# Chapter 7
# Biomarkers of Gastric Premalignant Lesions


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## Epidemiology

Despite decreasing incidence in the last 50 years, gastric cancer remains the fifth most common cancer in the world, representing 6.8% of the total global cancer cases [1], and ranks third as the most common cause of cancer-related death in men. Almost one million new cases of stomach cancer were estimated to have occurred in 2012 [1, 2]. There is a wide geographic variation in gastric cancer incidence and mortality rates, with more than 70% of gastric cancer cases occurring in less developed countries [1]. In Eastern Asia and South and Central America, gastric cancer is a significant health burden [1, 2]. In addition, both gastric cancer incidence and mortality vary widely among different race/ethnic groups in the United States. Asian, Hispanic, non-Hispanic black, and Native American populations have up to 50% higher risk for gastric cancer than non-Hispanic white populations [3–5]. Similarly, gastric cancer survival is better in Asians than in Caucasian Americans, African Americans, and Hispanics [4, 6, 7]. Hispanics are younger and more often with stage IV disease when gastric cancer is diagnosed, and they present a shorter survival time than non-Hispanic whites [8]. Lower survival rates for non-Hispanic blacks compared to non-Hispanic whites have also been reported [9].

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## Etiology

## H. pylori

*Helicobacter pylori* (*H. pylori*) is among several factors associated with non-cardia intestinal-type gastric cancer development. It is the primary cause the in initiation of the disease and has been classified as a class I carcinogen [10]. Infection with *H. pylori* occurs mainly during childhood [11], and in a proportion of those chronically infected, it results in the transformation of the normal gastric mucosa into non-atrophic gastritis (NAG), followed by multifocal atrophic gastritis without intestinal metaplasia (MAG), intestinal metaplasia (IM), dysplasia, and finally cancer [12, 13].

Current estimates of *H. pylori* prevalence in the world range from 24 to 79% [14]. The highest prevalence is in Africa (79%) and Latin America and the Caribbean region (63.4%), and the lowest in Oceania (24.4%) and Northern America (37.1%). In regions of South and Central America, which include those with high gastric cancer risk, *H. pylori* prevalence can reach up to 80–85%, some of the highest prevalence in the world [15]. In the United States, the estimated *H. pylori* prevalence is 30% [15]. However, while *H. pylori* prevalence ranges from 18.4 to 26.9% in non-Hispanic whites, it can be as high as 51.1%, 57.9%, and 75% in non-Hispanic blacks, Hispanics, and Alaskan Native Americans, respectively [14, 16, 17]. This high prevalence likely contributes to the high incidence and mortality from gastric cancer in non-Hispanic blacks and Hispanics. Despite this high prevalence of infection, it is estimated that approximately 1% of those chronically infected with *H. pylori* will develop gastric cancer [18, 19]. In fact, the majority of the population will remain asymptomatic.

In the last decades, *H. pylori* prevalence has decreased around the world, especially in the more developed regions, mostly due to improved hygienic conditions, improved diet and food preservation, and broader access to antibiotics [2]. Recently, Hooi et al. [14] compared *H. pylori* prevalence from two time periods (1970–1999 and 2000–2016) and found that from one time period to the next, *H. pylori* prevalence significantly decreased in Europe (from 48.8 to 39.8%), Northern America (from 42.7 to 26.6%), and Oceania (from 26.6 to 18.7%) [14]. In contrast, *H. pylori* prevalence remained similar during the same periods in Asia (53.6% vs. 54.3%) and Latin America (62.8% vs. 60.2%) [14]. This geographical variability in *H. pylori* prevalence explains in part the higher gastric cancer incidence and mortality observed in Latin American countries compared to more developed countries as the United States. Furthermore, Porras et al. in a recent study of the epidemiology of *H. pylori* infection in six countries of Latin America did not observe any significant changes in *H. pylori* prevalence between the oldest and youngest participants in their study, suggesting that gastric cancer incidence is not going to decrease in those countries in the near future [15].

## Environmental Factors

Even though infection with *H. pylori* is considered necessary for the development of gastric cancer, it is not determinant; just 1–3% of those infected with *H. pylori* will develop gastric cancer in their lifetime [18, 19]. Additional environmental factors are associated with gastric cancer risk, including smoking, alcohol use, and a diet low in fresh produce and high in meats and salt [20]. In a recent meta-analysis, Bonequi et al. found that in Latin America, smoking and alcohol use were associated with a 47% and 61% increase of gastric cancer risk, respectively [21]. Regarding diet, the same study found that consumption of red and processed meats were associated with a 73% and 64% increase of gastric cancer risk, respectively. High salt intake was associated with 2.24-fold increase. In contrast, consumption of fruits and vegetables were associated with a 32% and 42% reduction of gastric cancer risk, respectively [21]. There is a high prevalence of smoking and alcohol use in Latin American populations [22, 23], and in regions with high gastric cancer rates as in the Andean mountains, the diet is poor in fruits and vegetables and excessively high in consumption of salt [24]. Data from the US National Health Interview Survey indicate that Hispanics have the lowest prevalence of smoking in all racial/ethnic populations and the highest consumption of fresh fruits and vegetables [25]. These habits are not in concordance with their gastric cancer incidence and mortality rates.

