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## *Helicobacter pylori* and cytokine gene variants as predictors of premalignant gastric lesions

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### Abstract

Gastric cancer remains the third leading cause of mortality from cancer worldwide and carries a poor prognosis, due largely to late diagnosis. The importance of the interaction between *Helicobacter pylori* (*H. pylori*) infection, the main risk factor, and host-related genetic factors has been studied intensively in recent years. The genetic predisposition for non-hereditary gastric cancer is difficult to assess, as neither the real prevalence of premalignant gastric lesions in various populations nor the environmental risk factors for cancer progression are clearly defined. For non-cardiac intestinal-type cancer, identifying the factors that modulate the progression from inflammation toward cancer is crucial in order to develop preventive strategies. The role of cytokines and their gene variants has been questioned in regard to non-self-limiting *H. pylori* gastritis and its evolution to gastric atrophy and intestinal metaplasia; the literature now includes various and non-conclusive results on this topic. The influence of the majority of cytokine single nucleotide polymorphisms has been investigated for gastric cancer but not for preneoplastic gastric lesions. Among the investigated gene variants only IL10T-819C, IL-8-251, IL-18RAP917997, IL-22 rs1179251, IL1-B-511, IL1-B-3954, IL4R-398 and IL1RN were identified as predictors for premalignant gastric lesions risk. One of the most important limiting factors is the inhomogeneity of the studies (e.g., the lack of data on concomitant *H. pylori* infection, methods used to assess preneoplastic lesions, and source population). Testing the modifying effect of *H. pylori* infection upon the relationship between cytokine gene variants and premalignant gastric lesions, or even testing the interaction between *H. pylori*

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and cytokine gene variants in multivariable models adjusted for potential covariates, could increase generalizability of results.

**Key words:** *Helicobacter pylori*; Gastritis; Premalignant; Glandular atrophy; Intestinal metaplasia; Single-nuclear polymorphism; Gene variants; Interleukins

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**Core tip:** The role of cytokines and their gene variants has been questioned in relation to *Helicobacter pylori* (*H. pylori*) gastritis and gastric cancer but only infrequently for preneoplastic lesions. To date, only the single nucleotide polymorphisms IL-10T-819C, IL-8-251, IL-18RAP917997, IL-22 rs1179251, IL1-B-511, IL1-B-3954, IL4R-398 and IL1RN appear to be predictors for premalignant gastric lesion susceptibility. In order to develop preventative strategies, further studies using multivariable models to test the modifying effect of *H. pylori* infection on the relationship between cytokine gene variants and premalignant lesions or to test the interaction between *H. pylori* and cytokine gene variants should be considered.

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## INTRODUCTION

Gastric cancer (GC) remains the third leading cause of mortality from cancer worldwide<sup>[1]</sup>, having the fifth highest incidence among cancers, despite the progress made in understanding its physiopathology, early detection, and treatment. Intestinal-type GC, the most frequent type of GC, is considered nowadays a consequence of the histopathologic cascade initialised by longstanding *Helicobacter pylori* (*H. pylori*) infection and gastritis, glandular atrophy (GA), intestinal metaplasia (IM), dysplasia, and cancer<sup>[2]</sup>. In the vast majority of cases, gastric atrophy, defined as “loss of appropriate glandular units”, is the result of a nonselflimiting inflammatory status<sup>[3]</sup>. The development of metaplasia (*i.e.* the transformation of gland structure to resemble intestinal glands) is considered an “adaptive” process that occurs in response to various endogenous or exogenous aggressors (*e.g.*, pH changes, hormones, chemicals, and microbiota), while the progression of metaplasia to dysplasia may be viewed as an “oncogenic” phase<sup>[4,5]</sup>. The latest research results suggest that the risk for GC should be considered a consequence of the complex interplay between the aggressiveness of *H. pylori* strains, its genetic background, and host response, as well as the effect of various other environmental factors (*e.g.*, diet habits, smoking, *etc.*)<sup>[6]</sup>.

The poor prognosis of GC and recent advances in the assessment of genetic predisposition emphasize the importance of early diagnosis and the possible role of biomarkers in the surveillance of at-risk individuals<sup>[7]</sup>. *H. pylori*-associated inflammation is considered the most important trigger of the cascade, and one of the suggested pathways of progression to GC is represented by the variability of the host inflammatory response against different strains of *H. pylori*<sup>[8]</sup>. Even though GC is a heterogeneous molecular disease, a growing body of evidence supports the influence of cytokine gene variants on the progression of *H. pylori* infection toward premalignant lesions<sup>[9]</sup>.

The objective of the present review was to synthesize the current knowledge of the relationship between certain single nucleotide polymorphisms (SNPs) of cytokines and premalignant gastric lesion susceptibility by reviewing the relevant studies published between 2005-2018.

## EPIDEMIOLOGY OF PRENEOPLASTIC LESIONS AND GC RISK

It is accepted today that both host and *H. pylori* genetics influence susceptibility to the development of chronic inflammation and to molecular and cellular events related to carcinogenesis, but they depend strongly on context<sup>[10]</sup>. In a recent meta-analysis, the pooled frequency of GC was 17.4% (95%CI: 16.4–18.5) in an *H. pylori*-infected population but varied markedly across countries; the highest rate of GC was observed in Asian *H. pylori*-infected individuals<sup>[11]</sup>. The differences between the prevalence of infection and the burden of GC in an African population, for example, are attributable to genetic modulation of the host response against infection, non-*H. pylori* gastric microbiota, possibly to a lack of *cag A* pathogenicity, or simply to inadequate samples or differences in life expectancy<sup>[6,12]</sup>.

The prevalence of GA and IM worldwide is largely unknown<sup>[13]</sup>. In Western populations, a 7% prevalence of IM has been found in patients who underwent upper endoscopy in the United States<sup>[14]</sup>. In comparison, in a Romanian population of 300 consecutive patients investigated by endoscopy, the frequency of GA ± IM was 18.5%<sup>[15]</sup>, comparable to a similar series of a Turkish endoscopic population (13.8%)<sup>[16]</sup>. Nevertheless, in a Japanese population for which endoscopy was performed for a health check-up, the frequency of GA was 29%, while GA + IM was 16.9%<sup>[17]</sup>. In certain subgroups of patients in whom endoscopy was performed for symptoms or anaemia, the frequency of premalignant gastric lesions increased to 32% among patients with previous gastric surgery for peptic ulcer<sup>[18]</sup>, or 44% in consecutive patients treated with aspirin and proton pump inhibitors (PPIs) referred for digestive symptoms or anaemia<sup>[19]</sup>.

Long-term follow-up observational studies in Western populations have demonstrated an increasing risk for GC based on progression on the Correa cascade; the standardised incidence ratios with gastritis at baseline are 1.8 (1.7 to 1.9), 2.8 (2.3 to 3.3) for GA and 3.4 (2.7 to 4.2) for IM<sup>[20]</sup>. A recent meta-analysis calculated an odds ratio (OR) of 3.58 (95%CI: 2.71–4.73, in 4,535 GC patients from among 402,636 participants) for the risk of GC in patients with IM, without data about the follow-up time<sup>[21]</sup>; yet, another failed to calculate a pooled OR due to the high heterogeneity of the studies<sup>[22]</sup>. Based on a Swedish population cohort study, even familial GA, IM, and dysplasia in first-degree relatives are associated with an increased risk for non-cardia GC<sup>[23]</sup>, emphasizing the role of genetic predisposition. Despite the proven role of *H. pylori* eradication in decreasing the risk of cancer, certain histologic features, such as severe atrophy, IM in the gastric corpus, or treatment with PPI can still predispose to cancer development<sup>[24]</sup>.

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## H. PYLORI GASTRITIS – PATHOLOGICAL ASSESSMENT CHALLENGE

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In the first stage of *H. pylori* infection, active chronic inflammation with gastric gland preservation (non-atrophic gastritis) develops, which can lead to multifocal atrophic gastritis and IM<sup>[25,26]</sup>.

