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Risk Factors for Gastric Intestinal Metaplasia

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The infection with *Helicobacter pylori* affects more than 50% of the world adult population, and approximately two thirds of all cases of stomach cancer are attributed to it, but a large proportion of the infected subjects will never develop cancer. Gastric carcinogenesis is currently interpreted as a multifactorial and multistage process, with environmental exposures (*H. pylori* infection and behavioural factors), and genetic susceptibility contributing for the occurrence of cancer. The study of the risk factors for precancerous lesions is a major field of research with potential to clarify the aetiology of gastric cancer, namely through the understanding of the mechanisms that modulate the progression to cancer among the infected.
Key-words: gastric cancer; precancerous lesions; intestinal metaplasia; *Helicobacter pylori*; risk factors.

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BACKGROUND

A continued international decline in gastric cancer mortality has been observed in the last century (1), but it remains the fourth most common cancer and the second leading cause of cancer-related deaths (2), with a wide variation in incidence rates across geographical areas (3). There is also a large heterogeneity across countries in the magnitude of the overall decline in gastric cancer frequency (4, 5). A decrease in the frequency of the intestinal type tumours accounts for most of the recent decline in stomach cancer rates worldwide, since the diffuse type adenocarcinomas seem to have remained stable over time (6, 7) or even increased in incidence (8). An increasing trend has also been observed with cardia cancer in most regions (9-11). Portugal presents the highest mortality rates in Western Europe, since its reduction started later and has been slower than in most European countries (5, 12).

Gastric cancer screening in Japan contributes to an early detection of stomach cancer and a 5-year relative survival rate of 62% (13). However, survival rates are globally low, and only moderate improvements have been achieved in the last decades. In the United States, the 5-year relative survival rate increased from 15% to 23% from 1974 to 2000 (14), and a similar trend was observed in Europe with an increase from 18% to 22% for adults diagnosed during the period 1990-1994 (15).

Helicobacter pylori infection (16-18), smoking (19, 20), and fruit and vegetables consumption (21, 22) are the environmental factors more consistently associated with gastric cancer, and potential targets for prevention. In addition to the challenge of developing an effective vaccine against *H. pylori* infection (23), randomised controlled trials have been conducted to test the eradication of infection as a strategy to prevent gastric cancer. However, the latter are still inconclusive (24), and there is conflicting evidence regarding a beneficial effect of eradication in subjects having gastric precancerous lesions (24-26).

GASTRIC CARCINOGENESIS

Gastric cancer appears in two forms - familial and sporadic, the latter accounting for 90% of the cases (27). Over 95% of gastric malignancies are adenocarcinomas, but these comprise a spectrum of different conditions classified according to the site of tumour origin and the histomorphology of the lesion.

In epidemiological studies, gastric adenocarcinomas are usually divided into proximal (cardia) and distal (non-cardia). In addition to the differences in the trends of proximal and distal cancers of the stomach, *H. pylori* infection increases the risk of the noncardia carcinomas but is not associated with the cardia cancer (28, 29), supportive of the hypothesis that these two gastric tumour types may represent distinct diseases with different aetiologies.

From a histological standpoint, several classification systems have been established for gastric cancer. Laurén's is one of them and has been widely applied on epidemiological research (30). It subdivides tumours in two main histological types - diffuse (undifferentiated) and intesti-

nal (well-differentiated). Still, the histological classification of an individual gastric adenocarcinoma is sometimes complex because a tumour often comprises a mixture of intestinal and diffuse tissue types. Intestinal type is more common in males, blacks and older age groups, while the diffuse type has a similar incidence in both genders and is more frequent in younger individuals (31, 32). Also, there is a wide geographical variation in the distribution of intestinal type tumours, whereas the occurrence of diffuse adenocarcinomas is more uniform across regions (33).

A model for the progression of tumours of the intestinal type has been proposed by Correa et al., according to which precancerous lesions occur in sequential steps (34): chronic atrophic gastritis, intestinal metaplasia, and dysplasia. Chronic atrophic gastritis is a result of chronic active inflammation that may ultimately lead to the destruction of gastric glands and the loss of normal mucosa architecture. Intestinal metaplasia consists of the replacement of the gastric mucosa by an epithelium that histologically resembles the intestinal mucosa. Dysplasia is regarded as an early step towards transformation into neoplasia.

Two main types of intestinal metaplasia have been identified through histopathological and histochemical studies. The complete type (or type I) is characterised by the presence of absorptive cells and goblet cells secreting sialomucins, and corresponds to the small intestine phenotype. The incomplete type (encompassing types II and III) is characterised by the presence of columnar and goblet cells secreting sialo and/or sulfomucins (35). Columnar cells produce neutral and acid sialomucins in type II, while in type III they secrete sulfomucins. The patterns of mucin expression according to the type of intestinal metaplasia are in the basis of a new model hypothesised for the gastric carcinogenic process (36).

The classical sequential pathway (from type I intestinal metaplasia to type III via a type II intermediate step) was challenged and it was proposed that the complete and incomplete types of intestinal metaplasia may represent two alternative pathways, rather than successive steps of phenotypic modification of gastric mucosa; or that type II of incomplete intestinal metaplasia may represent a first step in the pathway, which may evolve to type I or to type III intestinal metaplasia.

Even though precancerous lesions and respective types are already recognised, the sequence by which they occur and the specific factors that influence each step of the chain of events leading to stomach cancer are still poorly understood.

