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# Advances in Gastric Carcinogenesis Related to *Helicobacter Pylori*

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## Rezumat

***Progrese în carcinogeneza gastrică legată de Helicobacter Pylori***

*Helicobacter pylori* (*H. pylori*) reprezintă o bacterie Gram-negativă, care a fost clasificată drept factor carcinogenic din Grupa I, de către Organizația Mondială a Sănătății. De asemenea, reprezintă cel mai important factor de risc modificabil pentru neoplasmul gastric, în special pentru subtipul intestinal. Deşi prevalența infectiei la nivel global este in scădere, rolul său în oncogeneza gastrică rămâne unul bine definit, în special în zonele cu rate de incidență ridicate. Această analiză consolidează cunoştințele actuale despre căile moleculare şi imunologice prin care *H. pylori* contribuie la dezvoltarea tumorilor gastrice, accentul fiind pus pe modularea epigenetică, interacțiunile dintre gazdă şi microorganism, respectiv influența microbiotei gastrice. Inflamația cronică, determinată de infecția cu *H. pylori*, prin mecanismul cascadei Correa, determina ulterior procesul de transformare neoplazică. Principalii factori determinanți ai virulenței, inclusiv CagA şi VacA, acționează asupra barierelor epiteliale şi inițiază rețele de semnalizare oncogenică precum NF-κB, STAT3, Wnt/ß-catenină şi Hippo/YAP. Infecția este, de asemenea, asociată cu o remodelare epigenetică extinsă, în special hipermetilarea promotorului genelor supresoare tumorale precum CDH1 şi reglarea ARN-urilor necodificatoare (inclusiv miRNA, lncRNA şi circRNA). Colonizarea susținută determină polarizarea imună către răspunsurile Th1 şi Th17, promovează mecanisme de tipul supraexprimării PD-L1 şi modifică compoziția microbiomului gastric. Descoperirile recente evidențiază rolul potențial oncogenetic al speciilor microbiene non-H. pylori în progresia tumorală. Deşi eradicarea *H. pylori* reduce riscul de cancer gastric, aceasta nu conferă protecție completă, în special la pacientii cu modificări mucoase preexistente sau dismicrobism la acest nivel. Dezvoltarea neoplasmului gastric asociat cu *H. pylori* este un proces multifactorial, modelat de virulența microbiană, genetica gazdei, schimbările epigenetice şi dinamica imună. O

înțelegere mai profundă a acestor mecanisme interconectate este crucială pentru îmbunătățirea măsurilor preventive, a acurateței diagnosticului şi a abordărilor terapeutice.

**Cuvinte cheie:** *Helicobacter pylori*, cancer gastric, microbiom, carcinogeneză

## Abstract

*Helicobacter pylori (H. pylori)*, a Gram-negative bacterium, has been classified as a Group I carcinogen by the World Health Organization. It represents the most significant modifiable risk factor for gastric cancer (GC), particularly the intestinal subtype. Although global infection rates are on the decline, its role in gastric oncogenesis remains prominent, especially in areas with elevated incidence rates. This review consolidates current insights into the molecular and immunological pathways through which *H. pylori* contributes to gastric tumorigenesis, with a focus on epigenetic modulation, host-microbe interactions, and the influence of the gastric microbiota. Chronic inflammation, instigated by *H. pylori* infection, advances through the Correa cascade, culminating in neoplastic transformation. Principal virulence determinants, including CagA and VacA, compromise epithelial barriers and initiate oncogenic signaling networks such as NF-κB, STAT3, Wnt/ß-catenin, and Hippo/YAP. The infection is also associated with extensive epigenetic remodeling, notably promoter hypermethylation of tumor suppressor genes like CDH1, and regulation of non-coding RNAs (including miRNAs, lncRNAs, and circRNAs). Sustained colonization drives immune polarization toward Th1 and Th17 responses, promotes immune escape mechanisms such as PD-L1 overexpression, and alters the composition of the gastric microbiome. Recent findings highlight the potential role of non-*H. pylori* microbial species in supporting tumor progression. While eradication of *H. pylori* lowers the risk of gastric cancer, it does not confer complete protection, particularly in individuals with pre-existing mucosal alterations or microbial dysbiosis. The development of *H. pylori*-associated gastric cancer is a multifactorial process, shaped by microbial virulence, host genetics, epigenetic shifts, and immune dynamics. A deeper understanding of these interrelated mechanisms is crucial for refining preventive measures, diagnostic accuracy, and therapeutic approaches.

**Keywords:** *Helicobacter pylori*, gastric cancer, microbiome, carcinogenesis

## Introduction

Gastric Cancer (GC) remains a major global health concern, with more than one million new cases and over 768,000 deaths recorded in 2020. It is currently the sixth most common cancer and the fourth leading cause of cancer-related death worldwide. The highest incidence rates are observed in East Asia, where *Helicobacter pylori (H. pylori)* infection is endemic. Notably, most GCs (90–95%) are adenocarcinomas arising via chronic gastritis and metaplasia; only a small fraction of cases are gastric lymphomas (e.g. MALT lymphoma) or stromal tumors (1).

Oncology remains one of the most dynamically evolving domains within medical science. Continuous updates to therapeutic guidelines and regulatory frameworks provide patients with access to emerging and innovative treatment modalities. Translational medicine - often described by the phrase "from bench to bedside" - plays a pivotal role in cancer research by bridging preclinical discoveries with the design of clinical trials (2).

Over time, scientific investigations have uncovered a wide array of mechanisms involved in tumorigenesis. Both genetic predispositions and environmental exposures are recognized as key contributors (3).

Another essential factor is epigenetics, which has gained prominence for its role in modulating gene expression and promoting malignant transformation. In addition, microbial involvement in carcinogenesis has become increasingly evident.

Among the most notable microbial agents linked to cancer development are viruses such as human papillomavirus (HPV), hepatitis B and C viruses (HBV and HCV), and Epstein-Barr virus (EBV). Beyond viral pathogens, certain bacterial species have also been implicated in cancer pathophysiology (4).

A well-established example is the association between *H. pylori* infection and gastric malignancies.

Recent research has increasingly focused on the broader role of bacteria in cancer biology. Investigations into the gut microbiome and the presence of intratumoral bacteria have revealed potential impacts on tumor behavior and responsiveness to therapy (5).

*H. pylori* represents the primary risk factor for the development of GC, alongside other contributors such as tobacco use and alcohol intake. Additional dietary behaviors linked to a heightened risk include frequent consumption of salt-preserved foods and insufficient fruit intake. *H. pylori* is a Gram-negative, spiral-shaped, microaerophilic bacterium that exhibits a particular affinity for colonizing the gastric mucosa (6). It is responsible for the most widespread bacterial infection globally (7).

Although the majority of individuals infected with *H. pylori* remain without symptoms, virtually all will ultimately develop gastritis. Over time, this chronic inflammatory condition can evolve into gastroduodenal ulcers and may eventually lead to gastric adenocarcinoma or mucosa-associated lymphoid tissue (MALT) lymphoma (8).

The wide variation in clinical outcomes remains incompletely understood, though current evidence suggests an interplay between microbial virulence and host-specific factors (9).

Notably, *H. pylori* infection typically initiates a chronic non-atrophic gastritis that can advance through stages of intestinal metaplasia and dysplasia, potentially culminating in gastric malignancy (1,2).

First cultured by Marshall and Warren in 1982 and long associated with peptic ulcer disease, *H. pylori* was classified as a Group I carcinogen by IARC in 1994. This designation (along with a 2021 US carcinogen report) underscores its definite causal link to GC. Over the ensuing decades, it became clear that nearly all *H. pylori* - infected individuals develop chronic gastritis, which is often progressive. In many, chronic non-atrophic gastritis advances over decades to atrophic gastritis, intestinal metaplasia and dysplasia – a stepwise "Correa" cascade culminating in intestinal-type gastric adenocarcinoma (10). Indeed, prospective epidemiologic studies found that *H. pylori* seropositivity in asymptomatic individuals strongly predicts later development of GC, especially of the intestinal (vs diffuse) type. Conversely, the eradication of *H. pylori* markedly reduces GC incidence in high-risk populations, confirming its etiologic role (2,11).

