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Risk factors in gastric cancer

D. COMPARE, A. ROCCO, G. NARDONE

Department of Clinical and Experimental Medicine, Gastroenterology Unit, University of Naples "Federico II", Naples (Italy)

Abstract. – *State of the Art:* Gastric cancer (GC) is still a major health problem worldwide due to its frequency, poor prognosis and limited treatment options. At present prevention is likely to be the most effective means of reducing the incidence and mortality from this disease. The most important etiological factors implicated in gastric carcinogenesis are diet and *Helicobacter pylori* (*H. pylori*) infection.

High intake of salted, pickled or smoked foods, as well as dried fish and meat and refined carbohydrates significantly increased the risk of developing GC while fibers, fresh vegetables and fruit were found to be inversely associated with GC risk.

Epidemiological investigations (retrospective, case-control and prospective) and several meta-analyses have demonstrated that concurrent or previous *H. pylori* infection is associated with an increased risk of GC in respect to uninfected people. *H. pylori* colonizes gastric mucosa where it induces a complex inflammatory and immune reaction that on time leads to a severe mucosal damage i.e., atrophy, intestinal metaplasia (IM) and dysplasia. The risk of GC is closely related to the grade and extension of gastric atrophy, IM and dysplasia.

***Perspectives and Conclusions:* Today a plausible program for GC prevention means: (1) a correct dietary habit since childhood increasing vegetables and fruit intake, (2) a decrease of *H. pylori* spread improving family and community sanitation and hygiene, (3) a search and treat *H. pylori* strategy in offspring of GC, (4) a search and treat *H. pylori* strategy in patients with chronic atrophic gastritis and intestinal metaplasia (IM), (5) a careful endoscopic and histologic follow-up if precancerous lesions persist irrespective of *H. pylori* eradication.**

Key Words:

H. Pylori, Diet, Gastric cancer.

Introduction

Gastric cancer (GC) is still a major health problem worldwide due to its frequency, poor prognosis and limited treatment options. Currently, the 5-year-relative survival rate is about 20%. According to the International Gastric Cancer Society, more than 800,000 people are affected by GC every year and up to 650,000 people have succumbed to gastric cancer[1]. It is likely that in 2020 GC will increase by 10% in developing countries[2].

At present, primary (addressing etiological factors) and secondary (addressing patients at risk) prevention are likely to be the most effective means of reducing the incidence and mortality from this disease.

GC is a multifactorial disease resulting from an interplay between host genetic susceptibility and environmental factors[3].

Genetic susceptibility play a trivial role in the pathogenesis of this condition accounting for about 1% of all GCs. Microsatellite instability and E-cadherin are the most frequent genetic alterations associated with a family history of GC (more than two relatives in two successive generation)[4]. At present the International Gastric Cancer Consortium recommends prophylactic gastrectomy in carriers of E-cadherin germline mutation belonging to familial GC[5].

Studies of migrants moving from a high- to a low risk area have shown that the migrants acquire the cancer pattern of the host country within a single generation suggesting that environmental factors play a trigger role in the carcinogenic process[6]. The most important environmental factors implicated in gastric carcinogenesis are diet and *Helicobacter pylori (H. pylori)* infection.

Diet

Diet, to which we are necessarily exposed every day, can either inhibit or induce carcinogenic process: high intake of salted, pickled or smoked foods, as well as dried fish and meat and refined carbohydrates significantly increased the

Corresponding Author: Gerardo Nardone, MD; e-mail: nardone@unina.it

risk of developing GC while fiber, fresh vegetables and fruits were found to be inversely associated with GC risk[7-11].