Histologically, non-atrophic gastritis is characterized by the infiltration of lamina propria with chronic inflammatory cells (*e.g.*, lymphocytes and plasma cells) and acute inflammatory cells (*e.g.*, polymorphonuclear neutrophils). A marked acute inflammation can progress in the glandular epithelium, leading to the formation of microabscesses, whereas a marked chronic inflammation in the lamina propria can be accompanied by lymphoid aggregates with germinal centres<sup>[27,28]</sup>. In this stage, changes may be reduced by *H. pylori* eradication, however, longstanding chronic inflammation promotes the inhibition of gastric acid secretion *via* proinflammatory cytokines, ultimately influencing lesion progression<sup>[29]</sup>.

Early *H. pylori* gastritis is typically antrum-predominant, with minimal involvement of the oxyntic mucosa. In some individuals, prolonged infection with *H. pylori* determines the extension of inflammation towards the gastric body. Hypochlorhydria, induced by the reduction of acid-producing mucosa, which can be exaggerated with use of PPI, and the progression of the disease from the antral mucosa promotes the proximal migration of the bacteria, facilitating the development of corpus gastritis<sup>[30]</sup>. In this stage, the determination of *H. pylori* infection and the assessment of extending lesions are highly dependent on the site, number and size of gastric biopsies<sup>[31,32]</sup>.

The staining used to visualize the bacteria as well as the pathologist's experience to reduce false-positive or false-negative interpretations are also very important. Histochemical non-silver-based stains (*e.g.*, Giemsa stain or Diff-Quik) are less expensive but have a blue background that makes it difficult to detect the bacteria. Silver-based stains (*e.g.*, El-Zimaty dual stain or triple stain, Leung stain) are more sensitive, with the bacteria appearing larger, and provide a visible contrast with the

background while having the additional benefits of intermediate cost and short technical time (9–10 min). Silver-based stains also make it easier to identify low numbers of bacteria, this being particularly useful in patients on PPI in whom bacteria are smaller<sup>[33,34]</sup>. Immunohistochemistry represents the gold standard to confirm the presence of *H. pylori*, reducing the false-positive rate and being more specific and more sensitive than the silver-based stains<sup>[35,36]</sup>. Both polyclonal and monoclonal antibodies are available, and an immunohistochemical staining can be performed using an autostainer with a shorter technical time and less technical errors. The coccoid shapes of the bacteria are also coloured and identified by this method, but there are still cases interpreted as false-negative, especially when the number of bacteria is very low.

## GASTRIC ATROPHY, IM – HISTOLOGY DIAGNOSIS CHALLENGE

Although it is the most important parameter in the progression to carcinoma, GA is the most difficult stage to recognize during a routine microscopic examination<sup>[37–39]</sup>. GA, characterized by destruction of the atrophied glands and replacement with fibrous tissue (non-metaplastic atrophy) or a different type of epithelium (metaplastic atrophy), is considered the first step in the cascade of intestinal-type carcinoma<sup>[30,40]</sup>. A special category is represented by atrophic lesions localized exclusively in the corporeal region. These cases are considered autoimmune metaplastic atrophic gastritis associated with pernicious anaemia, having an increased risk of developing GC<sup>[41]</sup>.

Several forms of metaplasia are described in the gastric mucosa, two of them with implications in the pathogenesis of GC: Pseudopyloric metaplasia and IM, classified as complete or incomplete<sup>[28]</sup>. Pseudopyloric metaplasia, also called spasmolytic polypeptide-expressing metaplasia, is characterized by TFF1 and TFF2 spasmolytic polypeptide expression and it is considered another pathway for the development of gastric carcinoma<sup>[28,38,42]</sup>.

Differential diagnosis between an oxyntic mucosa with pseudopyloric metaplasia of an antral mucosa or mucosa from the transitional area can be a diagnostic challenge, especially if the exact location of the biopsy is not known. This may be facilitated by certain particularities, some identifiable both on haematoxylin-eosin colouring and immunohistochemistry<sup>[43–45]</sup>.

Histologically, the presence of sialomucin-secreting goblet cells, absorptive cells, and Paneth cells on the foveolar or glandular epithelium is defined as complete IM or small intestinal-type I metaplasia. Incomplete IM, also called enterocolic (or type IIA/II) and colonic (or type IIB/III), is defined by the presence of neutral/acid sialomucin-secreting goblet cells in type II as well as sulfomucin-secreting goblet cells in addition to columnar non-absorptive cells<sup>[25,26]</sup>. The presence of IM type III increases the risk of GC development six times compared to that for lesion-free individuals<sup>[46]</sup>. Differentiation is facilitated by histochemical stains, such as periodic acid Schiff, alcian blue, and high iron diamine.

To assess the presence of metaplasia, besides the usual histochemical methods, immunohistochemical determinations are also used. MUC1 and MUC5AC are expressed in the superficial epithelium, and MUC6 is specific for the deep part of the antral glands but is also expressed in the mucous neck cells of the oxyntic glands. MUC2 is an intestinal epithelium-specific mucin, expressed in both columnar and goblet cells of the metaplastic epithelium<sup>[47,48]</sup>. Thus, in IM there is a decrease in MUC1, MUC5AC and MUC6 immunoeexpression, with *de novo* expression of MUC2<sup>[49,50]</sup>. Unique and multivariate immunohistochemical studies have identified MUC6 as an important marker for the malignant transformation of IM. This is positive in areas with high-grade dysplasia and intramucosal GC, and frequently associated with genetic alterations, especially microsatellite instability<sup>[51,52]</sup>.

Runt-related transcription factor 3 (known as RUNX3) is a member of the RUNX family and plays an important role in normal developmental processes as well as in the suppression of cell proliferation by tumour suppressor activity. On immunohistochemistry, RUNX3 expression is diminished or even absent in IM and GC due to the hypermethylation of CpG islands<sup>[51,52]</sup>.

A marker used in the staging of IM and the diagnosis of GC is TFF1. This trefoil peptide is a key protein in the defence and regeneration of gastric mucosa after certain conditions<sup>[51]</sup>. It is co-expressed with MUC5AC in foveolar cells in the gastric mucosa and similarly expressed in GC, suggesting that decreased co-expression would play an important role in gastric carcinogenesis<sup>[53,54]</sup>.

The caudal-related homeobox transcription factor (known as CDX2, and re-

presenting the suppressive gene involved in the development of colorectal cancer), has been studied in various types of GC and preneoplastic gastric lesions, being normally expressed by intestinal epithelial cells<sup>[55]</sup>. Under normal conditions, it is predominantly found in the small and large intestine and is missing in the gastric mucosa. Some studies have suggested that CDX2 immunoreexpression decreases progressively with IM and dysplasia<sup>[55]</sup> and can be considered a prognostic factor in intestinal-type GC<sup>[50]</sup>.

The chronic inflammatory changes in gastric mucosa related to *H. pylori* infection through the various and complex molecular events, including production of inflammatory mediators, create a “tumour microenvironment” that is thought to play an important role in lesion progression<sup>[56,57]</sup>. The studies questioning the potential effect of eradication therapies on regression of IM have generated discordant results, but it is accepted today that eradication does not prevent lesion progression in all patients, particularly in those with severe IM involving the corpus<sup>[58]</sup>.

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## STAGING SYSTEMS

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With the overwhelming frequency of *H. pylori* infection and related conditions in some populations<sup>[12]</sup>, the importance of clinicopathological individual risk assessment for cancer is crucial. The gold standard for assessing the severity and distribution of any predisposing and premalignant gastric lesions is high-definition endoscopy with chromoendoscopy, which can guide biopsies for staging atrophic and metaplastic changes<sup>[46]</sup>. The guidelines recommend the use of the grading and staging systems of Operative Link for Gastritis Assessment (commonly referred to as OLGA) and Operative Link on Gastric Intestinal Metaplasia Assessment (commonly referred to as OLGIM), based on a standardized protocol of gastric biopsy sampling. Although recommended, the protocols are difficult and laborious to use and their contribution in improving the prognosis of patients with GC in real life should be assessed further<sup>[37,58]</sup>.

