Systematic Review
DOI: https://doi.org/10.70749/ijbr.v3i3.855

INDUS JOURNAL OF BIOSCIENCE RESEARCH
https://induspublishers.com/IJBR
ISSN: 2960-2793/ 2960-2807

Crossref

OPEN ACCESS

Role of *Helicobacter pylori* Infection and Host Genetic Polymorphisms in Gastric Cancer Susceptibility: A Systematic Review

Kashmala Shah[1], Brekhna Shah[1], Majid Shah [2], Safa Shah[3]

[1]Khyber Medical College, Peshawar, Pakistan
[2]Saidu Medical College, Swat, Pakistan
[3]Department of Medical Sciences and Biology, Western University, London, Ontario, Canada

ARTICLE INFO

Keywords

Gastric Cancer, *H. Pylori*, Environmental Factors, Genetic Susceptibility, Cancer

Corresponding Author: Brekhna Shah, M.B.B.S. Khyber Medical College, Peshawar, Pakistan
Email: brekhnashahhh@gmail.com

Declaration

Authors' Contribution: All authors equally contributed to the study and approved the final manuscript.
Conflict of Interest: No conflict of interest.
Funding: No funding received by the authors.

Article History

Received: 03-01-2025, Revised: 26-02-2025
Accepted: 13-03-2025, Published:19-03-2025

ABSTRACT

Background

Despite ongoing efforts, gastric cancer remains a leading cause of cancer-related death worldwide, with its high risk primarily attributed to *Helicobacter pylori* (*H. pylori*) infection. However, the development of gastric cancer is influenced not only by bacterial virulence but also by host genetic susceptibility. **Methods:** To determine the potential association between specific SNPs, such as IL-6 rs1800795, PRKAA1 rs13361707, and HULC rs7770772, and gastric cancer risk in *H. pylori*-infected populations, a systematic review of cohort and case-control studies was conducted. **Results:** In the presence of risk alleles of inflammatory cytokine genes, such as IL-6 rs1800795 and IL-10, the amplification of susceptibility to gastric carcinoma was significantly higher in *H. pylori* positive individuals. In East Asians, the PRKAA1 rs13361707 polymorphism had an additive effect with *H. pylori* infection and with CagA-positive strains. Additionally, the HULC rs7770772 polymorphism synergistically enhanced gastric cancer risk in conjunction with bacterial infection. Other SNPs, including IL-18RAP rs917997 and IL-32 rs2015620, were associated with chronic atrophic gastritis and intestinal metaplasia and were implicated in the progression of gastric cancer. A Hispanic group with *H. pylori* infection and gastric cancer showed a common increase in HLA-Class II polymorphisms, such as HLA-DQA101 and HLA-DQB106, which are associated with decreased *H. pylori* susceptibility and an increased risk of gastric cancer. Furthermore, *H. pylori* influences host immunity through the regulation of microRNA-mediated modifications of HLA-II expression, which manipulates the immune response and facilitates immune evasion. **Conclusion:** Our findings demonstrate that the pathogenesis of gastric cancer involves an intricate interplay between *H. pylori* infection, host genetic susceptibility, and environmental factors.

INTRODUCTION

Helicobacter pylori is a bacterial pathogen found in the gastrointestinal (GI) tract. More than half of the global population harbors *H. pylori* infection [1]. The International Agency for Research on Cancer [2] classified this spiral shaped microorganism as a Group I carcinogen. It has the ability to withstand stomach acid, which allows the bacteria to colonize GI tract cells. However, *H. pylori* is implicated in up to 75% of non-cardia gastric malignancies and in 98% of gastric cardia malignancies [3].

The progression of cancer has been linked to several virulence factors (cagPAI, VacA) of *H. pylori* [4,5]. It has a 40 kb locus that has about 31 genes coding for a type IV secretion system present on the pathogenicity island [5,6]. One of the most important virulence factors is the VacA gene, which has extensive genetic variability in relation to the formation of gastric lesions [4].

H. pylori-induced gastric diseases depend on host genetic factors [7,8]. Relevant human genes were specifically identified to have key cancer-related single nucleotide polymorphisms. Notably, these include specific SNPs in different cytokine production (IL-1β, IL-6, IL-8, IL-17A/B, TNF, and IFN-γ) and receptors involved in the immune response (TLR2, TLR4, and CD14), which increase a host's susceptibility to developing gastric cancer after infection with *H. pylori* [9].

H. pylori infection, genetic susceptibility, and environmental influences such as tobacco use, alcohol consumption, dietary habits, and socioeconomic conditions may further elevate the risk of gastric cancer [10].

The objective of this review is to critically review

literature on the gene-environment interactions, genetic susceptibility to *H. pylori* infection, and association with greater risk of gastric cancer.

METHODOLOGY

Study Design

The purpose of this systematic review was to review research articles written in English from 2010 to 2024, using the genetic susceptibility to *H. pylori* and genetic risks of gastric diseases as keywords to determine the correlation between the two. Furthermore, the review discusses the gene-environment interactions in the development of gastric cancer.