High consumption of refined carbohydrates has been shown to be associated with a significant increased risk of developing GC with an estimated Odds ratio (OR) ranging from 1.5[12] to 8.73 per 100 mg of daily intake[13]. High consumption of saturated fat and cholesterol enhanced the risk of cancer for intestinal type GC (OR Q4 vs Q1 4.37; 95% CI 1.89-10.12 for saturated fat and OR Q4 vs Q1 2.39; 95% CI 1.23-4.64 for cholesterol)[11]. Analysis of the data obtained in 21 studies involving a total of 1,651,231 individuals, followed for periods ranging between 3.3 and 25 years, substantially confirmed the significant increased risk of developing GC due to high intake of total carbohydrates, salted fish, processed meat, refined grains and saturated fat[14]. A large prospective study on diet and cancer carried out on 521,457 individuals aged 35-70 years recruited in 10 European countries (EPIC – European Prospective Investigation into Cancer and Nutrition study), by analysing 314 incident cases of GC that had occurred after 6.6 average years of follow-up, reported a significant increase of non-cardia GC risk associated with intake of total meat (calibrated hazard risk [HR] 100 g/day increase 3.52; 95% CI 1.96-6.34), red meat (calibrated HR per 50 g/day increase 1.73; 95% CI 1.03-2.88), and processed meat (calibrated HR per 50 g/day increase 2.45; 95% CI 1.43-4.21). The endogenous formation of nitroso compounds (ENOC) was significantly associated with non-cardia cancer risk (HR 1.42; 95% CI 1.14-1.78 for an increase of 40 mg/day) especially in those cases with *H. pylori* infection (*p* for interaction = 0.09)[15].

The beneficial effect of fresh fruit and vegetables on the mucosa of the gastrointestinal tract is mainly the consequence of anti-oxidant properties of micronutrients whose intake inversely correlated with the risk of GC[16-18]. Correa et al[19] have shown that dietary supplementation with anti-oxidant micronutrients, such as ascorbic acid or beta-carotene, in a GC high-risk population, significantly increased the rate of regression of cancer precursor lesions to a similar extent as that observed with *H. pylori* eradication. Considerable evidence supports the hypothesis that flavonoids and other polyphenolic phytochemicals contained in certain foodstuffs, for example onions, red grapes, nuts, and green tea, mediate, or contribute to the putative cancer chemopreventive properties of their dietary sources. Their ability to reduce cancer incidence in population studies is likely related to their ability to induce apoptosis and inhibit neaongiogenesis[20-23]. Also, extra-virgin olive oil component, oleocanthal, has been demonstrated to exert ibuprofen-like activity being able to significantly inhibit cyclooxygenase activity[24]. A recent study has shown that polyphenol extracts obtained from apple prevent reactive oxygen species (ROS) and indomethacin-induced injury to gastric epithelial cells *in vitro* and to the rat stomach *in vivo* and this effect is mediated by the anti-oxidant activity of catechin and chlorogenic acid[25].

Helicobacter Pylori Infection

Helicobacter pylori is one of the most frequent infection affecting more than 50% of the worldwide population. Most infected individuals have a symptomatic chronic gastritis, a subgroup peptic disease and a small minority develops GC (lifetime risk, 0.1%)

Exposure of gastric epithelial cells to *H. pylori* results in a complex inflammatory and immune reaction with the generation of ROS and increased levels of nitric oxide synthase which in turn can induce oncogene activation and oncosuppressor gene inactivation and ultimately GC development[26].

The extent and severity of gastric mucosal inflammation, as well as the clinical outcome of the infection, depend on a number of factors including the virulence of the bacterium, host genetic susceptibility, immune response, age at the time of initial infection and environmental factors[27]. Epidemiological investigations (retrospective, case-control and prospective) and several meta-analyses have demonstrated that concurrent or previous *H. pylori* infection is associated with an increased risk of GC in respect to uninfected people (OR 3.0; 95% CI 2.3-3.8); the risk was stronger when the infecting *H. pylori* strain was CagA-positive and blood samples for *H. pylori* serology were collected ten years before cancer diagnosis (OR 5.9; 95% CI 3.4-10.3)[28].

Helicobacter pylori, indeed, is characterized by several putative virulence factors, i.e., *vacA, iceA,* and particularly *cagA,* with the cag pathogenicity island (PAI), that are variously associated with the risk of gastric disease[29].