The global prevalence of *H. pylori* is declining in many regions, due to improved sanitation and widespread antibiotic use. Even so, significant heterogeneity remains: current prevalence remains ~80% in many parts of Africa and Latin America, ~50–60% in Asia, and ~25–40% in North America and Europe. Because transmission occurs primarily in childhood and colonization is lifelong, cumulative exposure is large in older cohorts. Various host factors (genetic polymorphisms in cytokines, acid secretion genes, etc.) also modulate the risk that an infected person will progress to cancer. In summary, the modern view is that *H. pylori* infection serves as a chronic, long-term inflammatory stimulus in the stomach, creating a milieu (oxidative stress, genomic damage, aberrant signaling, etc.) that, together with dietary and genetic cofactors, drives multistage gastric carcinogenesis (1,2).

### *Major Risk Factors*

Besides *H. pylori*, dietary and lifestyle factors contribute to GC risk. High intake of salt-preserved foods and nitrates, smoking, and heavy alcohol use are also implicated. Conversely, diets rich in fresh fruits and vegetables appear protective. Age, male gender, and family history are additional risk factors. However, among all these factors, *H. pylori* infection is the most important modifiable cause: chronic infection with a virulent *H. pylori* strain confers a relative risk of GC often >5-fold compared to uninfected individuals. In light of this evidence, screening for and eradicating *H. pylori* has become a key preventive strategy in high-risk regions (2).

### *Pathological Types*

Gastric adenocarcinomas are classically divided into intestinal and diffuse types. *H. pylori* is most strongly linked to the intestinal type, which follows the Correa sequence of gastritis → atrophy → metaplasia → dysplasia → carcinoma (12).

The diffuse (signet-ring) type appears less tightly linked to *H. pylori*. In addition, *H. pylori* infection predisposes to gastric mucosa-associated lymphoid tissue (MALT) lymphoma: more than 90% of gastric MALT lymphomas harbor *H. pylori*, and early-stage MALT often regresses with antibiotic therapy (13).

(Notably, MALT is a hematolymphoid malignancy but is considered a neoplastic consequence of chronic antigenic stimulation by *H. pylori*). Thus *H. pylori* can induce both epithelial and lymphoid malignancies in the stomach (11,14).

### *Aim of the Review*

The objective of this literature review is to critically examine recent findings on the role of *H.pylori* in gastric carcinogenesis, with a focus on molecular, epigenetic, and immunological mechanisms, as well as potential implications for prevention and therapeutic intervention.

## Materials and Methods

This review of the literature was conducted by performing a comprehensive literature search using PubMed and Google Scholar databases. The search strategy included the terms: "*Helicobacter pylori*" AND "carcinogenesis" AND "gastric cancer". Articles were filtered to include meta-analyses, systematic reviews, and narrative reviews published between January 2023 and April 2025. Only English-language publications with full-text access were considered. Emphasis was placed on high-impact journals and studies offering novel mechanistic or translational insights. A total of 79 articles from the literature were reviewed, of which 11 were deemed unrelated to the study and therefore excluded from analysis. References were systematically imported using the Mendeley reference management software to ensure accurate citation handling and organization. Subsequently, Microsoft Excel was utilized to construct and manage the comprehensive database of the study, facilitating data sorting, filtering, and analysis. The retrieved data were synthesized to highlight the molecular mechanisms, immune pathways, and therapeutic implications associated with *H. pylori* - driven gastric carcinogenesis.

## Results

### *Epidemiology of H. pylori and Gastric Cancer*

As of 2020, GC ranks as the fifth most commonly diagnosed malignancy worldwide and the fourth leading cause of cancer-related mortality. Despite progress in multimodal therapeutic strategies, clinical outcomes for patients with locally advanced GC remain suboptimal, with a median survival duration of 34.4 months and a five-year survival rate of merely 38.7%. Although the overall incidence of GC has declined over recent decades, recent epidemiological trends reveal a rising occurrence among individuals under the age of 50. GC is more prevalent in males and demonstrates significant geographical variability, with the highest incidence rates reported in Eastern and South-Eastern Asia (15).

*H. pylori* affects nearly half the global population, though its prevalence is falling in high-income countries due to better hygiene and antibiotics. A meta-analysis showed a drop from 58.2% in the 1980s to 43.1% by 2022. In contrast, prevalence remains high in low- and middle-income regions, reaching 70% in some African populations. Infection usually occurs in childhood and persists without treatment. *H. pylori* is involved in up to 75% of non-cardia GC and over 95% of cardia GC. Eradication programs have reduced GC rates. Its link to esophageal cancer is still unclear (16).

The global distribution of *H. pylori* colonization is extensive yet uneven. Contemporary meta-analyses indicate a consistent decline in infection prevalence over the last few decades. A comprehensive systematic review including approximately 3 million individuals demonstrated a drop in global prevalence from 58% (95% CI: 50.7–65.8%) during 1980–1990 to roughly 43% (95% CI: 40.3–45.9%) in 2011–2022. The most notable reductions occurred after 2010, particularly in high-income regions, likely reflecting improved public health measures and aggressive eradication policies (17).

Nevertheless, *H. pylori* remains highly prevalent in numerous regions; for instance, near-universal colonization persists among adults in select East Asian and South American populations. These geographic patterns mirror those of GC incidence, which is up to eightfold higher in countries such as Japan, China, and Korea compared to North America. Age-related trends are also apparent, with younger birth cohorts generally exhibiting lower infection rates - likely a result of birth cohort effects (17,18).

A meta-analysis of 149 studies across 32 countries revealed significant regional differences in *H. pylori* prevalence among gastric cancer (GC) cases. In East Asia, particularly Japan, about 91% of GC tumors are linked to *H. pylori*, whereas Western countries like Sweden report as low as 0.1%. These disparities may be due to differences in lifetime exposure, diagnostic methods, or biopsy sampling. The data underscore *H. pylori's* critical role in GC, justifying region-specific prevention strategies, such as mass screening and eradication programs in high-risk Asian populations (19).

In a cross-sectional analysis, the estimated prevalence of GC among *H. pylori*-positive individuals was 19.46% (95% CI: 18.34–20.57; N = 69; $I^2$ = 98.59%), suggesting that between 183 and 206 per 1,000 infected individuals may develop GC. Other investigations reported lower

estimates, with a pooled GC prevalence of 8.97% (95% CI: 8.62–9.33; N = 149; $I^2$ = 98.68%) among those infected with *H. pylori*, indicating that approximately 8.62 to 9.33 out of every 1,000 infected individuals may be at risk for GC.

Among individuals younger than 50 years, *H. pylori* prevalence was reported at 41.9%. These findings emphasize that even in the absence of gastric mucosal atrophy, *H. pylori* - induced non-atrophic gastritis serves as a significant and independent risk factor for GC (20).

This observation aligns with the classification issued by the International Agency for Research on Cancer (IARC) and the World Health Organization (WHO) in 1994. An earlier meta-analysis conducted prior to 1998, encompassing approximately 800 GC cases, revealed a relative risk of 2.5 (95% CI: 1.9–3.4) in seropositive subjects, reinforcing the significant link between *H. pylori* infection and gastric malignancy (21).

### *Virulence Factors of H. pylori*

*H. pylori*, a WHO class I carcinogen, is linked to gastric adenocarcinoma and MALT lymphoma. Chronic inflammation drives carcinogenesis, though direct mechanisms remain unclear. Antral colonization may be protective (7).

Key virulence factors of *H. pylori* include CagA, VacA, and components of the Cag pathogenicity island (Cag PAI) (22,23). These contribute directly to mucosal damage and neoplastic transformation (24).

CagA-positive strains induce stronger inflammation, increasing atrophic gastritis and gastric cancer (GC) risk, although CagA-negative strains can also be oncogenic. Geographic differences in CagA isoforms, especially between East and West, affect cancer risk. Gastric MALT lymphoma appears independent of CagA and atrophic gastritis, indicating different mechanisms. Both autoimmune and *H. pylori* - related gastritis predispose to gastric neuroendocrine tumors, with autoimmune gastritis posing higher risk via oxyntic mucosal atrophy and hypergastrinemia (25).

Overall, while *H. pylori* significantly contributes to gastric carcinogenesis, its role as a direct carcinogen remains complex and incompletely understood (26).

Gastrin's trophic effect on enterochromaffin-like cells is well-documented, promoting neoplastic changes in oxyntic mucosa seen in Zollinger-Ellison syndrome and experimental hypergastrinemia. This highlights gastrin's central role in *H. pylori* - associated GC, linking infection to ulcerogenesis and oncogenesis. Eradication of *H. pylori* remains key, but patients with advanced oxyntic atrophy may benefit from gastrin receptor antagonists. Combining eradication, gastrin inhibition, and acid suppression minimization could significantly reduce GC risk. Recent evidence supports the use of gastrin blockers like netazepide in hypergastrinemic patients for chemoprevention after *H. pylori* eradication (25).