Extension of GA into the corpus mucosa and increased intragastric pH seem to influence the efficacy of eradication therapy regimens; therefore, clinicians should be aware of these aspects when eradication therapy is offered to patients with severe scores, alongside timing of the histological follow-up<sup>[58]</sup>. The persistence of *H. pylori* infection and the severity of gastritis is influenced by the host inflammatory response, which itself is modulated by the host’s cytokine gene polymorphisms<sup>[9]</sup>. Current evidence support that the types and amounts of cytokines made in response to *H. pylori* infection have a significant impact on the risk of developing gastric cancer<sup>[59,60]</sup>, but there are not published researches correlating the level of cytokine with OLGA/OLGIM score. The studies of cytokine SNPs in premalignant gastric lesion susceptibility have revealed different results in various populations, with no clear adjustment for the concomitant and/or persistent *H. pylori* infection, which could, alongside with race and other environmental factors, explain the different findings.

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## ROLE OF CYTOKINES AND THEIR SNPs IN *H. PYLORI*-RELATED CONDITIONS

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Persistent infection with *H. pylori* is one of the triggers of chronic inflammation<sup>[61]</sup>. Inflammation is a key component of the tumour’s microenvironment, and it is considered to represent the seventh hallmark of cancer<sup>[62]</sup>. Extensive studies have unravelled the processes by which chronic inflammation predisposes to various types of cancer<sup>[63,64]</sup> and determined that the state is responsible for approximately 25% of cancer cases<sup>[65]</sup>. Chronic inflammation is associated with the generation and release of various mediators, including proinflammatory and oncogenic ones. During inflammation, the released mediators that may predispose to tumorigenesis are reactive nitrogen oxygen species, inflammatory cytokines [*i.e.* interleukins (ILs), tumour necrosis factor-alpha (TNF- $\alpha$ ), interferon (IFN), *etc.*], growth factors, and chemokines<sup>[64]</sup>.

An important role in inflammatory response regulation is attributed to the cytokines. Cytokines are classified into two groups: Proinflammatory (IL-1 $\beta$ , IL-1 $\alpha$ , IL-6, IL-8, IL-12, IL-17, IL-18, TNF- $\alpha$ , IFN- $\gamma$ , *etc.*)<sup>[66]</sup> and anti-inflammatory (IL-4, IL-10, IL-13, *etc.*). Some of the cytokines have a dual role (*e.g.*, IL-10, IL-22, and TGF- $\beta$ 1)<sup>[67]</sup>. Anti- and proinflammatory cytokines are involved in various cellular events, such as the induction of expression of other cytokines, proliferation and differentiation of cells, adhesion, angiogenesis, necrosis, and apoptosis, all these processes being influenced by the presence of *H. pylori* infection<sup>[8,68]</sup>. The inflammation induced by *H.*

*pylori* infection leads to an increased gastric endothelial cell turnover and the deregulation of this inflammation, especially when it is associated with more virulent strains of *H. pylori*<sup>[8]</sup>.

Genetic polymorphisms, such as SNPs, has been described in cytokine genes, and certain alleles of those genes are responsible for variations in cytokine expression and plasma levels, and may influence immune response, being therefore associated with susceptibility to cancer<sup>[69,70]</sup>. Furthermore, it was considered that cytokine SNPs may play important roles in *H. pylori* pathogenicity<sup>[71]</sup>. According to El-Omar *et al*<sup>[72]</sup> and Figueiredo *et al*<sup>[71]</sup>, host genetic factors that influence cytokine SNPs may establish why certain subjects infected with *H. pylori* develop gastric malignancies while others do not. Therefore, cytokine SNPs are thought to be linked to individual susceptibility to *H. pylori* infection and to the development of GC. Indeed, SNPs of ILs and their receptors have been found to influence chronic inflammation and the risk of cancer lesions<sup>[73]</sup>.

*H. pylori* also stimulates the production of various ILs (IL-1 $\beta$ , IL-2, IL-10, IL-12), IFN and TNF in the gastric immune response<sup>[8]</sup>. The IL factors IL-4 and IL-6, in particular, are involved in inflammation processes and are considered to be responsible for inflammatory cascade activation<sup>[74]</sup>.

### TNF- $\alpha$

TNF- $\alpha$  levels may be influenced by SNPs. Most of the studied TNF- $\alpha$  SNPs are located in the promoter region of the TNF- $\alpha$  gene, those being -308G>A (rs1800629), -238G>A (rs361525), and -376G>A (rs1800750). In a study performed on a Slovenian population, the presence of the variant genotype of TNF $\alpha$  -308G>A was not associated with the risk of developing intestinal adenocarcinoma and atrophic gastritis<sup>[75]</sup>. In a German study performed on 534 older adults with chronic atrophic gastritis and 534 adult controls with non-chronic atrophic gastritis, the variant genotype of TNF $\alpha$  -308G>A was not associated with an increased risk of chronic atrophic gastritis (OR = 1.02, 95% CI: 0.77-1.34)<sup>[76]</sup>. In a meta-analysis of seven studies performed by Peleteira *et al*<sup>[77]</sup>, the TNF $\alpha$  -308 genotypes were not associated with premalignant gastric lesions (AA vs GG: OR = 0.93, 95% CI: 0.35-2.43;  $I^2$  = 0.0%). In a study using classification by country, Zhao *et al*<sup>[78]</sup> identified an association between the TNF- $\alpha$  gene 308G>A SNP and the risk to developing GC in a Chinese population (in the case of heterozygous AG genotype: OR = 1.57, 95% CI: 1.24-1.99,  $P_{\text{heterogeneity}}$  = 0.133,  $P$  = 0.000, and in the case of variant AA + AG genotype: OR = 1.61, 95% CI = 1.27-2.03,  $P_{\text{heterogeneity}}$  = 0.104,  $P$  = 0.000)<sup>[78]</sup>.

### IL-1

IL-1, a proinflammatory cytokine inhibiting the secretion of gastric acid, supports an increase in the colonization of *H. pylori* which leads to a more severe gastritis<sup>[79]</sup>, being involved in the subsequent tumorigenesis and tumour progression<sup>[80,81]</sup>. IL-1 comprises three related genes, namely IL-1A, IL-1B, and IL-1RN, which encode the IL-1 $\alpha$ , IL-1 $\beta$ , and IL-1 receptor antagonist (IL-1ra). IL-1ra (an anti-inflammatory cytokine) binds to the corresponding receptor for IL-1 and controls its action. IL1 $\beta$  is involved in initiating and amplifying the inflammation that manifests as a response to the *H. pylori* infection, decreasing the secretion of gastric acid<sup>[72]</sup>. Regarding IL-1ra, it binds to the IL-1 $\beta$  receptors; therefore, it may influence the effects of IL-1 $\beta$ <sup>[82]</sup>.

The most studied SNPs for the IL1B gene in GC are -511C>T, -31T>C, and +3954C>T. In 2000, the association between IL-1B -511C>T and IL-1B -31T>C polymorphisms and the risk of developing GC was investigated by El-Omar *et al*<sup>[72]</sup>, who reported that the *IL-1* gene polymorphisms are associated with a high risk of both hypochlorhydria produced by *H. pylori* and GC. For the IL1B -511 (TT vs CC) gene polymorphism, a meta-analysis of 13 studies did not find an association with premalignant gastric lesions (OR = 1.34, 95% CI: 0.87-2.07,  $I^2$  = 65.7%), even though the Peruvian study by Gehmert *et al*<sup>[83]</sup> found an increased risk for atrophic gastritis (OR = 5.60, 95% CI: > 2.02-15.51.6) associated with the IL-1B-511 C allele.