The vacA gene, which encodes a vacuolating cytotoxin and is present in ~50% of *H. pylori* isolates comprises two variable regions: the s region (s1a, s1b, s1c, or s2 allele), and the m re-

gion (m1, m2a, or m2b allele)[30]. The vacAs1 and vacAm1 strains appear to be more virulent than type s2 strains, presenting a higher degree of inflammation and higher risk for peptic ulcer disease, gastric atrophy, and GC[31].

The cagA gene is a marker for the presence of the PAI[32]. Only one-half of Western isolates carry the cag PAI, whereas nearly all East Asian strains carry the cag PAI[33]. Infection with cagA-positive *H. pylori* strains is associated with higher levels of mononuclear and neutrophilic infiltrates, more severe atrophy, intestinal metaplasia and alterations in the gastric epithelial cell cycle[34]. Pooled data have shown that cagA positive strains of *H. pylori* are associated with a higher risk of GC (OR 2.01; 95% CI 1.21-3.32) in respect to cagA negative strains[35]. Two studies conducted in the United States and one in Japan have shown that the cagA-positive strain was more closely related to intestinal type GC than the cagA-negative strain[36-38]. A large population-based case-control study from Los Angeles County confirmed this positive association[39]. However, currently, the presence of a functional cagA pathogenicity island has no predictive value for the presence or future development of a clinically significant outcome[40]. Therefore, the question of whether certain *H. pylori* strains are more carcinogenic than others still remains to be elucidated and may vary in relation to the different geographical areas.

Genetic Factors

Early studies[41] revealed that GC was less common in patients with blood group 0, but was frequently associated with blood group A which increases the risk by 16-20%[42]. A positive family history of GC has been associated with an increased (~three-fold) risk of GC[43]. Interestingly, subjects with both a positive family history and infection with cagA-positive *H. pylori* strains had a 16-fold increased risk of non-cardia GC[44].

Polymorphisms in a wide variety of genes, present in a significant proportion of the normal population, may affect the activity of key inflammatory molecules and modify the effect of environmental exposures. Thus, gene-environmental interactions could explain the high inter- individual and/or geographic variations in the GC incidence. Interleukin (IL)-1beta and IL-1 receptor antagonists (IL-1ra) are potent cytokines that play a key role in regulating gastric acid secretion, showing a 100-fold greater potency than proton pump inhibitors[45]. An important case-control study conducted in Scotland and Poland showed that individuals with particular IL-1beta gene polymorphism presented an increased risk of GC in the presence of *H. pylori* infection[46].

A variety of associations between GC risk, *H. pylori* infection, and specific HLA alleles have been described. In a case-control study in the United States, the HLA-DQB1*0301 as well as the HLA-DRB1*1601 alleles were more common in GC than in controls (OR 3.2)[47]. Another case-control study suggested that the absence of HLA-DQA1*0102 may be a host genetic risk factor for *H. pylori* infection and the intestinal type GC[48]. An European study has confirmed absence of the HLA-DQA1*0102 allele as a risk factor for *H. pylori* infection, but it did not find any association with GC risk[49]. Taken together, these results appear to indicate the existence of a variable genetic susceptibility that may confer differential risk for *H. pylori* infection and GC. Cohort studies, taking into account both the different genetic and environmental factors, are needed to establish not only the relative contribution of these factors to tumour development but also the contribution of their putative interaction.

Age

It has been proposed that age at the time of onset of *H. pylori* infection may be another determinant of disease outcome[27]. Onset of *H. pylori* infection early in life has been associated with an increased risk of GC[36]. Epidemiological studies have revealed a high incidence of adult GC in areas with a high prevalence of *H. pylori* infection in childhood[35,50,51]. In the younger Japanese generation, a OR 13.3 was shown for the relationship between *H. pylori* infection and GC[52].