CagA is the most studied virulence protein, translocated into gastric epithelial cells via a type IV secretion system. Nearly all Asian strains carry cagA, while 60-70% of Western strains are positive. Infection with CagA-positive strains notably raises GC risk. A meta-analysis in the Indo-Pacific showed GC patients are 2.5 times more likely to harbor CagA-positive *H. pylori* compared to those with non-malignant gastritis (27).

Phosphorylated CagA disrupts multiple host signaling pathways by binding kinases and scaffolding proteins, causing cytoskeletal changes and increased cell motility. It activates NF-κB and STAT3 in gastric epithelium, promoting expression of inflammatory and proliferative mediators like IL-8, driving chronic inflammation and epithelial proliferation. CagA also boosts Th1 and Th17 responses, intensifying inflammation. Overall, CagA hijacks host signaling, especially via NF-κB and STAT3, fostering mucosal hyperproliferation and genomic instability that contribute to tumor development (28).

CagA interaction with gastric epithelial cells upregulates inflammasome activity, leading to excess reactive oxygen species (ROS) production and cytokine-driven inflammation. Pyroptosis, an inflammatory programmed cell death involving caspases and gasdermin D (GSDMD), varies in role across gastric cancer stages and affects key transcriptional regulators like CD44, LGR5, COX-2, and PCDH10, promoting uncontrolled proliferation and malignancy. Meanwhile, microRNA-1290 (miR-1290) shows altered expression in *H. pylori* - associated gastric lesions, highlighting its potential as a biomarker in gastric carcinogenesis (29).

Functionally, miR-1290 exerts oncogenic effects by targeting tumor suppressor genes such as FOXA1, NKD1, and FBP2, thus disrupting cell cycle control. Overexpression of miR-1290, induced by CagA, further amplifies these disruptions, facilitating the molecular cascade leading to malignant transformation in gastric epithelium (29).

VacA is a key *H. pylori* virulence factor with

allelic variants influencing its pathogenicity. It induces intracellular vacuolation and modulates apoptosis, either promoting epithelial cell death or inhibiting it to allow survival of damaged cells (30). VacA also impairs T-cell activation, aiding immune evasion and chronic infection. Though not essential for carcinogenesis, VacA's toxic and immunomodulatory effects contribute to mucosal damage and cancer risk (28). Additionally, adhesins BabA and SabA and enzymes like urease and catalase promote colonization and inflammation. BabA binds Lewis b antigens, enhancing adherence. VacA induces autophagy and oxidative stress, disrupting mucosal integrity, impairing neutrophils, and causing epigenetic changes such as DNA methylation, all driving gastric carcinogenesis (31).

### *Signaling Pathways and Molecular Mechanisms in H. pylori – Driven Carcinogenesis*

*H pylori* activates oncogenic pathways beyond CagA, altering gastric epithelial signaling and promoting cancer. CagA-positive strains trigger NF-κB via IκBα degradation, leading to anti-apoptotic, proliferative, and pro-inflammatory gene expression, including IL-32, which sustains NF-κB activation. This mechanism is confirmed both in vitro and in vivo. NF-κB also interacts with STAT3 and Hippo pathways, enhancing neoplastic transformation (32).

### *STAT3 and Immune Modulation*

STAT3, activated mainly via IL-6 and IL-17 through JAKs, is sustained in *H. pylori* infection due to increased cytokine production and CagA-driven SHP-2 signaling. Toll-like receptor engagement, especially via TLR2, further supports STAT3 activation. Once in the nucleus, STAT3 promotes genes linked to proliferation, epithelial-mesenchymal transition (EMT), and immune evasion - linking chronic inflammation to gastric epithelial transformation (2).

### *Chronic Inflammation and Additional Virulence Determinants*

Host-related variables also modulate susceptibility; for example, individuals with blood group A exhibit increased vulnerability to *H. pylori* infection, likely due to preferential binding of BabA and SabA to ABO and Lewis blood group antigens (33).

### *Wnt/β-catenin and Hippo (YAP/TAZ) Signaling*

The Hippo pathway controls cell proliferation and tissue balance through YAP and TAZ activation. In gastric cancer and *H. pylori* infection, Hippo signaling is often disrupted. *H. pylori* - induced inflammation promotes nuclear β-catenin accumulation and CagA impairs Hippo kinases via Src/FAK activation, allowing YAP/TAZ nuclear translocation. YAP/TAZ cooperate with NF-κB and STAT3 to drive oncogenic genes. *H. pylori* - triggered NF-κB also induces YAP-dependent genes like CTGF, altering the tumor micro-environment. Wnt/β-catenin signaling further suppresses Hippo kinases, reinforcing tumorigenic feedback loops (34).

### *MAPK/ERK and PI3K/Akt Pathways*

*H. pylori* exploits key signaling pathways like ERK/MAPK and PI3K/Akt via CagA, promoting cell motility, the "hummingbird" phenotype, and apoptosis resistance. MAPK signaling drives proliferation, invasion, and metastasis in gastric cancer, often altered by genetic and epigenetic changes. VacA and outer membrane proteins also activate ERK and Akt, enhancing survival of damaged epithelial cells (35).

*H. pylori* orchestrates a complex oncogenic network involving STAT3, NF-κB, Wnt, and Hippo pathways. These interact extensively: NF-κB upregulates β-catenin and STAT3, which boosts Hippo effectors. This cross-talk drives proliferation, apoptosis evasion, epithelial-mesenchymal transition, and genomic instability, leading to gastric cancer progression (36).

### *Host Response: Inflammation and Immune Modulation*

Gastric cancer remains a leading cause of cancer worldwide despite a declining incidence, ranking fifth in new cases and fourth in cancer mortality. *H. pylori* infection induces chronic gastric inflammation that drives malignant transformation through sustained production of pro-inflammatory cytokines, genomic instability, angiogenesis, and suppression of antitumor immunity (36,37).

Chronic infection causes gastric atrophy and hypochlorhydria, promoting precancerous changes such as intestinal metaplasia and dysplasia. *H. pylori* colonization provokes cytokine release from immune cells, regulated by suppressors of cytokine signaling (SOCS) proteins. Dysregulation

of SOCS, especially SOCS1, SOCS2, SOCS3, and SOCS6, facilitates immune evasion and persistent inflammation contributing to gastric carcinogenesis (38). The bacterium also triggers production of reactive oxygen and nitrogen species (ROS/RNS) by neutrophils and epithelial cells. Although these species are part of host defense, *H. pylori* counters oxidative stress via antioxidant enzymes, yet chronic ROS exposure leads to DNA, lipid, and protein damage, disrupting cell signaling and function, and sustaining inflammation that promotes tumor progression (39).

Cytokines shape the tumor microenvironment (TME), affecting gastric cancer (GC) progression and immunity. IL-17, elevated in *H. pylori* infection and autoimmune gastritis, links chronic Th17 inflammation to gastric neoplasia. IL-17A has dual roles: promoting tumor growth via proliferation, angiogenesis, and immune recruitment, or supporting anti-tumor immunity. Its effect depends on TME context. Though a potential immuno-therapy target, IL-17's complex actions require further study, especially regarding combination with checkpoint inhibitors (40).

A key element of the host immune response to *H. pylori* involves the interleukin-1 (IL-1) cytokine family, comprising IL-1α, IL-1β, IL-1 receptor antagonist (IL-1RA), IL-18, IL-33, and the IL-36 subfamily (41). Among these, IL-1β is the most extensively characterized due to its strong pro-inflammatory properties. Early during infection, gastric epithelial and immune cells produce substantial amounts of cytokines such as IL-1β, IL-6, IL-8, IL-17, and tumor necrosis factor-alpha (TNF-α). IL-1β is secreted by diverse immune and stromal cell types - including neutrophils, monocytes, macrophages, lymphocytes, fibroblasts, dendritic cells, and endothelial cells - and plays a central role in orchestrating inflammatory responses to infection and tissue injury.

Within *H. pylori* - induced inflammation, interleukin-1 beta (IL-1β) is a key mediator in gastric cancer (GC) pathogenesis. It contributes to tumor initiation and progression by promoting immune-driven tissue injury, inhibiting gastric acid secretion, recruiting bone marrow-derived cells, enhancing angiogenesis, and facilitating cancer cell invasion and metastasis (42). IL-1β also upregulates adhesion molecules like ICAM-1, VCAM-1, E-selectin, and E-cadherin, as well as cytokines including IL-6, IL-8, IL-10, IL-13, MCP-4, TNF-α, and IP-10. Although IL-1β's pro-inflammatory role is established, its direct impact on tumor progression remains under investigation (42).