## Genetic Bases of the Gastric Inflammatory Cascade (Correa's Cascade)

### *Single-Nucleotide Polymorphisms (SNPs)*

In 1975, Correa et al. analyzed 1500 stomachs obtained at autopsy to estimate the prevalence of intestinal metaplasia [26]. As a result of that analysis and later updates, Correa et al. proposed that gastric adenocarcinoma is the final stage of an inflammatory cascade that leads the normal gastric epithelia to non-atrophic gastritis (NAG), multifocal atrophic gastritis (MAG), complete intestinal metaplasia (IM), incomplete intestinal metaplasia, dysplasia, and cancer [13, 27–30]. It was shown that single-nucleotide polymorphisms (SNPs) in the cytokine gene encoding interleukin-1β (IL1B) are associated with the risk of gastric cancer [31]. Since then, others have shown the association of cytokine SNPs with gastric cancer risk in several populations [32–36]; however, very few works have centered on defining the association of cytokine SNPs and the presence of advanced gastric lesions as precursors of gastric cancer. Our work has led to the identification of SNPs and haplotypes in the *IL1B* gene associated with advanced gastric premalignant stages in African American and Caucasian individuals [37, 38]. Our studies have shown that African American individuals have a higher prevalence of MAG as well as a higher rate of *H. pylori* infection [37, 38]. Using DNA samples from healthy African

American and Caucasian newborns, we performed additional analyses of cytokine SNPs and haplotypes in cytokine genes which showed that there is a differential distribution of proinflammatory SNPs and haplotypes between these two ethnic groups [39]. In the case of *IL1B* gene, there is a strong linkage disequilibrium among the SNPs analyzed [39].

## *Stage-Specific and Evolution-Associated Gene Profiles*

The pioneer studies by Correa et al. led to the identification of a premalignant cascade suggested to precede gastric carcinogenesis [27]. However, the molecular basis for the intricate relationship between the different stages and their evolution over time is not fully known. Using baseline and 6-year follow-up samples from a cohort study established by Correa et al. in Colombia [40], we extracted RNA and performed a microarray analysis to find genes associated with stage and progression of premalignant lesions. Analyzing the genomics of lesion evolution over time, we found that the genes *CD44*, *NUMA*, and *LCN2* were associated with progression [41]. Interestingly, these three genes have been associated with several types of cancer and with advanced premalignant lesions [42–46]. Using mouse models of *H. pylori* infection in wild-type and *Cd44*$^{-/-}$ *H. pylori* mice, we found a significant activation of immune-related pathways in response to the infection, among them was the IFNγ pathway [41]. Interestingly, the gastric mucosa of *Cd44*$^{-/-}$ mice had significantly lower expression of *Ifng* and *Ifng*-related genes including *Irf7*, *Ifit3*, *Ifit2*, *Nos2*, and *Stat1* [41]. Reduction in *Stat1* expression was paralleled with reduction in phosphorylation of the Stat1 protein [41]. In order to correlate the differences found in global and immune gene expression with pathological changes in the gastric mucosa, we determined and compared the presence of gastric lesions between wild-type and *Cd44*$^{-/-}$ *H. pylori*-infected mice. We found that compared to the wild-type mice, the *H. pylori* infection did not induce tissue damage in the gastric mucosa of *Cd44*$^{-/-}$ *H. pylori*-infected mice. These data suggest that this gene, and the protein encoded by it, is essential to mount the Th1 responses associated with tissue damage induced by the infection [41, 47–49].

Using baseline samples from the same cohort of individuals described for our work with *CD44* [40], we identified 37 samples with MAG, 25 with IM, and 12 with dysplasia. Using the less advanced gastric precancerous lesion as reference (MAG), we identified 16 genes with at least a 30% change in their expression levels when compared with dysplasia [50]. However, the only one showing significantly higher expression was the gene *Deleted in Malignant Brain Tumor 1* (*DMBT1*), which was able to separate most dysplasia from MAG cases [50]. Interestingly, gastric tissue from African American and Caucasian individuals with advanced gastric lesions also had increased levels of expression of the gene [50], suggesting that this response is conserved across ethnicities. We also found that the expression of the *DMBT1* gene was significantly higher in individuals with advanced gastric lesions who also had infection with *H. pylori*, which highlights the role of the DMBT1 protein as an agglutinin [51–53]. Mouse models of *H. pylori* infection show that this gene acts as

a tumor suppressor by limiting tissue damage in response to the infection and through the activation of interleukin 33 (IL33) and pERK [50].

In summary, gastric cancer is a disease of disparities, with minority groups having increased prevalence and mortality of the disease. We have shown that precancerous lesions and their evolution over time are associated with specific patterns of genes that may be used as the basis to devise strategies for the prediction of disease aggressiveness and outcome.

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