For the IL-1RN gene, an 86-bp variable number of tandem repeats was described at the 2nd intron, and it was presumed that it may increase the risk of GC. In the meta-analysis by Peleteira *et al*<sup>[77]</sup>, the *IL1RN*\*22 genotype was associated with an increased risk of gastric precancerous lesions (22 vs LL: OR = 2.27, 95% CI: 1.40-3.70;  $I^2$  = 26.4%) when results from 12 studies were combined.

In two studies by Chiurillo *et al*<sup>[84,85]</sup>, an association was found between GA and IL-1B -511\*T, -31\*C, +3954\*C and *IL-1RN*\*2 polymorphisms but only in the presence of *H. pylori*-cag strains. Caleman *et al*<sup>[86]</sup> suggested that the TT genotype of IL-1B -31T>C represents a protective factor against infection with *H. pylori* in the Brazilian population investigated. Regarding the IL-1B 3954C>T SNP, a positive association was found between the mentioned polymorphism and susceptibility for IM in a population from Costa Rica<sup>[87]</sup>. Similarly, no association between the IL-1B 3954C>T

SNP and the risk of gastric lesions was found in Asians or Caucasians<sup>[88]</sup>.

### IL-2

IL-2 is an immunoregulatory cytokine produced by T cells, which induces the proliferation and differentiation of natural killer cells and stimulates the production of natural killer-derived cytokines, such as TNF- $\alpha$  and IFN- $\gamma$ <sup>[89,90]</sup>. A recent study showed that IL-2 polymorphisms, such as the presence of variant GG genotype for IL-2 -330T>G (rs2069762), are associated with an increased risk of GC among Brazilian patients with *H. pylori* infection (OR = 6.43, 95%CI: 1.47–28.10,  $P = 0.044$ )<sup>[89]</sup>. Similar findings were noticed for the IL-2 +114T>G (rs2069763) SNP<sup>[89]</sup>. Contrariwise, Shin *et al.*<sup>[90]</sup> showed that there was no relation between IL-2 SNPs and gastric ulcers, duodenal ulcers, and GC in cases from South Korea. Haplotype analysis of IL-2 -330T>G and IL-2 114T>G revealed that presence of the IL-2 -330G/ +114T haplotype was significantly associated ( $P = 0.012$ ) with a high risk of developing GC<sup>[89]</sup>.

A meta-analysis that included 3,060 patients and 3,435 controls indicated that the GG genotype of the IL-2 -330T>G SNP was significantly associated with cancer risk in Asians (OR = 2.03, 95%CI: 1.40–2.95)<sup>[91]</sup>. When Zhao *et al.*<sup>[91]</sup> then stratified the analysis by cancer types, they found no association of IL-2 -330T>G SNP with GC. In contrast, Liu *et al.*<sup>[92]</sup> reported no association between IL-2 -330T>G and IL-2 114T>G and GC risk.

### IL-4

IL-4 is an important immunomodulatory cytokine that plays a major role in regulating the differentiation and activation of lymphocytes. In addition, IL-4 inhibits the secretion of proinflammatory cytokines to promote tumour cells, affecting IL-1, IL-6 and TNF- $\alpha$  in particular<sup>[93]</sup>. The IL-4 -590T (OR = 2.2, 95%CI: 1.1–4.4,  $P = 0.04$ ) and IL-4 -33T (OR = 3.9, 95%CI: 1.7–8.9,  $P = 0.001$ ) variant alleles were found to be more frequent among intestinal-type GC cases and to be associated with intestinal-type GC occurrence. A higher prevalence of IL-4 -590TT (OR = 6.7, 95%CI: 1.4–32.4,  $P = 0.01$ ) and IL-4 -33TT (OR = 2.2, 95%CI: 1.7–2.8,  $P = 0.002$ ) genotypes was found in intestinal-type GC patients<sup>[94]</sup>. Another study performed on 308 GC patients and 308 controls from South-Western China found the variant genotype of IL-4 590 C>T (rs2243250) to not be associated with overall GC risk (OR = 0.89, 95%CI: 0.61–1.28 for CT or CC *vs* TT)<sup>[95]</sup>.

A small increase in susceptibility for GA was found in a Venezuelan study of 2033 subjects from a region with high prevalence of *H. pylori* infection conducted by Kato *et al.*<sup>[96]</sup>, specifically for the homozygous allele (GG) of the 398 A/G polymorphism in the IL-4R gene

### IL-6

A previous study showed that IL-6 and IL-8 appear early during the inflammation process. IL-6 is a multifunctional cytokine that functions both as an endocrine regulator and as an inflammatory mediator. Moreover, IL-6 has a substantial role in host defence mechanisms, serving as a messenger between the innate and adaptive systems<sup>[97]</sup>. Some studies observed that presence of the IL6 -174G allele is associated with a higher production of IL-6<sup>[98]</sup> compared to that detected in individuals with the CC genotype. Another study revealed higher levels of IL-6 in the gastric mucosa in *H. pylori*-positive patients compared to *H. pylori*-negative cases<sup>[99]</sup>.

Recently, it was reported that the IL6 -174C allele (OR = 2.7, 95%CI: 1.5–4.8,  $P = 0.0006$ ) and IL-6 -174CC genotype (OR = 3.8, 95%CI: 1.7–8.7,  $P = 0.002$ ) showed higher prevalence in diffuse-type GC, while the IL-6 -174CG genotype showed a higher prevalence (95%CI: 2.7–20.3, OR = 7.3) in a series of Portuguese intestinal-type GC cases<sup>[94]</sup>. The most recent published meta-analysis found that genetic polymorphisms of the IL-6 promoter are not associated with increased risk for GC, despite their role in susceptibility or prognosis of other cancers (*e.g.*, breast, lung, *etc.*)<sup>[100]</sup>. Other studies have reported that there is no association between the IL-6 SNPs and gastritis or *H. pylori* infection, but an association was observed between the IL-6 -174CG genotype and adenocarcinoma, regardless of the histological type of the tumour in a study from northern Brazil<sup>[101]</sup>.

### IL-8

IL-8 is considered to be one of the most important cytokines associated with both the immune response and the inflammatory process against *H. pylori*; indeed, increased IL-8 expression has been detected in patients with *H. pylori* infection and gastric disorders<sup>[8]</sup>. In a Japanese study, the IL-8 -251 A/A genotype, which is associated with higher expression of the IL-8 protein, found an increased susceptibility for neutrophil infiltration in gastric mucosa and for GA (OR = 2.35, 95%CI: 1.12–4.94) compared with the T/T genotype<sup>[102]</sup>. A high risk of developing severe chronic GA

was found in Chinese cases with the IL-8 rs4073 AA homozygous genotype (OR = 2.62, 95%CI: 1.23–5.72) or for A allele carriers (OR = 1.81, 95%CI: 1.06–3.09). Similarly, an increased risk of IM was found in patients with heterozygous AT for the IL-8 rs4073 genotype (OR = 2.27, 95%CI: 1.25–4.14) or A allele carriers (OR = 2.07, 95%CI: 1.16–3.69)<sup>[103]</sup>. The same study reported an interaction between A allele carriers for IL-8 rs4073 and *H. pylori* infection and the risk to develop severe chronic atrophic gastritis (OR = 6.70, 95%CI: 1.29–9.78)<sup>[103]</sup>.