The host immune reaction to *H. pylori* presents a paradox. On one side, the infection provokes a vigorous inflammatory response capable of causing tissue damage; on the other, the bacterium has developed strategies to evade immune clearance, enabling persistent colonization. Typically, the infection stimulates a Th1/Th17-dominant immune profile in the gastric mucosa, characterized by elevated levels of interferon-gamma (IFN-γ), IL-1ß, IL-17, and TNF-α (24).

*H. pylori* also activates regulatory immune pathways. Gastric tissues from infected patients often show increased $CD4^+FOXP3^+$ regulatory T cells (Tregs) and elevated IL-10 and TGF-ß, which suppress antibacterial responses (43). In children with high *H. pylori* colonization, a lower IL-17A/FOXP3 mRNA ratio suggests Treg dominance over Th17 cells, promoting immune tolerance and bacterial persistence while potentially aiding tumor immune evasion. Systemic inflammation is also enhanced, with meta-analyses showing higher IL-6 and TNF-α levels in *H. pylori* - positive individuals compared to controls. Gastric cancer patients display broader cytokine elevations, including IL-6, IL-7, IL-10, IL-12, and TNF-α. Elevated IL-6 correlates geographically with GC incidence. IL-6-driven STAT3 activation links chronic inflammation to tumor growth, while IL-10 from Tregs and tumor cells may suppress anti-tumor immunity (24).

A particularly recent discovery reveals that *H. pylori* can manipulate immune checkpoint pathways. Studies have shown that the bacterial virulence factor CagA upregulates programmed death-ligand 1 (PD-L1) expression on gastric epithelial cells, thereby inhibiting T-cell function. For instance, Liu and colleagues demonstrated that CagA induces squalene epoxidase (SQLE), an enzyme that promotes palmitoylation and stabilization of PD-L1. This results in enhanced PD-L1-driven suppression of cytotoxic T lymphocytes, facilitating immune escape (44).

Further work indicates that CagA elevates PD-L1 levels in tumor-derived exosomes by inhibiting the tumor suppressor p53 and microRNA miR-34a, which suppresses $CD8^+$ T-cell proliferation. These findings highlight the ability of *H. pylori* to foster an immunosuppressive tumor microenvironment through PD-L1 pathways, akin to intrinsic cancer mechanisms. This immune evasion strategy is an active focus of research with important implications for immunotherapy approaches in GC (45,46).

A comprehensive review has also explored possible links between *H. pylori* infection and

extra-gastric malignancies. Virulence factors secreted by *H. pylori*, potentially disseminated via exosomes or other molecular vehicles, can modulate immune responses, perpetuate chronic inflammation, and disrupt cellular processes such as proliferation and apoptosis. These mechanisms suggest a potential role in tumorigenesis beyond the stomach. Although *H. pylori* - derived exosomes have been implicated in several inflammatory diseases, including atherosclerosis, hepatic fibrosis, and neurodegenerative disorders like Alzheimer's disease, definitive evidence directly associating them with extra-gastric cancers remains limited, likely reflecting the complexity and emerging nature of this research area.

Research into the carcinogenic role of *H. pylori* -associated exosomes faces several technical challenges. These include the need for reliable, long-term animal models, fine-tuning protocols for exosome delivery, and pinpointing the exact molecular agents driving cancer development. Furthermore, the epithelial barriers of the host, along with immune defenses, and resident microbiota - especially in organs like the intestines and lungs - are crucial for preserving tissue equilibrium, which may be disrupted by persistent *H. pylori* infection, thereby enabling malignant transformation.

Shifts in the gut and systemic microbiome, frequently observed in cancers such as colorectal and prostate malignancies, may result from chronic inflammation and immune dysregulation induced by pathogens including *H. pylori* (22). Emerging evidence indicates that *H. pylori* infection can cause microbial community changes beyond the stomach, influencing both bacterial and viral populations. Nonetheless, detailed mechanistic understanding of these alterations and their direct links to cancer outside the gastric environment remain limited. Cutting-edge methods such as spatial transcriptomics and viral metagenomics offer promising avenues to unravel the spatial and functional interactions between microbes and host cells in the context of extra-gastric cancers (47).

### *Epigenetic and Post-Transcriptional Regulation*

Gastric cancer (GC) shows significant phenotypic heterogeneity, often classified into gastric, intestinal, mixed, and unclassified types based on mucin expression. MUC5AC and MUC6 indicate the gastric subtype, while MUC2 and CD10 mark the intestinal type. Tumor progression frequently involves a shift from gastric to intestinal mucin profiles, especially in intestinal-type adenocarcinomas. MUC5AC protects the gastric mucosa from acid, whereas MUC6 limits *H. pylori* colonization. Loss of MUC6, common in advanced GC or complete intestinal metaplasia, may weaken this defense and promote carcinogenesis (48).

Gastric-type tumors often display microsatellite instability, CDH1 mutations, and MLH1 methylation, while intestinal-type cancers typically show TP53 mutations, APC deletions, and MGMT promoter methylation. SOX2 sustains gastric identity by enhancing MUC5AC and pepsinogen A, while suppressing CDX2, which drives intestinal differentiation (49). Gastric-type tumors tend to respond better to fluorouracil-based chemotherapy and have a better prognosis, while intestinal-type tumors are frequently chemoresistant due to anti-apoptotic proteins like REG4 and ABCB1. Experimental therapies targeting mucin pathways, including MAPK inhibitors and mucin-directed drugs, offer promising personalized strategies (48).

The infectious basis of most gastric cancers has focused attention on *H. pylori* virulence factors, especially VacA and CagA, which drive chronic inflammation, epithelial damage, and carcinogenesis. VacA induces vacuolization, mitochondrial dysfunction, and apoptosis, while CagA, injected via a type IV secretion system, disrupts cell cycle control and apoptosis. *H. pylori* evades immunity by modulating autophagy and apoptosis, promoting bacterial survival and antibiotic resistance. Early in infection, bacteria are sequestered in autophagosomes within 12 hours, shielding them from gastric acid and immune attack. This suggests therapeutic options like exosome-based or nanomedicine targeting intracellular *H. pylori*. Acute infection promotes autophagosome formation but impairs their degradation, enabling intracellular replication. Additionally, *H. pylori* alters host metabolism by increasing tricarboxylic acid cycle and amino acid activity, possibly influencing MTORC1 signaling in immune and gastric epithelial cells (50).

*H. pylori* uses its type IV secretion system (T4SS) to inject effectors like CagA and LPS intermediates (ADP-heptose, HBP) into host cells. ADP-heptose activates NF-κB via the ALPK1–TIFA pathway. CagA, once phosphorylated, activates ERK, inhibits tumor suppressors (p14^ARF, Siva1), promotes anti-apoptotic cIAP2, and disrupts cell polarity and adhesion through interactions with ZO-1, E-cadherin, and claudin-7, supporting EMT and invasion. CagA enhances bacterial survival in iron-deficient conditions by promoting iron uptake and increasing T4SS expression. Additionally,

*H. pylori* depletes membrane cholesterol via cholesterol-α-glucosyltransferase, weakening IFN-γ signaling and facilitating immune evasion.

*H. pylori* induces genomic instability by impairing DSB repair—CagA suppresses Rad51 and BRCA1 nuclear entry, and T4SS activity, combined with ROS production, promotes DNA damage. Nucleotide excision repair enzymes XPG and XPF contribute to DSB formation, especially in telomeric and active genomic regions, mirroring mutations seen in gastric cancers (51).

Chronic *H. pylori* infection triggers profound epigenetic reprogramming within the gastric epithelium, a key factor in GC development (52). A primary mechanism involves aberrant DNA methylation, especially hypermethylation of tumor suppressor gene promoters like CDH1, p16, p14^ARF, and FOXD3. These methylation changes impair genes critical for genomic stability, apoptosis, and cell cycle control, locking cells into aberrant proliferation. Concurrently, demethylation of oncogenic loci such as GNB4, which activates the Hippo/YAP signaling pathway, further enhances cell proliferation and malignant transformation. Alterations in histone modifications caused by *H. pylori* also contribute to chromatin remodeling that favors neoplastic progression (53).

*H. pylori* profoundly alters non-coding RNA expression, impacting microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs). Oncogenic miRNAs like miR-21 are upregulated, while tumor-suppressive miRNAs such as miR-34a are downregulated, partly through CagA-mediated p53 disruption. These miRNAs control proliferation, apoptosis, immune evasion, and genomic stability, and may serve as early biomarkers for *H. pylori* - induced precancerous changes.