RISK FACTORS FOR GASTRIC CANCER AND PRECURSOR LESIONS

The decrease in mortality by gastric cancer was primarily attributed to an increase in fruit and vegetables consumption and a decrease in exposure to salty foods that accompanied the general improvement in the living conditions of the populations (37). The finding of *H. pylori* (38), classified as a human carcinogen in a ten-year time (39), brought a new paradigm to interpret gastric carcinogenesis and temporal/geographical variation in gastric cancer frequency.

H. pylori infection affects more than 50% of the world adult population, and approximately two thirds of all cases of stomach cancer are attributed to it (40), but a large proportion of the infected subjects will never develop cancer. Uemura et al. prospectively studied 1526 individuals and found that 2.9% of the *H. pylori*-infected subjects developed gastric cancer after a mean follow-up of 7.8 years (41). Stomach cancer is currently interpreted as the result of a variety of exposures or causes, with environmental factors (*H. pylori* infection and lifestyles), and genetic susceptibility contributing for its occurrence.

For instance, *H. pylori* infection tends to be more frequent in regions with high gastric cancer incidence and mortality, but African and many Asian countries present low gastric cancer rates and high *H. pylori* prevalence, which has been labelled as the African and Asian "enigma" (42, 43). Differences in the host response to infection (44), its genetic profile (45), environmental hazards and lifestyles (46), *H. pylori* virulence (47), or combined bacterial/host genotypic features have been proposed as possible explanations for the so-called enigmas.

Some studies support the hypothesis that the carcinogenic effect of *H. pylori* differs with the levels of other environmental exposures, and depends on the host's individual susceptibility, but the available evidence is still scarce and inconsistent. It has been suggested that the intake of fruit and vegetables may modify the association between *H. pylori* infection and gastric cancer occurrence (48, 49). In addition, the risk of *H. pylori*-associated gastric cancer is higher in smokers compared to non-smokers (50, 51). Despite the alcohol-related adverse effects in the gastrointestinal tract, the hypothesis of a causal role in gastric carcinogenesis has not been proven (52). However, it was suggested that tobacco and alcohol could have a synergistic effect on stomach cancer: while smoking plays a major role in initiation, alcohol promotes the development of adenocarcinoma, especially in the cardia (53). An interaction has also been observed between *H. pylori* infection and pro-inflammatory polymorphisms, since these have been associated with an increased risk of gastric cancer in *H. pylori*-infected individuals compared with non-infected (54, 55).

Gastric carcinogenesis depends on the influence of multiple factors and is also a multistage process. Therefore, the study of risk factors for surrogate endpoints may contribute to the understanding of the mechanisms that modulate the progression to cancer among *H. pylori*-infected subjects.

Studies specifically addressing the determinants of dysplasia are scarce, reflecting the low frequency of this precancerous lesion, and indicate that its occurrence is influenced by the same factors as gastric cancer (56-59).

Chronic atrophic gastritis is a relatively common gastric lesion (60) and can be assessed either by endoscopy

or pepsinogens measurement. Although biopsy by endoscopy is often considered the gold standard for diagnosis, intra and interobserver variation concerning the presence and the severity of the lesion is rather large (61-63), even when a criteria such as those defined by the Sydney system (64, 65) are available. The measurement of pepsinogen concentrations has the advantage of being a less invasive technique, but the use of different definitions and cut-points restricts the comparability of studies. Also, this method does not take into account the fact that atrophy is often associated with intestinal metaplasia (65).

Intestinal metaplasia is more strongly associated with gastric cancer than gastric atrophy, and much more frequent than dysplasia (41). Similarly to gastric cancer, intestinal metaplasia develops in a small proportion of subjects infected with *H. pylori* (41), and is likely to result from distinct adaptative responses to selection pressures from environmental and genetic factors.

The association between tobacco smoking and intestinal metaplasia has been widely studied, with most papers showing that smokers have an increased risk of intestinal metaplasia or progression to intestinal metaplasia (25, 56, 57, 66-71). The findings regarding the effect of alcoholic beverages consumption are inconclusive (56, 57, 66, 72). No evidence was found to support that salt intake induces intestinal metaplasia (56, 57, 68, 73-75), except from an increased risk with frequent eating of cured meat (71) and/or dried fish (72), surrogates for salt consumption. A protective effect for fruit, vegetables, or antioxidant nutrients intake was identified in a few studies (68, 71, 76-78), but no association was found in others (69, 72, 79).

H. pylori and host genetic characteristics have also been shown to increase the risk of intestinal metaplasia. *H. pylori* strains with the genotypes *cagA*$^+$, *vacA* s_1, *vacA* m_1 and *babA*$_2$ are considered high-virulent (29, 80-84), while polymorphisms in MUC1 mucin gene (85, 86) and in genes coding for pro-inflammatory cytokines (interleukin-1B and its receptor antagonist) (87-90) are responsible for an increased susceptibility towards the development of intestinal metaplasia.

CONCLUSIONS

The assessment of the joint contribution of individual genetic susceptibility, *H. pylori* characteristics, and exposure to environmental factors in the occurrence of precancerous lesions is a major field of research with potential to clarify the aetiology of gastric cancer, namely through the understanding of the mechanisms that modulate the progression to cancer among the *H. pylori*-infected.

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