rb, CDC25B, E2F results in a genomic instability, uncontrolled cell proliferation and tumor development gástrico.
It can be observed that gastric cancer genomic level is a heterogeneous disease and that the different genetic and molecular changes have an impact on medical practice, since it can be associated with distinct clinical pictures in patients.

Environmental factors

H. pylori

Helicobacter pylori is a gram-negative bacterium that infects spiral more than half the population mundial. In addition to his undisputed role in chronic gastritis and peptic ulcer disease, the association between h. pylori and gastric cancer is also well accepted and epidemiological studies estimate that the risk of gastric cancer in individuals infected with h. pylori is increased in 20 vezes. Currently, Helicobacter pylori infection is considered to be the most important risk factor for the onset of cancer gastrico.

H. pylori gastritis is characterized by a severe and chronic inflammation that can last for decades if left untreated. The persistent inflammation can activate neutrophils, generate reactive oxygen species and nitrogen, important mutagens and carcinogênicos.

The first strain-specific gene identified in h. pylori was the citotoxin antigen associated (shits), which is strongly associated with the risk for development of gastric cancer. CagA + strains tend to be more virulent and induce higher levels of expression of cytokines, such as IL-1b and IL-8, showed that patients infected with strains that express shit + are likely three times higher to develop gastric cancer than those infected by cagA strains.

N-nitroso Compounds and salt

Studies have reported that the consumption of salty foods and N-nitroso compounds and a low intake of fruits and vegetables increases the risk of gastric cancer. Experimental animal models also gave support to the hypothesis that the salt promotes gastric carcinogenesis induced by carcinogenic N-nitroso, such as N-methyl-N-nitro-N-nitrosoguanidina (MNNG), or N-methyl-N-nitrosoureia (MNU). Thus, the association between the saturated NaCl and N-nitroso-carcinogen can promote stomach carcinogenesis in rats by inflammation, mutation, and cell proliferation compensatória.

The NaCl can act synergistically with h. pylori infection, as was shown in case control studies and animals studied, through mechanisms that include strengthening the expression of cagA, changes in viscosity of mucus, with subsequent loss of parietais.
In addition to causing chronic gastritis, diets high in NaCl can facilitate absorption of chemical carcinogens (polycyclic aromatic hydrocarbons), acting as a promoters of the development of tumors in roedores\textsuperscript{22}. 

The excess sodium chloride results in the formation of malonodialdehyde in the mucosa of the glandular stomach and increase their excretion through the urine. Thus, lipid peroxidation occurs in the glandular stomach due to damage caused by sodium chloride, which leads to formation of reactive oxygen species (ROS), which cause damage to DNA cellular\textsuperscript{23}. These molecules play a crucial role in carcinogenesis and may be targets for terapêuticas\textsuperscript{20} approach\textsuperscript{t}.

Alcohol

Considering the consumption of alcohol, some studies have shown increased risk for estômago\textsuperscript{24} cancer\textsuperscript{t}.

Alcohol induces several changes morphological and functional gastric. In fact, the ethanol harms the gastric mucosal defense mechanisms, by changing the composition and the release of mucus and bicarbonate, in addition to interfere in the renewal of gástrico\textsuperscript{25} epithel\textsuperscript{m}.

The increased levels of acetaldehyde induced by excessive consumption of alcohol can lead to DNA damage and subsequently increase the risk of cancer gástrico\textsuperscript{26}. Ethanol-induced gastric ulcers are caused due to several mechanisms, including the depletion of gastric mucus and mucosal permeability hearing, which leads to an increase in the release of hydrogen ions from the lumen and decrease the difference in membrane potential transluminal\textsuperscript{27}.

Alcohol breaks the barrier of gastric mucosa damage caustics, causing rupture of blood vessels, hemorrhage and necrosis of the mucosa. Predispose the formation of gastritis and may trigger the emergence of a cancerous process. The lesions in the gastric mucosa can decrease the production of extrinsic factor, causing the individual to a deficiency of vitamin B12 absorption\textsuperscript{28}.

Smoking

About 30\% of deaths from stomach cancer occur in smokers. Smoking has been consistently reported as the most important behavioral risk factor for cancer gástrico\textsuperscript{7}.

Epidemiological data show that cigarettes increase both the rate of incidental peptic disease relapse, but also slows down the healing of ulcers in humans. The extent to which the action is attributable to gene Ucero nicotine in
cigarette smoke is still bad defined\(^9\).

### 3.2 gastric secretion inhibitors

Drugs that inhibit acid secretion of the stomach such as cimetidine, ranitidine, and loxtidina, which blocks the receptor H2 of histamine on parietal cells of the stomach, and the blockers of K+, H+-ATPase (proton pump), such as omeprazole, reduce the acidity gástrica\(^2\). The state of hypochlorhydria or acloridria caused by these medicines or for other reasons, causes the pH of the stomach be conducive to formation of colonies and survival of microorganisms, which promotes a chronic inflammatory process in the mucosa, leading to atrophic gastritis, result in outbreaks of metaplasia, Dysplasia, evolving to preceding the onset of neoplasias\(^3\).

### 4 – conclusion

Based on the results found with the realization of this study concluded that the knowledge about the risk factors for Gastric Cancer is of great importance to the development of preventive and effective measures to combat gastrointestinal carcinogenesis and on improvement of the prognosis of people already affected by this pathology. The study also demonstrates that prudence is essential in clinical use of medicinal antacids because its indiscriminate use may result in the initiation and promotion of neoplasms.

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