In a Korean study-population, a significant positive association was found between the IL8 -251T>A polymorphism and risk of GC (OR = 1.70, 95%CI: 1.11–2.60,  $P = 0.0155$ ) and severe GA (OR = 2.03, 95%CI: 1.05–3.90,  $P = 0.035$ )<sup>[104]</sup>. The IL-8 -251T>A SNP was found to be associated with increased IL-8 production ( $P = 0.0229$ )<sup>[104]</sup> and the IL-8 -251 T>A variant genotype (AA or TA) was found to be associated with an increased risk for non-cardia GC (adjusted OR = 2.58, 95%CI: 1.19–5.57)<sup>[95]</sup>. IL-8 -251T>A leads to an increased IL-8 production, which is more pronounced in intestinal-type GC as the result of the changes in gastric mucosa over several years<sup>[105]</sup>. By multivariate analysis, it was revealed that patients carrying the AA genotype of the IL-8 -251T>A SNP had a 2-fold increased risk for GC (OR = 2.02, 95%CI: 1.27–3.21) compared with those carrying the wild-type genotype<sup>[105]</sup>. Another study that included Caucasians from European countries showed that presence of the IL-8 -251A allele was associated with a significantly decreased risk of non-cardia GC (OR = 0.57, 95%CI: 0.37–0.87,  $P = 0.01$ ) in *H. pylori* cases<sup>[100]</sup>. Wang *et al*<sup>[73]</sup> observed no significant correlation between IL-8 rs4073 and the risk of GC or chronic atrophic gastritis, IM and dysplasia in a high-risk Chinese population.

### IL-10

IL-10 is an anti-inflammatory cytokine that plays an important role in the inflammatory response, inhibiting the synthesis of proinflammatory cytokines such as IL-1 $\beta$ , IL-6, IL-12, and TNF- $\alpha$ , and down-regulating inflammation<sup>[64,76]</sup>; it is also considered to be involved in the immune response to *H. pylori* infection<sup>[76]</sup>. IL-10 may influence both the susceptibility and development of cancer due to its immunosuppressive (tumour inhibition) and immunostimulating (tumour promotion) functions. Recently, the role of IL-10 -1082A>G, -819C>T, and -592A>C SNPs in susceptibility to GC were investigated in a Chinese population<sup>[106]</sup>. The authors reported that the CC genotype of the IL-10 -819C>T (rs1800871) SNP was associated with a decreased risk of atrophic gastritis and GC compared with the TT genotype. The CC genotype carriers demonstrated a significantly increased risk of atrophic gastritis compared with healthy subjects (OR = 1.79, 95%CI: 1.02–3.13,  $P = 0.043$ ). The same study revealed no significant relationship between IL-10 -1082A>G and -592A>C polymorphisms and the risks of atrophic gastritis and GC. Furthermore, no interaction was found between IL-10 and *H. pylori*<sup>[106]</sup>.

In contrast, significant associations were observed between IL-10 -1082A>G<sup>[105]</sup>, IL-10 -592A>C<sup>[107]</sup> and GC risk only in cases with *H. pylori* infection. An elevated risk of GC has been identified in patients who carried the variant genotype of these SNPs and had *H. pylori* infection, indicating a synergistic effect for the combination of host genotype and the infection<sup>[105,107]</sup>. Ramis *et al*<sup>[108]</sup> demonstrated that, among Brazilian patients the IL-10 -819C/T genotype was not associated with either *H. pylori* infection or gastric carcinoma risk. In an Irish population study, carriage of the variant alleles IL-10-592, -819, and -1082 were not associated with IM or gastritis<sup>[109]</sup>. In a large epidemiological study, a significant association was found between the CC genotype of the IL-10 -819C>T (rs1800871) SNP and the risk of chronic atrophic gastritis among older adults from Germany (OR = 1.67, 95%CI: 1.01–2.76)<sup>[76]</sup>.

### IL-18

IL-18, a proinflammatory cytokine, plays an important role in chronic inflammation and is linked with tumorigenesis. Myung *et al*<sup>[110]</sup> investigated the association of IL-18 SNPs rs187238 (-137G>C), rs360718 (113T>G), and rs360717 (127C>T) with the susceptibility to *H. pylori* infection in a Korean population and the findings suggested that they each play a role in *H. pylori*-associated diseases. Leung *et al*<sup>[111]</sup> showed that IL-18607C>A and IL-18 137G>C were not associated with an increased risk of gastric IM in individuals from the Shandong Province of China. The homozygous AA genotype of IL-18RA rs917997 (IL-18 receptor accessory protein) may contribute to individual susceptibility to GC (OR = 1.83, 95%CI: 1.14–2.92) or precancerous lesions such as chronic atrophic gastritis (OR = 1.55, 95%CI: 1.07–2.24) in individuals from the Linqu County of China<sup>[73]</sup>.

IL-18 is also involved in cell-mediated immunity. Signalling of IL-18 requires an IL-1R-related protein (subunit of the receptor for IL18), encoded by IL-18RAP<sup>[73]</sup>. This protein enhances the IL-18-binding activity of the IL-18 receptor and plays a role in IL-18 signalling. Further, IL-18RAP has been shown to play an important role in the

IL-18 signalling pathway *via* production of IFN- $\gamma$ <sup>[112]</sup>.

### IL-22

IL-22 is a member of the IL-10 cytokine family<sup>[113]</sup>, its expression being reported in the gastric tissues of *H. pylori*-infected patients and GC patients<sup>[114]</sup>. In a study by Wang *et al.*<sup>[17]</sup>, elevated risks of atrophic gastritis (OR = 2.64, 95%CI: 1.89–3.69), IM (OR = 5.58, 95%CI: 3.86–8.05), and dysplasia (OR = 1.64, 95%CI: 1.18–2.26) were observed in Chinese subjects who carried the IL-22 rs1179251 CC genotype.

### IL-32

IL-32 is a cytokine involved in inflammation and cancer development, being induced mainly by pathogens and proinflammatory cytokines and more prominent in immune cells than in non-immune tissues<sup>[115]</sup>. In Chinese subjects, the risk for predisposing lesions for GC was elevated in those with the IL-32 rs2015620 A allele (AA+AT) or the IL-22 rs1179251 CC genotype and *H. pylori* infection, and significant interactions between these two SNPs and *H. pylori* infection were found<sup>[17]</sup>.

### IFN- $\gamma$

IFN- $\gamma$  is one of the main products of Th1-specific proinflammatory cytokines and exerts several effects on host defence and immune regulation through its antiviral, antimicrobial and antitumour activities. IFN- $\gamma$  can inhibit angiogenesis and exert direct antiproliferative and antimetabolic effects on a wide variety of tumour cells. In a study that included 1,339 subjects from the North of Portugal, it has been demonstrated that people under 40 years of age and who were TT homozygotes for IFN- $\gamma$ R1 -56C>T had a 4-fold increased risk for developing early-onset GC (OR = 4.1, 95%CI: 1.6–10.6)<sup>[116]</sup>.

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## RELEVANCE OF STUDIES QUESTIONING CYTOKINE GENE VARIANTS AND PREMALIGNANT GASTRIC LESIONS

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Extensive studies have aimed to correlate individual variations in inflammatory response with GC, but none with premalignant lesions. This is largely due to the inhomogeneity in study designs but is mostly due to the differences and the difficulties regarding the histological assessment of premalignant lesions and *H. pylori* infection<sup>[36]</sup>. To evaluate cytokine gene variants as univariate or multivariate predictors for premalignant gastric risk, we reviewed the mentioned scientific papers in an analytical scheme. We synthesized the sources of the data, the studied populations in whom clinical objectives were tested, the main outcomes, the potential confounding factors or other important covariates, the statistical control for bias, and the statistical methods used (Table 1).

In Table 2, we present the frequencies of the variant genotypes of the studied SNPs, along with the significance of the results obtained in Table 1. For every listed SNP of the cytokines, an association with GC was found in a specific population; whilst for premalignant gastric lesions, less association was detected. From among all the gene variants discussed above, only IL10T-819C, IL-8-251, IL-18RAP917997, IL-22 rs1179251, IL1-B-511, IL1-B-3954, IL4R-398 and IL1RN were predictors with age- and sex-adjustment for risk of premalignant gastric lesions. The different worldwide prevalence rates of infection and the risk of false-positive or false-negative results depends on the diagnostic method used (histological, serological, coproantigen or urea breath test)<sup>[12,36]</sup>.