*H. pylori* also modulates lncRNAs (e.g., HOTAIR, MEG3, ANRIL), which interact with NF-κB, Wnt/β-catenin, and EMT pathways, epigenetically silencing tumor suppressors and enhancing oncogenic signals.

Additionally, circRNAs like circMAN1A2, circFNDC3B, and circ_15430 are dysregulated during infection, promoting tumor growth by sponging tumor-suppressive miRNAs or releasing oncogenic factors. The complex interaction between *H. pylori*, host non-coding RNAs, and genetic susceptibility plays a key role in gastric carcinogenesis (54).

Genome-wide studies reveal *H. pylori* polymorphisms in outer membrane protein genes (babA, hop, cagX/Y) and iron acquisition/adhesion genes (fur, frpB3, oipA) that boost colonization and virulence. A key mutation (S171L) in the HtrA protease enhances CagA translocation, activates NF-κB, and stimulates epithelial proliferation.

Host genetics also influence gastric cancer risk; specific HLA class I/II alleles (e.g., HLA-DQB106, HLA-G01, HLA-DQB103) affect antigen presentation and immune response. Polymorphisms in cytokine and innate immunity genes (IL-1ß, TNF-α, TLRs) modulate inflammation and cancer progression.

These findings support a host-pathogen co-evolution model, where virulent *H. pylori* strains trigger oncogenic epigenetic and transcriptomic changes, particularly in genetically susceptible hosts, leaving lasting cancer-promoting effects even after transient infection (2).

Only some intestinal metaplasia (IM) cases progress to cancer, with high-risk lesion features still unclear. A study using FISH on gastrectomy samples from five patients identified short telomere lesions (STLs) within IM - regions with significant telomere shortening but no clear carcinoma. Histologically, STLs corresponded to dysplastic metaplasia (DM), showing enlarged nuclei without marked architectural atypia. In a larger cohort of 587 *H. pylori* - positive biopsies, 32 DM cases were found, 13 high-grade, characterized by severe telomere shortening (<60% lymphocyte signal), elevated TERT expression, and stem cell markers. About 15% showed low nuclear p53. Over ten years, 54% of high-grade DM progressed to gastric cancer. These data indicate high-grade DM as a telomere erosion-driven, dedifferentiated IM subtype with strong malignant potential, critical for early detection in *H. pylori* - infected patients (55),

### *Tumor Microenvironment and Immune Contexture*

*H. pylori* is definitively classified as a Group I carcinogen by both the World Health Organization (WHO) and the International Agency for Research on Cancer (IARC), playing a pivotal role in the pathogenesis of GC as well as gastric mucosa-associated lymphoid tissue (MALT) lymphoma (11).

Chronic infection with *H. pylori* represents the foremost risk factor for non-cardia GC. The carcinogenic process induced by *H. pylori* generally follows the sequence described in Correa's cascade, beginning with chronic active gastritis, advancing to atrophic gastritis, followed by intestinal metaplasia and dysplasia, culminating in gastric carcinoma (56).

### *Immune Evasion and Modulation by H. pylori*

Infection with *H. pylori* elicits intricate and sometimes contradictory immune responses, which are initially protective but may later become harmful. Natural Killer (NK) cells, key players in innate immunity, are activated early; however, *H. pylori* components can suppress their cytotoxic activity by decreasing production of interferon-gamma (IFN-γ) and interleukin-2 (IL-2), reducing perforin expression, and maintaining elevated levels of interleukin-10 (IL-10), an immuno-suppressive cytokine (57), Through the lipopolysaccharide (LPS) - Toll-like receptor 4 (TLR4) pathway, *H. pylori* may facilitate GC progression. The bacterial outer membrane protein HopQ binds to carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM1) on activated NK cells, directly impairing their function. Moreover, a specific *H. pylori* peptide, Hp(2-20), stimulates monocytes to generate reactive oxygen species (ROS), further dampening NK cell-mediated anti-tumor cytotoxicity and promoting apoptosis. The infection skews the immune milieu toward a type 2 response, mediated by group 2 innate lymphoid cells (ILC2s) and the transcription factor GATA-3, resulting in a suppressed Th1 immune axis. Prolonged activation of ILC2s may paradoxically enhance tumor growth (57).

### *Microenvironmental Alterations and Dysbiosis*

An expanding body of research has revealed a significant association between the gastric microbiota and both the pathogenesis and therapeutic outcomes of GC (58).

This growing evidence prompts reconsideration of GC development mechanisms, extending focus beyond *H. pylori* to encompass other microbial players (59). Metagenomic studies in humans consistently demonstrate dysbiosis in GC, supporting the emerging "*H. pylori* initiation – non-*H. pylori* acceleration" paradigm, as exemplified by the involvement of Streptococcus anginosus in gastric tumorigenesis. Furthermore, probiotics show potential in modulating GC risk either directly through interactions with the gastric mucosa or indirectly via antagonism of *H. pylori*. Continued research into the diagnostic, prognostic, and therapeutic roles of the gastric microbiome offers promising clinical implications (60).

A recent bibliometric analysis assessed the scientific landscape regarding GC and the gastric microbiota, aiming to map current research trends and highlight emerging focal points. Reviewing 215 publications, the study noted a steady increase in output over time, accompanied by a parallel rise in funding dedicated to this field. China led in publication volume, while the United States held the highest betweenness centrality, reflecting its critical role in fostering international research collaborations (61).

Within academic journals, *H. pylori* was most dedicated to this niche area, whereas Gut provided a strong scientific foundation for related investigations (5).

Citation burst analysis indicates that forthcoming research will likely concentrate on the clinical significance and pathogenic role of gastric microbes, particularly Fusobacterium nucleatum, in the context of GC diagnostics and treatment strategies (62).

*H. pylori* markedly modifies the gastric microenvironment, establishing conditions that favor its colonization and play a role in carcinogenesis. Through urease activity, it converts urea into ammonia and bicarbonate, which elevates gastric pH and neutralizes stomach acid, thereby promoting its survival and growth (56). This suppression of acid secretion, combined with glandular atrophy, induces notable alterations in gastric pH levels. Additionally, *H. pylori* can impair gastric motility, reducing the clearance of toxins and other microbial agents (63). The T4SS effector protein CagL facilitates the detachment of ADAM17 from α5β1 integrins, triggering ADAM17 activation and NF-κB-dependent downregulation of the H,K-ATPase α subunit (HKα), which results in hypochlorhydria. Pro-inflammatory cytokines, including IL-1β and TNF-α, also inhibit gastric acid production (64).

These environmental modifications lead to dysbiosis of the gastric microbiota, a critical contributor to GC development. In individuals infected with *H. pylori*, the bacterium predominates, causing a sharp decline in non-H. pylori microbial populations and reduced overall microbial diversity (65).

Network analyses reveal antagonism between Helicobacter and other gastric microbes, promoting ectopic colonization by oral bacteria (66). While *H. pylori* load initially increases, it declines as gastric lesions progress, allowing other species to thrive. Oral and intestinal commensals, once considered "passengers," become enriched and actively contribute to gastric cancer, either alongside residual *H. pylori* or independently. Helicobacter amplicon sequence variants (ASVs) show mutual exclusivity, reflecting niche competition. Gastric fluid microbiome dysbiosis parallels mucosal

changes during cancer development (64).

Recent research shows major changes in gastric microbiota during gastric cancer development, which may serve as biomarkers. These shifts promote an immunosuppressive tumor microenvironment aiding immune evasion. *H. pylori* modulates immunity, sometimes dampening responses and therapy effectiveness, but also activating immune pathways via virulence factors. However, the exact roles of gastric microbes in cancer and immune regulation are unclear. Conflicting retrospective data reflect complex host-microbiota-tumor interactions and methodological differences in sequencing. Future studies need standardized, longitudinal, high-resolution microbial analyses (66).

Data on non-*H. pylori* microbes in gastric cancer are limited. Research should focus on their tumorigenic roles beyond taxonomy. Clinical use is hindered by invasive sampling and stomach acidity. Non-invasive microbial biomarkers and innovative therapies like engineered probiotics show promise but require further validation.