Literature Search

To find the appropriate material, PubMed, EMBASE, and Scopus were searched for research published between January 2010 and December 2024. The search parameters used both keywords and Medical Subject Headings (MeSH) terms, such as '*Helicobacter pylori*,' genetic susceptibility, gastric disease, gene-environment interaction, gastric cancer, single nucleotide polymorphism, and host factors. The "AND" and "OR" operators were used to combine terms meaningfully, while database-specific filters were applied for date and study type. Further literature searches of the citation lists of included studies were also included to mitigate the limitation of relying solely on computerized search terms.

Inclusion and Exclusion Criteria

Studies included in this review focused on human participants with documented *H. pylori* infection or genetic susceptibility data. Eligible studies examined genetic factors, such as polymorphisms and mutations, and their interactions with environmental variables, including diet, smoking, alcohol consumption, and socioeconomic status. The primary outcomes of interest were the associations between genetic markers and the risk of gastric diseases, such as gastritis, peptic ulcers, and gastric cancer. Observational studies, including case-control and cohort studies, were considered. Only studies published between 2010 and 2024 were included, and the language was restricted to English or articles with accessible English translations. Studies were excluded if they involved animal models, lacked relevant genetic or environmental data, or were conference abstracts, editorials, or reviews. These criteria ensured that the review incorporated high-quality, human-focused research directly relevant to the objective.

RESULTS

The present systematic review provides strong and rigorous evidence that genetic polymorphisms of inflammation-associated and regulatory genes, in combination with *H. pylori* infection, increase the risk of gastric cancer and precancerous gastric lesions.

Genetic Polymorphisms and *H. pylori* Infection in Gastric Cancer Risk

Interactions between polymorphisms of cytokine genes, such as IL-6 rs1800795, and *H. pylori* infection increase the risk of gastric cancer. A recent study discussed this interaction within the context of two non-Mendelian inherited traits, showing that the risk allele in combination with *H. pylori* infection dramatically increased the likelihood of developing gastric cancer [9]. Research also indicates that the PRKAA1 rs13361707 polymorphism was associated with an increased risk of gastric cancer, resulting in a synergistic effect when combined with *H. pylori* infection and CagA [11]. Furthermore, studies have shown that the HULC rs7770772 polymorphism also has a synergistic effect with persistent *H. pylori* infection, further contributing to the risk [12]. Additionally, increased levels of IL-10 have been associated with the development of gastric cancer [13].

Role of Inflammatory Cytokine Gene Polymorphisms in GC Progression

Certain types of inflammatory genes are polymorphic and play an important role in gastric cancer. IL-18RAP rs917997 and IL-32 rs2015620 SNPs have been linked to an increased susceptibility to chronic atrophic gastritis (CAG) and intestinal metaplasia (IM), specifically in the presence of *H. pylori* infection [14]. Inflammatory gene SNPs and bacterial infection are emphasized as modulators of chronic inflammation, which contribute significantly to the development of gastric cancer. Moreover, a study demonstrated that the interaction between genetic elements, such as miRNA genes, also increases the risk of gastric cancer [15].

Insights from Genome-Wide Association Studies (GWAS)

Genome-wide studies have identified specific genes related to gastric cancer, as well as genes affected by *H. pylori* infection and lifestyle factors. For example, one study explored genes such as PSCA and PRKAA1 and proposed that the combined effect of lifestyle factors and genetic vulnerability can increase the risk of gastric cancer and precancerous lesions higher than the effect of environmental factors alone [4]. Similarly, GWAS SNPs (rs4072037, rs13361707) have been hypothesized to enhance the risk of gastric cancer when coexistent with *H. pylori* infection [10].

Role of HLA-Class II Genes in *H. pylori* Susceptibility

Recently, HLA-Class II genes have been shown to play a significant role in modulating host susceptibility to *H. pylori* infection and the progression of *H. pylori* infection into various gastric diseases, especially gastric cancer. Despite variations in the influence of HLA Class

II polymorphisms, it appears that host genetics significantly interact with microbial virulence factors. In some populations, *H. pylori*-induced gastric diseases are associated with certain HLA-DQ and HLA-DR alleles. An association between the HLA-DQA101 and HLA-DQB106 alleles with the development of gastric cancer and duodenal ulcers has been found in a study conducted on *H. pylori*-infected individuals in Turkey [16]. Similar findings were also reported in another Indonesian cohort, where DQB1*0401 genotypes were related to an increased risk of *H. pylori* infection, and DQB1 0301 genotypes provided protection [17].

Whereas in the European populations, no difference regarding HLA-DR or HLA-DQ allele frequencies or *H. pylori* infection rates was observed [18]. Furthermore, research on Iraqi patients with superficial gastritis revealed that the HLA-DRB103 and HLA-DRB115 alleles were linked to *H. pylori* infection [19].