One of the most important limiting factors in the studies' homogeneity is the lack of diagnosis of concomitant *H. pylori* infection. The most recent research, like that of Wang *et al.*<sup>[73]</sup> and Liu *et al.*<sup>[106]</sup>, has tested the effect of certain cytokine gene variants on the risk of premalignant gastric lesions, controlling for the presence of *H. pylori* infection; a significant association was found but only for specific populations. Logistic models with interaction terms should be considered for testing the effect of cytokine variant genes on the risk of premalignant gastric lesions modified by *H. pylori* infection. The Synergy Factor could be used to measure binary interaction between cytokine genetic variants and *H. pylori* infection.

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## OTHER

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Gastric cytokines are involved in the molecular events leading to proliferation, survival, angiogenesis, invasion, and metastasis of gastric tumour cells<sup>[117]</sup>. Except for cytokine gene variants, other molecular mechanisms have been questioned for

**Table 1** Statistical methods used in mentioned original research articles that analysed the relationship between cytokine gene variants and premalignant gastric lesions

Ref.	Target population (sample size)	Cytokine SNPs <sup>1</sup>	Outcomes	Confounding factors/other covariates	Control for confounding/covariate effect	Statistical methods
[73]	Chinese adult patients (1330)	IL-8-4073, IL-18RAP917997, IL-1Brs1143627, IL-1Brs1143634, IL-1Brs16944, IL-4Rrs2057768, IL-10rs1800896, IL-22rs1179251, IL-32rs2015620	ChAG risk IM risk DYS risk GC risk	Age, sex, smoking status, <i>H. pylori</i>	Stratification, adjustment	$\chi^2$ test, multivariable logistic model with interaction term, Synergy index
[75]	Slovenian adults (318)	TNF- $\alpha$ -308, IL-1RN, IL-1B -511	ChAG risk GC risk	Gender	Adjustment	$\chi^2$ test, Multivariable logistic model
[76]	German older adults (1068)	TNF- $\alpha$ -308, IL10T-819C, IL10A-1082G, IL1AC-889T, IL1B C-511T, IL1RN 9589T, IL8 T-251A	ChAG risk	Age, gender	Adjustment	Multivariable logistic model
[83]	Peruvian Amerindian adults (334)	IL-1B-511, IL-1RN	ChAG risk GC risk	Age, gender, <i>H. pylori</i>	Adjustment	$\chi^2$ test/Fisher's exact test, multivariable logistic model
[84]	Venezuelan adults (109)	IL-1B-31, IL-1B-511, IL-1B+13954, IL-1RN	ChAG risk GI risk LI risk	<i>H. pylori</i>	Adjustment	$\chi^2$ test/Fisher's exact test, univariable logistic model
[87]	Costa Rican adults (223)	IL-1 $\beta$ -511, IL-1 $\beta$ -3954, IL-1RN intron 2, IL-10 -1082, IL-10 -592	AG risk CoAG risk IM risk	Sex, age, <i>H. pylori</i>	Adjustment	$\chi^2$ test/Fisher's exact test, multivariable logistic model
[96]	Venezuelan adults (2033)	IL4 -590, IL4R -3223, IL4R -398, IL10 -1082	AG risk IM risk DYS risk	Age, sex, <i>H. pylori</i> , education, environmental factors	Adjustment	$\chi^2$ test/Fisher's exact test, multivariable logistic model
[101]	Brazilian adults (112)	IL-6	ChG GC	None	None	$\chi^2$ test/Fisher's exact test
[102]	Japanese adults (863)	IL-8 -251, IL-1B -511, IL-1RN	AG GC	Age, sex, <i>H. pylori</i>	Adjustment	$\chi^2$ test/Fisher's exact test, multivariable logistic model
[103]	Chinese adults (372)	IL-8-251	Severe ChAG risk IM risk	Age, gender	Stratification, adjustment	$\chi^2$ test, multivariable logistic model, Synergy index
[106]	Chinese adult patients (556)	IL-10-1082, IL-10-819, IL-10-592	AG risk GC risk	Age, sex, <i>H. pylori</i>	Stratification, adjustment	$\chi^2$ test, multivariable logistic model with interaction term
[108]	Brazilian adults (227)	IL-6-174, IL-8-251, IL-10-819	Gastritis, peptic ulcer, GC	<i>H. pylori</i> infection	Stratification	$\chi^2$ test/Fisher's exact test
[111]	Chinese adults <i>H. pylori</i> (302)	IL-1B-511	IM risk	Age	Adjustment	$\chi^2$ test/Fisher's exact test, univariable/multivariable logistic model

Only the original research articles containing analysis of cytokines' genotypes (not haplotypes) were included.

<sup>1</sup>Only the discussed cytokine SNPs of interest (and not all of SNPs mentioned in the above studies) are described. AG: Atrophic gastritis; CoAG: Corpus atrophic gastritis; ChAG: Chronic atrophic gastritis (the term used in original research); ChG: Chronic gastritis; DYS: Dysplasia; GC: Gastric cancer; GI: Granulocytic infiltration; IM: Intestinal metaplasia; LI: Lymphocytic infiltration; *H. pylori*: *Helicobacter pylori*.

potential relationship with the progression from inflammation toward GA and IM<sup>[118]</sup>.

Current data support that infection with *H. pylori* carrying specific virulence factors is associated with increased risk of neoplastic lesions<sup>[9]</sup>. Even that *H. pylori* often is undetectable in gastric biopsies of patients with IM or GC, *H. pylori* and its genes were detected inside metaplastic, dysplastic, and neoplastic epithelial cells, and *cagA* and *babA2* expression was co-localized<sup>[119]</sup>. The preneoplastic "acidic" MUC2 mucin was detected only in the presence of *H. pylori*, and MUC2 expression was higher in patients with IM, dysplasia, and cancer. The observations of Semino-Mora *et al*<sup>[119]</sup>.

**Table 2** Frequencies of studied cytokine SNP genotypes and significance of relationships with premalignant gastric lesions in the discussed scientific articles

Ref.	SNP <sup>†</sup>	Variant genotypes	Frequency (%) of variant genotypes in premalignant gastric lesions vs control	Premalignant gastric lesions
[73]	IL-8-4073	TA	145 (48.5)/144 (48.6)	ChAG susceptibility
		AA	53 (17.7)/50 (16.9)	
		TA	148 (49.5)/144 (48.6)	IM susceptibility
		AA	50 (16.7)/50 (16.9)	
		TA	140 (46.4)/144 (48.6)	DYS susceptibility
		AA	48 (15.9)/50 (16.9)	
	IL-18RAP917997	AG <sup>a</sup>	130 (43.9)/166 (56.3)	ChAG susceptibility
		GG	72 (24.3)/61 (20.7)	
		AG	167 (56.4)/166 (56.3)	IM susceptibility
		GG	57 (19.3)/61 (20.7)	
		AG	151 (50.0)/166 (56.3)	DYS susceptibility
		GG	66 (21.8)/61 (20.7)	
	IL-1Brs1143627	TC	152 (50.9)/144 (48.5)	ChAG susceptibility
		CC	59 (19.7)/66 (22.2)	
		TC	148 (49.3)/144 (48.5)	IM susceptibility
		CC	68 (22.7)/66 (22.2)	
		TC	158 (52.5)/144 (48.5)	DYS susceptibility
		CC	71 (23.6)/66 (22.2)	
	IL-1Brs1143634	CT	15 (5.0)/21 (7.1)	ChAG susceptibility
		TT	0 (0.0)/1 (0.3)	
		CT	14 (4.7)/21 (7.1)	IM susceptibility
		TT	0 (0.0)/1 (0.3)	
		CT	13 (4.3)/21 (7.1)	DYS susceptibility
		TT	0 (0.0)/1 (0.3)	
	IL-1Brs16944	GA	153 (51.2)/143 (48.2)	ChAG susceptibility
		AA	57 (19.0)/66 (22.2)	
		GA	147 (49.0)/143 (48.2)	IM susceptibility
		AA	67 (22.3)/66 (22.2)	
		GA	156 (51.6)/143 (48.2)	DYS susceptibility
		AA	70 (23.2)/66 (22.2)	
	IL-4Rrs2057768	AG	140 (46.8)/150 (50.7)	ChAG susceptibility
		GG	71 (23.8)/61 (20.6)	
		AG	129 (43.1)/150 (50.7)	IM susceptibility
GG		80 (26.8)/61 (20.6)		
AG		154 (51.2)/150 (50.7)	DYS susceptibility	
GG		59 (19.6)/61 (20.6)		
IL-10rs1800896	AG	61 (20.4)/53 (17.9)	ChAG susceptibility	
	GG	1 (0.3)/3 (1.0)		
	AG	53 (17.6)/53 (17.9)	IM susceptibility	
	GG	5 (1.7)/3 (1.0)		
	AG	52 (17.3)/53 (17.9)	DYS susceptibility	
	GG	2 (0.7)/3 (1.0)		
IL-32rs2015620	AT	135 (45.8)/133 (45.7)	ChAG susceptibility	
	TT	78 (26.4)/82 (28.2)		
	AT	144 (48.8)/133 (45.7)	IM susceptibility	
	TT	73 (24.8)/82 (28.2)		
	AT	151 (50.0)/133 (45.7)	DYS susceptibility	
	TT	76 (25.2)/82 (28.2)		
IL-22rs1179251	CG <sup>a</sup>	82 (27.4)/143 (48.1)	ChAG susceptibility	