### *Role of Non-*H. pylori Microbiota in Carcinogenesis*

Beyond *H. pylori*, additional microorganisms contribute to gastric carcinogenesis. Oral microbes are significantly enriched in GC compared to precancerous conditions. Specific oral bacteria including Prevotella, Rothia, Peptostreptococcus, Parvimonas, and Streptococcus species have been implicated in gastritis and intestinal metaplasia. Streptococcus anginosus promotes gastric inflammation, atrophy, and tumorigenesis in murine models by compromising barrier integrity and activating oncogenic MAPK signaling via its lipoprotein TMPC and Annexin A2 (ANXA2) receptor. Intestinal bacteria such as Romboutsia, Fusicatenibacter, Prevotellaceae-Ga6A1-group, and Intestinimonas are found in elevated abundance in gastric intraepithelial neoplasia (64,67).

Lactobacillus species frequently appear in GC patients; some hypotheses propose their involvement in GC pathogenesis through lactic acid production, induction of reactive oxygen species (ROS), and promotion of angiogenesis, whereas alternative theories suggest a potential anti-tumor role (64).

Lipopolysaccharide (LPS)-producing bacteria, such as Prevotella melaninogenica, are increased in GC and may drive inflammation and pre-neoplastic lesion formation via activation of the IL-6/JAK1/STAT3 pathway, often associated with bile acid metabolism. Microbes involved in nitrate and nitrite metabolism - including Clostridium, Lactobacillus, and Neisseria - are overrepresented in GC, facilitating conversion of nitrate to nitrite, a precursor for N-nitroso compounds (NOCs) known to induce DNA damage. Conversely, Nitrospira, a nitrite-oxidizing type, is reduced (68).

Epigenetic regulation mediated by the microbiota represents a novel mechanism in gastric carcinogenesis. Fusobacterium nucleatum has been shown to reduce DNA methylation of LINE1 elements. Species such as Kytococcus sedentarius, Actinomyces oris, and Staphylococcus saccharolyticus modulate DNA methylation patterns of immune-related genes, thereby facilitating metastatic processes. Additionally, F. nucleatum disrupts actin cytoskeletal dynamics and promotes exosomal transfer of HOTTIP, which accelerates progression of GC. Its virulence factors, Fap2 and FadA, assist in bacterial localization and activate ß-catenin/Wnt signaling pathways. Lipopolysaccharide (LPS) derived from F. nucleatum triggers NF-κB activation via TLR4/MYD88 signaling (69).

Non-bacterial constituents of the gastric microbiota, including fungi such as Candida species and Mycoplasma hyorhinis, also contribute to GC progression. M. hyorhinis mediates its effects through lipoprotein P37 and engages pathways involving EGFR-NF-κB, matrix metalloproteinase-2 (MMP-2), lysosome-associated membrane protein (LAMP), Toll-like receptor 2 (TLR2), NLRP3 inflammasome, and specific methyltransferases (64).

### *Persistence Mechanisms*

The chronic persistence of *H. pylori* infection is aided by biofilm formation, which protects against gastric acidity via urease activity and the BabA adhesin. Biofilm transcriptomics show increased expression of adhesins, flagella, toxins, efflux pumps, LPS, type IV secretion system components, urease, and hydrogenase, while genes for quorum sensing, metabolism, and translation decrease. Mature biofilms produce outer membrane vesicles, adopt a resistant coccoid form, generate extracellular matrix, and boost efflux pump activity (70). Collectively, these mechanisms improve its ability to penetrate the mucus barrier, adhere to epithelial cells, and colonize gastric glands. Furthermore, *H. pylori* evades complement-mediated clearance by exploiting L-lactate to inhibit C4b deposition on its surface via the classical complement pathway (71).

### *Prevention and Therapeutic Implications*

Eradication of *H. pylori* remains a key preventive measure against GC, reducing the risk by approximately 33% to 47%. However, eradication does not entirely abolish the risk of GC development, partly because fewer than 3% of infected individuals eventually develop the disease, and gastric microbial dysbiosis can persist post-eradication. The rising incidence of *H. pylori*-negative GC further emphasizes the role of non-*H. pylori* microbes in gastric carcinogenesis, acting either synergistically with residual *H. pylori* or independently (56,72).

Probiotics like Bifidobacterium and Lactobacillus may help restore balance, suggesting gastric cancer can progress independent of *H. pylori* via non-*H. pylori* microbial disruptions (60). Given that *H. pylori* is an established carcinogen, eradication strategies have been a major focus for GC prevention (73).

Recent evidence from meta-analyses of randomized and observational studies confirms that *H. pylori* eradication significantly lowers gastric cancer (GC) risk. A 2025 meta-analysis of 11 randomized controlled trials involving over 100,000 participants found a pooled relative risk (RR) of 0.61 (95% CI, 0.47–0.79) for GC in those receiving eradication therapy. Subgroup analyses indicated stronger effects in high-risk groups: patients treated with endoscopic mucosal resection (EMR) had a RR of 0.51 (95% CI, 0.36–0.71), while *H. pylori*-positive adults without precancerous changes showed a reduction around 0.67 (74).

A concurrent systematic review, combining both randomized and observational studies, echoed these findings. Eradication reduced GC risk to 0.64 (95% CI, 0.48–0.84) in healthy individuals and to 0.52 (95% CI, 0.38–0.71) post-EMR. Observational data yielded similar protective effects (RR ~0.56).

These outcomes emphasize the preventive benefit of *H. pylori* eradication, especially in East Asia. The number needed to treat (NNT) to prevent one GC case is about 332. However, despite reduced incidence, overall mortality remains unchanged, likely due to the aggressive course of *H. pylori*-associated cancers (75).

Behavioral and host-related factors play significant roles: smoking and alcohol consumption notably reduce treatment efficacy in men, likely due to alterations in gastric acid secretion and drug bioavailability. The MITS study identified that a high baseline bacterial load, assessed via DOB values, and elevated BMI in women are predictors of eradication failure, suggesting that longer therapy durations (10-14 days) may be advantageous. Missed doses, particularly among educated women, were also correlated with unsuccessful eradication. Moreover, host genetic polymorphisms - such as variants in CYP2C19 and IL1B - influence drug metabolism and acid suppression, thereby impacting therapeutic outcomes (76).

Surveillance of *H. pylori*-infected patients at risk for gastric cancer is evolving. Endoscopic monitoring is now advised for those with intestinal metaplasia or a family history of GC, regardless of infection status. Serologic screening using pepsinogen I/II ratios helps detect advanced atrophy in some populations, reflecting a shift toward cancer prevention (48).

Gastric cardiac carcinoma (GCC), arising near the gastroesophageal junction, is a slow-progressing but lethal cancer (77).

*H. pylori*, especially CagA- and VacA-positive strains, drives GC by causing inflammation, epithelial damage, DNA injury, and epigenetic changes. Rising antibiotic resistance threatens current eradication regimens, highlighting the need for alternative therapies (78).

## Conclusion

*H. pylori* infection represents the most well-established microbial cause of gastric cancer. Through a multifaceted mechanism involving virulence factors (e.g., CagA, VacA), immune evasion, chronic inflammation, and epigenetic remodeling, the bacterium fosters a microenvironment conducive to carcinogenesis. While eradication of *H. pylori* reduces gastric cancer incidence, it does not fully negate oncogenic risk, particularly in patients with established atrophic gastritis or intestinal metaplasia. Moreover, emerging data implicate additional components of the gastric microbiota in tumor progression. As such, effective cancer prevention strategies must extend beyond bacterial eradication to encompass host susceptibility, microbial dysbiosis, and immune modulation. Future directions include the development of microbiome-informed diagnostics, risk stratification tools, and novel interventions targeting both *H. pylori* and the broader gastric ecosystem.

### *Conflict of Interests*

The authors declare no conflicts of interests.