Gastric cancer tends to occur in older people and it seems more likely to occur in a stomach that has been inflamed for many years. Indeed, continuous infection with *H. pylori* during childhood, or the teenage years, may induce in adulthood irreversible harm to the gastric mucosa[53]. Therefore, it is mandatory that *H. pylori* be eradicated in childhood or early teens, since eradication after the irreversible gastric mucosa lesions have been inflicted, does not prevent carcinogenesis at all. In a prospective, randomized, placebo-controlled study carried out in 1,630 subjects showed that there was no significant difference concerning GC incidence between patients treated or not treated with *H. pylori* eradication therapy. However, if the Authors initially excluded pa-

tients with atrophy or intestinal metaplasia (IM), expression of a long-standing infection, the difference was significant ($p<0.02$)[54].

Precancerous Lesions

The secondary prevention focuses on patients at risk of developing GC. Gastric atrophy, indeed, is considered the first relevant step in the histogenesis of intestinal type GC according to the multistep process suggested by Correa[55]. In fact, the risk of GC is closely related to the grade and extension of gastric atrophy being up to 80-90 folds higher in respect to the general population in patients with severe atrophy involving both antrum and body[56]. Gastric atrophy assumes a precancerous meaning particularly when it is located or extended in the corpus. This latter condition, indeed, damaging parietal cells decreases the acidity in the stomach and provokes the transformation of nitrates food components in nitrites and nitrosamides which are critical for the onset of the gastric carcinogenic process. This hypothesis links the theory of "N-nitroso compounds-mediated GC risk" with that of "*H. pylori*-related GC risk" suggesting an "integrated model" of gastric carcinogenesis[57].

Chronic atrophic gastritis is often associated with IM, the subsequent step in the Correa model of *H*- related gastric carcinogenesis[55,58,59]. The prevalence of IM was significantly higher in *H. pylori*-positive (43%) than in *H. pylori*-negative subjects (6.2%)[60].

Intestinal metaplasia has been classified according to Jass and Filipe as complete or type I, or incomplete which comprises types II and III[61]. Based on retrospective data, the risk of GC is related to the type of IM[56]. In a 10-year follow-up study from Slovenia, patients with IM showed an overall 10-fold increased risk of GC compared with those without IM[62]. In another study, the risk of GC was four-fold higher in patients with IM type III than in those with type I[63]. A Japanese study reported that IM was the only criterion associated with the development of intestinal type GC[64].

The association between the risk of GC development and IM subtypes is, however, not universally accepted. Cassaro et al[65] have shown that IM involving the lesser curvature, from the cardia to the pylorus, or the entire stomach, was associated with a higher risk of GC than focal or antral predominant IM. Thus, the distribution of IM rather than IM subtype may provide a higher predictive value of cancer risk.

The next step in the cascade of morphological changes in gastric carcinogenesis is dysplasia that usually develops in the *H. pylori* infection, atrophy and IM setting[55]. The development and progression of dysplastic changes[66] is clearly associated with *H. pylori*[67]. This process includes a continuum of progressively dedifferentiated phenotypes which may result in a new cell. According to the definition of the World Health Organization, dysplasia is now called non-invasive gastric neoplasia, indicating a pre-invasive neoplastic change in the gastric glands[68]. The higher the grade of dysplasia, the greater the risk of developing invasive GC[69].

The majority of carcinoma found in follow-up studies and which were discovered within one year of the diagnosis of dysplasia may indicate that the carcinoma was already present at the time of diagnosis of dysplasia[66].

Conclusion

Today, GC remains a major clinical challenge due to its frequency, poor prognosis and limited treatment options. Therefore, one of the primaty objective of World Health Organization and researchers is to arrange programs for GC prevention that means:

- A correct dietary habit increasing vegetable and fruit intake since childhood;
- Decrease *H. pylori* spread improving family and community sanitation and hygiene;
- Testing for E-cadherin germline mutations in relatives of familial GC patients;
- Search and treat *H. pylori* in offspring of GC patients;
- Search and treat *H. pylori* in patients with chronic atrophic gastritis and IM and, if precancerous lesions persist, a careful endoscopic and histologic follow-up have to be scheduled irrespective of *H. pylori* eradication.

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