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EDITORIAL

Genetic Variations and Gastric Cancer Risk

Alterações Genéticas e Risco de Cancro Gástrico

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Gastric cancer used to be the leading cause of cancer deaths in the world until the 1980 when it was overtaken by lung cancer.[1] Nowadays, stomach cancer is the second leading cause of cancer death in both sexes worldwide. In spite of worldwide global decrease, in 2020 (using computing models), the prevalence of gastric cancer is expected to rise in Portugal, for both sexes (Globocan). Most patients die during the first year after the diagnosis, even if submitted to costly and aggressive therapy.[2]

Intestinal type is more frequently observed in older patients and represents the end product of a cascade of events that begin with multifocal atrophic gastritis after exposure to environmental risk factors like *Helicobacter pylori* (*H. pylori*) infection. This is usually accompanied by intestinal metaplasia and leads to cancer via dysplasia.[3] This lengthy process, commonly known as Correa Cascade, is dependent on continued chronic inflammation.[4–6]

Unlike intestinal gastric cancer, the diffuse type typically develops following chronic inflammation without passing through the intermediate steps of glandular atrophy and intestinal metaplasia. So far, *H. pylori* gastritis is the only universal precursor condition for this subtype of gastric cancer.[7,8]

Significant advances toward the understanding of gastric carcinogenesis have been achieved since the identification of *H. pylori* by Marshall and Warren in 1984,[9] and its latter classification as a class I carcinogen by the International Agency for Research on Cancer. Colonization is usually asymptomatic and tumor progression only occurs in a subset of individuals and is dependent on the host response as well as genetic variation of the bacteria.[10]

An immensity of genes and genetic variations and its implications in gastric carcinogenesis has been addressed although its relevance is not always clear. In the last few years, the role of host genetic interleukin polymorphisms has been widely studied regarding premalignant lesions and as biomarkers for genetic susceptibility in gastric cancer development. The best characterized by population-association studies are those respecting the inflammatory response to *H. pylori* infection and the damage-induced inflammation of the gastric mucosa leading to mucosal atrophy and progression to gastric cancer, mainly IL-1β, IL1 Receptor Antagonist (IL-1RN), IL8IL10 and TNF-α. Genetic polymorphisms directly influence inter-individual variation in the magnitude of cytokine response and this clearly contributes to an individual's ultimate clinical outcome. Early studies by El-Omar showed an association of gastric cancer risk with the genotypes carrying IL-1β-511T, IL-1β-31T and IL-1RN*2/*2 with OR of 2.5, 2.6 and 3.7 for the homozygotes.[11] Studies on Portuguese population confirmed the relevance of some of the proinflammatory polymorphisms and genetic variations of *H. pylori*.[12–15] Following results were inconsistent because of variation of allele frequencies in different ethnic groups, tumor type and location, *H. pylori* infection, methodologies and quality of studies.[16,17]

The study of host genetics brought a better understanding of disease pathogenesis and helped in confirming two key-points: the important role of *H. pylori* infection in gastric carcinogenesis and the role of chronic inflammation with its long-term deleterious effects on gastric physiology. However, the heterogeneity of results at the present time makes it difficult to translate them into recommendations for daily clinical practice.

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In this issue of GE, Carvalho L et al describes the association between host cytokines polymorphisms and gastric cancer risk, namely IL-4 and IL-6.[18] It concludes that specific IL-4 and IL-6 polymorphisms are associated with GC risk either the Lauren's diffuse type and/or the intestinal type. Some limitations could be pointed such as the low number of patients and controls in the context of genetic association studies, the representativeness of population and the accuracy of the data. Nevertheless, new insights about the role of IL-6 and IL-4 expression variants and gastric inflammation/cancer risk in a Portuguese population are presented.

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