## References


1. Salvatori S, Marafini I, Laudisi F, Monteleone G, Stolfi C. *Helicobacter pylori* and gastric cancer: pathogenetic mechanisms. Int J Mol Sci. 2023; 24(3):2895.
2. Duan Y, Xu Y, Dou Y, Xu D. *Helicobacter pylori* and gastric cancer: mechanisms and new perspectives. J Hematol Oncol. 2025;18(1):10.
3. Tan Y, Matsuzaki J, Saito Y, Suzuki H. Environmental factors in gastric carcinogenesis and preventive intervention strategies. Genes Environ. 2025;47(1):5.
4. Kashyap D, Rele S, Bagde PH, Saini V, Chatterjee D, Kumar Jain A, et al. Comprehensive insight into altered host cell-signaling cascades upon *Helicobacter pylori* and Epstein–Barr virus infections in cancer. Arch Microbiol. 2023;205(7):262.
5. Vanoli A, Parente P, Fassan M, Mastracci L, Grillo F. Gut inflammation and tumorigenesis: every site has a different tale to tell. Intern Emerg Med. 2023; 18(8):2169-2179.
6. Chey WD, Howden CW, Moss SF, Morgan DR, Greer KB, Grover S, et al. ACG Clinical Guideline: treatment of *Helicobacter pylori* infection. Am J Gastroenterol. 2024;119(9):1730-1753.
7. Melit LE, Marginean CO, Borka Balas R. The most recent insights into the roots of gastric cancer. Life (Basel). 2024;14(1):95.
8. Chivu R, Evanghelides A, Georgescu DE, Patrascu T. Navigating through surgical implications of *Helicobacter pylori*: an up-to-date comprehensive literature review. Chirurgia (Bucur). 2023;118(6):568-583.
9. de Assumpção PP, Genta RM, Camargo MC, da Silva JMC, Amieva MR, Rugge M. The Landscape of *Helicobacter pylori* - related gastric carcinogenesis. J Gastrointestin Liver Dis. 2024;33(4):524-534.
10. Liao W, Wang J, Li Y. Natural products based on Correa's cascade for the treatment of gastric cancer trilogy: Current status and future perspective. J Pharm Anal. 2025;15(2):101075. Epub 2024 Aug 19.
11. Mobley HLT, Mendz GL, Hazell SL. *Helicobacter pylori*: physiology and genetics. Chapter 40 - Gastric Cancer. Asaka M, Sepulveda AR, Sugiyama T, Graham DY, eds. Washington (DC): ASM Press; 2001.
12. Sugano K, Moss SF, Kuipers EJ. Gastric intestinal metaplasia: real culprit or innocent bystander as a precancerous condition for gastric cancer? Gastroenterology. 2023;165(6):1352-1366.e1.
13. Myrou A. Molecular mechanisms and treatment strategies for *Helicobacter pylori* - induced gastric carcinogenesis and mucosa-associated lymphoid tissue (MALT) lymphoma. Cureus. 2024;16(5):e60326.
14. Drnovsek J, Homan M, Zidar N, Smid LM. Pathogenesis and potential reversibility of intestinal metaplasia - a milestone in gastric carcinogenesis. Radiol Oncol. 2024;58(2):186-195.
15. Mostaghimi T, Bahadoran E, Bakht M, Taheri S, Sadeghi H, Babaei A. Role of lncRNAs in *Helicobacter pylori* and *Epstein-Barr* virus associated gastric cancers. Life Sci. 2024;336:122316.
16. Banisefid E, Nasiri E, Leilabadi SP, Hamzehzadeh S, Akbarzadeh MA, Hosseini MS. The paradox of *Helicobacter pylori*: how does H. pylori infection protect against esophageal cancer? Ann Med Surg (Lond). 2024;86(12):7221-7226.
17. Li Y, Choi H, Leung K, Jiang F, Graham DY, Leung WK. Global prevalence of *Helicobacter pylori* infection between 1980 and 2022: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol. 2023;8(6):553-564.
18. Takahashi-Kanemitsu A, Knight CT, Hatakeyama M. Molecular anatomy and pathogenic actions of *Helicobacter pylori* CagA that underpin gastric carcinogenesis. Cell Mol Immunol. 2020;17(1):50-63.
19. Shirani M, Pakzad R, Haddadi MH, Akrami S, Asadi A, Kazemian H, et al. The global prevalence of gastric cancer in *Helicobacter pylori* -infected individuals: a systematic review and meta-analysis. BMC Infect Dis. 2023;23(1):543.
20. Delgado-Guillena P, Jimeno M, López-Nuñez A, Córdova H, Fernández-Esparrach G. The endoscopic model for gastric carcinogenesis and *Helicobacter pylori* infection: a potential visual mind-map during gastroscopy examination. Gastroenterol Hepatol. 2024;47(10):502214.
21. Chivu RF, Bobirca F, Melesteu I, Patrascu T. The role of *Helicobacter pylori* infection in the development of gastric cancer - review of the literature. Chirurgia (Bucur). 2024;119(eCollection):1-10.
22. Chattopadhyay I, Gundamaraju R, Rajeev A. Diversification and deleterious role of microbiome in gastric cancer. Cancer Rep (Hoboken). 2023;6(11):e1878.
23. Zhang C, Chen Y, Long Y, Zheng H, Jing J, Pan W. *Helicobacter pylori* and Gastrointestinal Cancers: Recent Advances and Controversies. Clin Med Insights Oncol. 2024;18:11795549241234637. eCollection 2024.
24. Yu B, Xiang L, Peppelenbosch MP, Fuhler GM. Overlapping cytokines in *H. pylori* infection and gastric cancer: A tandem meta-analysis. Front Immunol. 2023; 14:1125658.
25. Waldum H, Mjønes P. The central role of gastrin in gastric cancer. Front Oncol. 2023;13:1176673.
26. Waldum H, Fossmark R. Inflammation and digestive cancer. Int J Mol Sci. 2023;24(17):13503.
27. Naing C, Aung HH, Aye SN, Poovorawan Y, Whittaker MA. CagA toxin and risk of *Helicobacter pylori* infected gastric phenotype: A meta-analysis of observational studies. PLoS One. 2024;19(8):e0307172.
28. Elbehiry A, Marzouk E, Abalkhail A, Sindi W, Alzahrani Y, Alhifani S, et al. Pivotal role of *Helicobacter pylori* virulence genes in pathogenicity and vaccine development. Front Med (Lausanne). 2025;11:1523991. eCollection 2024.
29. Gu Y, Xu Y, Wang P, Zhao Y, Wan C. Research progress on molecular mechanism of pyroptosis caused by *Helicobacter pylori* in gastric cancer. Ann Med Surg (Lond). 2024;86(4):2016-2022.
30. Lim MCC, Jantaree P, Naumann M. The conundrum of *Helicobacter pylori* - associated apoptosis in gastric cancer. Trends Cancer. 2023;9(8):679-690.
31. Han L, Shu X, Wang J. *Helicobacter pylori* - mediated oxidative stress and gastric diseases: A Review. Front Microbiol. 2022;13:811258.
32. Ray A, Moore TF, Pandit R, Burke AD, Borsch DM. An overview of selected bacterial infections in cancer. Their virulence factors, and some aspects of infection management. Biology (Basel). 2023;12(7):963.
33. Xu H, Huang K, Shi M, Gong H, Han M, Tian W, et al. MicroRNAs in *Helicobacter pylori* - infected gastric cancer: function and clinical application. Pharmacol Res. 2024;205:107216.
34. Messina B, Lo Sardo F, Scalera S, Memeo L, Colarossi C, Mare M, et al. Hippo pathway dysregulation in gastric cancer: from Helicobacter pylori infection to tumor promotion and progression. Cell Death Dis. 2023;14(1):21.
35. Yuan W, Shi Y, Dai S, Deng M, Zhu K, Xu Y, et al. The role of MAPK pathway in gastric cancer: unveiling molecular crosstalk and therapeutic prospects. J Transl Med. 2024;22(1):1142.
36. Shirani M, Shariati S, Bazdar M, Ghamnak FS, Moradi M, Khozani RS, et al. The immunopathogenesis of Helicobacter pylori-induced gastric cancer: a narrative review. Front Microbiol. 2024;15:1395403.
37. Wang X, Zhao G, Shao S, Yao Y. Helicobacter pylori triggers inflammation and oncogenic transformation by perturbing the immune microenvironment. Biochim Biophys Acta Rev Cancer. 2024;1879(5):189139.
38. Jafarzadeh A, Jafarzadeh Z, Nemati M, Yoshimura A. The interplay between *Helicobacter pylori* and suppressors of cytokine signaling (SOCS) molecules in the development of gastric cancer and induction of immune response. Helicobacter. 2024;29(3):e13105.
39. Wu S, Chen Y, Chen Z, Wei F, Zhou Q, Li P, et al. Reactive oxygen species and gastric carcinogenesis: The complex interaction between *Helicobacter pylori* and host. Helicobacter. 2023;28(6):e13024.
40. Li W, Huang X, Han X, Zhang J, Gao L, Chen H. IL-17A in gastric carcinogenesis: good or bad? Front Immunol. 2024;15:1501293.
41. Ge Y, Janson V, Dong Z, Liu H. Role and mechanism of IL-33 in bacteria infection related gastric cancer continuum: from inflammation to tumor progression. Biochim Biophys Acta Rev Cancer. 2025;1880(2):189296.
42. Yuan XY, Zhang Y, Zhao X, Chen A, Liu P. IL-1$\beta$, an important cytokine affecting *Helicobacter pylori* - mediated gastric carcinogenesis. Microb Pathog. 2023; 174:105933. Epub 2022 Dec 6.
43. Zhang L, Zhao M, Fu X. Gastric microbiota dysbiosis and *Helicobacter pylori* infection. Front Microbiol. 2023;14:1153269.
44. Liu S, Zhang N, Ji X, Yang S, Zhao Z, Li P. *Helicobacter pylori* CagA promotes gastric cancer immune escape by upregulating SQLE. Cell Death Dis. 2025;16(1):17.
45. Ziogou A, Giannakodimos A, Giannakodimos I, Schizas D, Charalampakis N. Effect of *Helicobacter pylori* infection on immunotherapy for gastrointestinal cancer: a narrative review. Immunotherapy. 2025;17(5):355-368.
46. Wang J, Deng R, Chen S, Deng S, Hu Q, Xu B, et al. *Helicobacter pylori* CagA promotes immune evasion of gastric cancer by upregulating PD-L1 level in exosomes. iScience. 2023;26(12):108414.
47. Zhao SQ, Zheng HL, Zhong XT, Wang ZY, Su Y, Shi YY. Effects and mechanisms of *Helicobacter pylori* infection on the occurrence of extra-gastric tumors. World J Gastroenterol. 2024;30(37):4090-4103.
48. Arai J, Hayakawa Y, Tateno H, Fujiwara H, Kasuga M, Fujishiro M. The role of gastric mucins and mucin-related glycans in gastric cancers. Cancer Sci. 2024; 115(9):2853-2861.
49. Danilova NV, Oleynikova NA. E-cadherin: structure and functions, role in gastric cancer carcinogenesis. Arkh Patol. 2023;85(4):70-77. Russian
50. Nabavi-Rad A, Yadegar A, Sadeghi A, Asadzadeh Aghdaei H, Zali MR, Klionsky DJ, et al. The interaction between autophagy, *Helicobacter pylori*, and gut microbiota in gastric carcinogenesis. Trends Microbiol. 2023;31(10):1024-1043.