		GG <sup>a</sup>	20 (6.7)/29 (9.8)	
		CG <sup>a</sup>	47 (15.7)/143 (48.1)	IM susceptibility
		GG <sup>a</sup>	12 (4.0)/29 (9.8)	
		CG	111 (36.7)/143 (48.1)	DYS susceptibility
		GG	28 (9.3)/29 (9.8)	
[75]	TNF-α -308	GA	15 (29.4)/22 (20.4)	ChAG susceptibility
		AA	0 (0)/3 (2.8)	
	IL-1B -511	CT	18 (35.3)/53 (49.1)	ChAG susceptibility
		TT	3 (5.9)/13 (12.0)	
	IL-1RN	L/2	15 (29.4)/32 (29.6)	ChAG susceptibility
		2/2	2 (3.9)/13 (12.0)	
[76]	TNF-α -308	GA	125 (23.4)/129 (24.2)	ChAG susceptibility
		AA	13 (2.4)/8 (1.5)	
	IL10T-819C	TC	200 (37.5)/199 (37.3)	ChAG susceptibility
		CC <sup>a</sup>	44 (8.2)/28 (5.2)	
	IL10 A-1082G	AG	246 (46.1)/262 (49.1)	ChAG susceptibility
		GG	109 (20.4)/116 (21.7)	
	IL1A C-889T	CT	213 (39.9)/203 (38.0)	ChAG susceptibility
		TT	37 (6.9)/43 (8.1)	
	IL1B C-511T	CT	205 (38.4)/230 (43.1)	ChAG susceptibility
		TT	59 (11.0)/52 (9.7)	
	IL1RN	AT	212 (39.7)/219 (41.0)	ChAG susceptibility
		TT	39 (7.3)/35 (6.6)	
	IL8T-251A	TA	273 (51.1)/254 (47.6)	ChAG susceptibility
		AA	100 (18.7)/114 (21.3)	
[83]	IL-1B-511	CT <sup>a</sup>	21 (48.8)/28 (32.6)	ChAG risk
		CC <sup>a</sup>	7 (16.3)/3 (3.5)	
	IL-1RN	2/L	21 (50.0)/46 (53.5)	ChAG risk
		2/2	8 (19.0)/10 (11.6)	
[84]	IL-1B 31C	CC+CT	70 (84.3)/21 (80.8)	ChAG risk
	IL-1B 31C	CC+CT	18 (100)/73 (80.2)	moderate/severe GI risk
	IL-1B 31C	CC+CT	22 (91.7)/69 (81.2)	moderate/severe LI risk
	IL-1B 511T	TT+CT	71 (85.5)/20 (76.9)	ChAG risk
	IL-1B 511T	TT+CT	18 (100)/73 (80.2)	Moderate/severe GI risk
	IL-1B 511T	TT+CT	22 (91.7)/69 (81.2)	Moderate/severe LI risk
	IL-1RN*2	*1/* 2+*2/* 2	40 (48.2)/10 (38.5)	ChAG risk
	IL-1RN*2	*1/* 2+*2/* 2	7 (38.9)/43 (51.8)	Moderate/severe GI risk
	IL-1RN*2	*1/* 2+*2/* 2	12 (50.0)/38 (44.7)	Moderate/severe LI risk
[87]	IL-1β-511	TT	16 (27.6)/26 (15.8)	AG risk
		TC	30 (51.7)/88 (53.3)	
		TT	8 (25.8)/34 (17.7)	CoAG risk
		TC	16 (51.6)/102 (53.1)	
		TT	8 (34.8)/34 (15.2)	IM risk
		TC	12 (52.2)/106 (47.5)	
	IL-1β+3954	TT	1 (1.7)/2 (1.2)	AG risk
		TC	33 (56.9)/77 (46.7)	
		TT	0 (0.0)/3 (1.6)	CoAG risk
		TC	19 (61.3)/91 (47.4)	
		TT <sup>a</sup>	0 (0.0)/3 (1.3)	IM risk
		TC <sup>a</sup>	18 (78.2)/92 (41.2)	
	IL-1RN intron2	2/2	13 (22.4)/20 (12.1)	AG risk
		2/L	18 (31.0)/49 (29.7)	
		2/2	9 (29.0)/24 (12.5)	CoAG risk
		2/L	8 (25.8)/59 (30.7)	
		2/2 <sup>a</sup>	8 (34.8)/25 (11.2)	IM risk
		2/L	5 (21.7)/62 (27.8)	