H. pylori Influence on HLA Gene Expression and Immune Evasion

In addition, HLA Class II gene expression is influenced by *H. pylori* itself. *H. pylori* has already been shown to inhibit antigen presentation through microRNAs that upregulate the expression of certain microRNAs that impair HLA-II expression in macrophages, blocking the immune system from being able to reject the infection [20]. The study also showed that *H. pylori* infection can cause HLA-C to be upregulated on *H. pylori*-associated gastric adenocarcinoma cells, thereby enabling tumor cells to evade immune surveillance by natural killer (NK) cells [21].

Host-Pathogen Genetic Mismatch and Gastric Cancer Risk

Host genetic factors also act in synergy with highly virulent *H. pylori* strains. The literature on high-risk Mongolian and Colombian populations supported that host-pathogen genetic dissimilarities elevate the risk of gastric cancer. A recent study found that the virulence factors CagA and VacA of different *H. pylori* strains increased during their interactions with sensitive host genotypes [22]. Similarly, research has noted that an *H. pylori* strain (African lineage) also exacerbated gastric lesions in Amerindian hosts due to distributed co-evolution between the host and pathogen genomes [23]. According to these results, gastric cancer is not endemic to specific regions, but regional and localized genomic factors are not to be ruled out while considering the gastric cancer risk of an individual.

Cumulative Risk Analysis and Clinical Implications

In addition, the findings from the cumulative risk analysis were used to better understand the interactions between genetic susceptibility and *H. pylori* infection for gastric cancer. A study has found that carriers of germline pathogenic variants in homologous recombination genes had a lifetime gastric cancer risk of 45.5%, compared to 14.4% for noncarriers when infected with *H. pylori* [8]. The results support the hypothesis that multiple gene-environment interactions (G x E) are responsible for the progression of gastric cancer and highlight the need to incorporate genetic and bacterial eradication strategies in the management of high-risk populations.

DISCUSSION

Based on the results of this systematic review, data for genetic, *H. pylori*, and environmental factors is strongly supported in gastric cancer development. The analysis emphasizes the significant importance of gene-environment interactions in elevating the risk of gastric cancer.

The dynamics between *H. pylori* infection and host genetic polymorphisms are, therefore, major contributors to gastric carcinogenesis. Polymorphisms in genes involved in inflammation (IL-6 rs1800795, IL-10) elevate the risk of gastric cancer in *H. pylori*-positive individuals [9,13]. Various studies revealed that *H. pylori* causes chronic inflammation, leading to increased cytokine overproduction, which aggravates damage to the gastric epithelium [24]. The PRKAA1 rs-13361707 polymorphism, along with *H. pylori* infection, also aggravates the risk of gastric cancer [11]. These results agree with the hypothesis that suggests *H. pylori* density (driven by its virulence factors, such as CagA and VacA) enhances pro-inflammatory and oncogenic pathways in genetically susceptible hosts. The complex pathogenesis of gastric cancer is also further supported by the involvement of SNP-SNP interactions. For example, interactions between HULC rs7770772, IL-18RAP rs917997, and IL-32 rs2015620 with *H. pylori* significantly elevate the risk for precancerous lesions and gastric cancer [14,15]. Some functional studies also observed that polymorphisms in these genes modulate cytokine production, immune response to *H. pylori*, and epithelial injury, leading to induction of the carcinogenic processes [25]. The presented results strongly support the idea that SNP-SNP interactions, alongside environmental factors, play a critical role in increasing gastric cancer risk in *H. pylori*-positive individuals.

Together, the newly identified GWAS genetic loci enhance our understanding of host factors that predispose individuals to gastric cancer. Certain genes (PSCA, PRKAA1, and SLC52A3), together with *H. pylori* infection and other lifestyle risk factors, contribute to increasing the risk of gastric cancer and precancerous lesions [7,10]. Moreover, meta-analysis of East Asian populations also showed that gastric cancer risk is increased by genetic predisposition and *H. pylori* infection [26].

Another crucial predictor of gastric cancer development is co-pathogen history with host-pathogen co-evolution.

Analysis of Mongolian and Colombian populations showed an increase in the disease risk due to differences in the *H. pylori* strains and host genetics. For instance, African *H. pylori* strains increased gastric cancer risk specifically among Amerindians [23]. A recent study found that the Mongolian population with high-risk factors is also exposed to highly virulent *H. pylori* strains, which carry specific gene clusters [22, 27].

H. pylori increases cancer risk in individuals deficient in DNA repair genes to counteract the oxidative damage and genetic instability caused by chronic infection [28]. These results demonstrate the importance of developing tailored approaches that incorporate both genetic testing and *H. pylori* eradication to mitigate the risk of gastric cancer.

CONCLUSION

This detailed review analyzes the complex relationship between host genetic susceptibility, *Helicobacter pylori* infection, and environmental factors in gastric cancer development. It places special focus on how gene-environment interactions give rise to cancer. With increasing understanding of gastric cancer, it is essential that future studies and medical practices use both genetic and microbial information to gain a more holistic picture of the disease pathology. This approach will improve clinical outcomes and support the development of personalized treatment based on an individual's personal risk. Gastric cancer control strategies may be of value for transforming prevention and treatment programs into patient-specific goals.

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