51. Beccaceci G, Sigal M. Unwelcome guests – the role of gland-associated *Helicobacter pylori* infection in gastric carcinogenesis. Front Oncol. 2023; 13:1171003.
52. Xi Y, Zhang XL, Luo QX, Gan HN, Liu YS, Shao SH, et al. *Helicobacter pylori* regulates stomach diseases by activating cell pathways and DNA methylation of host cells. Front Cell Dev Biol. 2023;11:1187638.
53. Muhammad JS, Eladl MA, Khoder G. *Helicobacter pylori* - induced dna methylation as an epigenetic modulator of gastric cancer: recent outcomes and future direction. Pathogens. 2019;8(1):23.
54. Ma Q, Yang F, Xiao B, Guo X. Emerging roles of circular RNAs in tumorigenesis, progression, and treatment of gastric cancer. J Transl Med. 2024; 22(1):207.
55. R. Fujiwara-Tani, Takagi T, Mori S, Kishi S, Nishiguchi Y, Sasaki T, et al. Short telomere lesions with dysplastic metaplasia histology may represent precancerous lesions of *Helicobacter pylori* - positive gastric mucosa. Int J Mol Sci. 2023;24(4):3182.
56. Guo Y, Cao XS, Zhou MG, Yu B. Gastric microbiota in gastric cancer: different roles of *Helicobacter pylori* and other microbes. Front Cell Infect Microbiol. 2023;12:1105811.
57. Gilabert-Estellés J, Götte M, McCormack B, Jiao Y, Yan Z, Yang A. The roles of innate lymphoid cells in the gastric mucosal immunology and oncogenesis of gastric cancer. Int J Mol Sci. 2023;24(7):6652.
58. Sgamato C, Rocco A, Compare D, Priadko K, Romano M, Nardone G. Exploring the link between *Helicobacter pylori*, gastric microbiota and gastric cancer. Antibiotics (Basel). 2024;13(6):484.
59. Wu M, Tian C, Zou Z, Jin M, Liu H. Gastrointestinal microbiota in gastric cancer: potential mechanisms and clinical applications - a literature review. Cancers (Basel). 2024;16(20):3547.
60. Zeng R, Gou H, Lau HCH, Yu J. Stomach microbiota in gastric cancer development and clinical implications. Gut. 2024;73(12):2062-2073.
61. Lopes C, Almeida TC, Pimentel-Nunes P, Dinis-Ribeiro M, Pereira C. Linking dysbiosis to precancerous stomach through inflammation: Deeper than and beyond imaging. Front Immunol. 2023;14:1134785.
62. Ke Y, Tan C, Zhen J, Dong W. Global status and trends of gastric cancer and gastric microbiota research: a bibliometric analysis. Front Microbiol. 2024; 15:1341012.
63. Zhou C, Bisseling TM, van der Post RS, Boleij A. The influence of *Helicobacter pylori*, proton pump inhibitor, and obesity on the gastric microbiome in relation to gastric cancer development. Comput Struct Biotechnol J. 2023;23:186-198.
64. Li Y, Hu Y, Zhan X, Song Y, Xu M, Wang S, et al. Meta-analysis reveals *Helicobacter pylori* mutual exclusivity and reproducible gastric microbiome alterations during gastric carcinoma progression. Gut Microbes. 2023; 15(1):2197835.
65. Wang Z, Shao SL, Xu XH, Zhao X, Wang MY, Chen A, et al. *Helicobacter pylori* and gastric microbiota homeostasis: progress and prospects. Future Microbiol. 2023;137-157.
66. Liu Z, Zhang D, Chen S. Unveiling the gastric microbiota: implications for gastric carcinogenesis, immune responses, and clinical prospects. J Exp Clin Cancer Res. 2024;43(1):118.
67. Liao O, Ye G, Du Q, Ye J. Gastric microbiota in gastric cancer and precancerous stages: mechanisms of carcinogenesis and clinical value. Helicobacter. 2023; 28(3):e12964.
68. Lei X, Cui ZY, Huang XJ. Exploration of gastric carcinogenesis from the relationship between bile acids and intestinal metaplasia and intragastric microorganisms (*H. pylori* and non-*H. pylori*). J Cancer Res Clin Oncol. 2023; 149(18):16947-16956.
69. Petkevicius V, Lehr K, Kupcinskas J, Link A. Fusobacterium nucleatum: unraveling its potential role in gastric carcinogenesis. World J Gastroenterol. 2024;30(35):3972-3984.
70. Choi E, Murray B, Choi S. Biofilm and cancer: interactions and future directions for cancer therapy. Int J Mol Sci. 2023;24(16):12836.
71. Xia M, Lei L, Zhao L, Xu W, Zhang H, Li M, et al. The dynamic oral-gastric microbial axis connects oral and gastric health: current evidence and disputes. NPJ Biofilms Microbiomes. 2025;11(1):1.
72. Wang Y, Wang Y, Han W, Han M, Liu X, Dai J, et al. Intratumoral and fecal microbiota reveals microbial markers associated with gastric carcinogenesis. Front Cell Infect Microbiol. 2024;14:1397466.
73. Hatta W, Koike T, Asano N, Hatayama Y, Ogata Y, Saito M, et al. The impact of tobacco smoking and alcohol consumption on the development of gastric cancers. Int J Mol Sci. 2024;25(14):7854.
74. Wu Z, Tang Y, Tang M, Wu Z, Xu Y. The relationship between the eradication of *Helicobacter pylori* and the occurrence of stomach cancer: an updated meta-analysis and systemic review. BMC Gastroenterol. 2025;25(1):278.
75. Ford AC, Yuan Y, Park JY, Forman D, Moayyedi P. Eradication therapy to prevent gastric cancer in *Helicobacter pylori* - positive individuals: systematic review and meta-analysis of randomized controlled trials and observational studies. Gastroenterology. 2025;S0016-5085(25)00041-1.
76. Liu Z, Xu H, You W, Pan K, Li W. *Helicobacter pylori* eradication for primary prevention of gastric cancer: progresses and challenges. J Natl Cancer Cent. 2024;4(4):299-310.
78. Huang Q, Cheng YQ, Hu KW, Ding Y. Gastric cardiac carcinoma: recent progress in clinicopathology, prognosis, and early diagnosis. J Dig Dis. 2025;26(1-2): 22-30.
79. Shah SAR, Mumtaz M, Sharif S, Mustafa I, Nayila I. *Helicobacter pylori* and gastric cancer: current insights and nanoparticle-based interventions. RSC Adv. 2025;15(7):5558-5570.