	IL-10 -1082	AA	35 (60.3)/81 (49.1)	AG risk
		GA	17 (29.3)/56 (33.9)	
		AA	17 (54.8)/99 (51.6)	CoAG risk
		GA	10 (32.3)/63 (32.8)	
		AA	12 (52.2)/104 (46/6)	IM risk
		GA	10 (43.5)/63 (28.3)	
	IL-10 -592	AA	8 (13.8)/12 (7.3)	AG risk
		CA	19 (32.8)/58 (35.1)	
		AA	4 (12.9)/16 (8.3)	CoAG risk
		CA	10 (32.3)/67 (34.9)	
		AA	4 (17.4)/16 (7.2)	IM risk
		CA	8 (34.8)/69 (30.9)	
[96]	IL4-590	CT	111 (38.4)/414 (38.2)	AG risk
		CC	134 (46.3)/506 (46.7)	
	IL4-590	CT	197 (36.2)/414 (38.2)	IM risk
		CC	264 (48.6)/506 (46.7)	
	IL4-590	CT	48 (40.7)/414 (38.2)	DYS risk
		CC	51 (43.2)/506 (46.7)	
	IL4R-3223	CT	96 (33.2)/362 (33.4)	AG risk
		CC	22 (7.6)/74 (6.8)	
	IL4R-3223	CT	175 (32.2)/362 (33.4)	IM risk
		CC	36 (6.6)/74 (6.8)	
	IL4R-3223	CT	42 (35.6)/362 (33.4)	DYS risk
		CC	6 (5.1)/74 (6.8)	
	IL4R-398	AG	128 (44.3)/488 (45.1)	AG risk
		GG <sup>a</sup>	71 (24.6)/201 (18.6)	
		AG	243 (44.8)/488 (45.1)	IM risk
		GG	106 (19.5)/201 (18.6)	
		AG	49 (41.5)/488 (45.1)	DYS risk
		GG	26 (22.0)/201 (18.6)	
	IL10-1082	AG	102 (35.3)/406 (37.5)	AG risk
		AA	142 (49.1)/508 (46.9)	
		AG	201 (37.0)/406 (37.5)	IM risk
		AA	274 (50.5)/508 (46.9)	
		AG <sup>a</sup>	51 (43.2)/406 (37.5)	DYS risk
		AA <sup>a</sup>	60 (50.8)/508 (46.9)	
[101]	IL-6	GC	26 (46%)/27 (48%)	ChG <sup>9</sup>
		CC	5 (9%)/6 (11%)	
[102]	IL-8 -251	AA <sup>a</sup>	26 (12.1%)/22 (8.7%)	AG risk
		AT	99 (46.0%)/105 (41.7%)	
	IL-1B -511	TT	46 (21.4%)/49 (19.6%)	AG risk
		CT	104 (48.4%)/133 (53.2%)	
	IL-1RN	2/2	0 (40%)/2 (0.8%)	AG risk
		2/L	17 (8.2%)/21 (8.8%)	
[103]	IL-8-251	TA	70 (52.2)/64 (46.7)	Severe ChAG risk
		AA <sup>a</sup>	25 (18.7)/14 (10.2)	
		TA <sup>a</sup>	65 (64.4)/64 (46.7)	IM susceptibility
		AA	11 (10.9)/14 (10.2)	
[106]	IL-10-1082	AG	15 (12.9)/18 (7.8)	AG susceptibility
		GG	0 (0)/1 (0.4)	
	IL-10-819	CT	47 (40.5)/104 (44.8)	AG susceptibility
		CC	28 (24.1)/36 (15.5)	
	IL-10-592	AC	46 (39.7)/96 (41.4)	AG susceptibility
		CC	31 (26.7)/52 (22.4)	
[108]	IL-6-174	GC	47 (35.9)/13 (34.2)	Gastritis
		CC	14 (10.7)/2 (5.3)	

	IL-8-251	TA	67 (51.1)/20 (52.6)	Gastritis
		AA	29 (22.1)/7 (18.4)	
	IL-10-819	CT	55 (41.9)/21 (55.3)	Gastritis
		TT	10 (7.6)/6 (15.8)	
	IL-6-174	GC	22 (44.9)/13 (34.2)	Peptic ulcer
		CC	3 (6.1)/2 (5.3)	
	IL-8-251	TA	27 (55.1)/20 (52.6)	Peptic ulcer
		AA	15 (30.6)/7 (18.4)	
[111]	IL-10-819	CT	21 (42.9)/21 (55.3)	IM susceptibility
		TT	5 (10.2)/6 (15.8)	
		TT	5 (10.2)/6 (15.8)	
	IL-1B-511	CT	67 (54.5)/88 (49.2)	IM susceptibility
		TT	34 (27.6)/40 (22.3)	

<sup>1</sup>Only the cytokine SNPs of interest (mentioned in the above studies) are described; relative frequencies (%) are described in relation to the size of each of the two groups (cases and control group);

<sup>2</sup> $P < 0.05$ . AG: Atrophic gastritis; CoAG: Corpus atrophic gastritis; ChAG: Chronic atrophic gastritis (the term used in original research); ChG: Chronic gastritis; DYS: Dysplasia; GC: Gastric cancer; GI: Granulocytic infiltration; IM: Intestinal metaplasia; LI: Lymphocytic infiltration.

support the hypothesis that the persistent intracellular expression of *H. pylori* virulence genes, mainly *cagA* associated with aberrant expression of the MUC2 gene, play an important role in gastric carcinogenesis process<sup>[119]</sup>.

An important study of Houghton *et al*<sup>[120]</sup> demonstrated that epithelial cancers emerge from the transformation of tissue stem cells and inflammation that favours the development of neoplasia has been linked to bone marrow-derived cells (BMDCs). Therefore, it was hypothesised that BMDCs, that are recruited to the location of inflammation may represent a possible source of neoplasia. The same mouse model study<sup>[120]</sup> reveal that chronic infection of C57BL/6 mice with *H. pylori* may lead to the repopulation of the stomach with BMDCs. The findings of Houghton *et al*<sup>[120]</sup> indicate that epithelial malignancies can arise from BMDCs and therefore it have an important role in the multistep cancer progression. It was showed that several cytokines are critical for recruitment of BMDCs<sup>[120]</sup>. Considerable other data indicates that gastric cancer, and most of the cancers, may arise from aberrant stem cells that accumulate gene mutations<sup>[121]</sup>.

A study of gene polymorphisms involved in oxidative stress (of *CAT*, *MnSOD* and *GPX1* genes) in relation to premalignant gastric lesions demonstrated contradictory results in different populations<sup>[122-124]</sup>, despite the accepted role of oxidative stress as a consequence of *H. pylori* being a contributing factor in gastric carcinogenesis<sup>[118]</sup>. The gene variants of glutathione S-transferases (GSTs) involved in the metabolism of carcinogens, drugs, and reactive oxygen species were shown to be involved in GC predisposition, but with discordant results<sup>[125]</sup>. The GSTM1 and GSTT1 null genotypes seemed to increase the risk for premalignant lesions in a Caucasian population<sup>[126]</sup> but were not associated with GC in an Asian population in a study carried out by Chen *et al*<sup>[125]</sup>. The GSTP1Val allele seemed to reduce the risk of gastric premalignant lesions in Caucasians<sup>[126]</sup> but increased the risk for cancer in Asians<sup>[125]</sup>. The renin-angiotensin system component in the gastric mucosa seems to mediate inflammation and fibrosis<sup>[127]</sup>, and the variant homozygous CC genotype of the AGT A-20C gene polymorphism was shown to increase the risk for peptic ulcer bleeding in Japanese aspirin consumers<sup>[128]</sup>. In a Romanian study, the frequency of premalignant gastric lesions decreased with increased AGT production according to genotype (AA 37.7% < AC 25.3% < CC 16.7%) but increased the risk of ulcer in carriers of the variant homozygous CC genotype<sup>[129]</sup>.

Despite the lack of functional evaluation of all gene variants harbouring a risk for preneoplastic and neoplastic gastric lesions, the current research has increased our knowledge regarding GC, but while generating confusing results frequently. Our work summarized herein aimed to highlight the importance of research in populations with different prevalence rates of *H. pylori* infection and strains, with different genetic backgrounds and environmental exposures, linking inflammatory mechanisms with the neoplastic transformation of the gastric mucosa.

## CONCLUSION

Even though the role of extension, localisation, or phenotype of premalignant lesions

on GC risk is still a matter of debate, risk stratification and surveillance are nowadays unanimously accepted in order to decrease the burden of mortality<sup>[130,131]</sup>. At the same time, there are significant differences in the risk of progression to cancer in various populations. The endoscopic and histologic surveillance of premalignant gastric lesions should be continually evaluated, as recent research supports the importance of genetic events (*e.g.*, genetic instability, DNA damage, abnormal methylation, *etc*), rather than a direct transition from metaplasia to cancer<sup>[130]</sup>. The changes in acid secretion, pH, or gastric microbiota induced by gastric atrophy seem to be more important than the presence of histologic lesions<sup>[57]</sup>.

Among all the gene variants studied for GC risk, only IL10T-819C, IL-8-251, IL-18RAP917997, IL-22 rs1179251, IL1-B-511, IL1-B-3954, IL4R-398 and IL1RN were predictors for premalignant gastric lesion occurrence. Further studies should question the role of cytokine polymorphisms in both premalignant lesions and GC risk, in order to clarify the mechanisms that link inflammatory response with gastric carcinogenesis. Larger studies in different populations assessing gene-gene and gene-environment interactions can also facilitate improvements in prevention and treatment strategies.

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