

The Role of *Helicobacter pylori* Infection in the Development of Gastric Cancer – Review of the Literature

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Abbreviations:

H. pylori: *Helicobacter pylori*;

UBT: urea breath test;

GC: Gastric Cancer;

PG I: pepsinogen I;

CagA: Cytotoxin-associated gene A;

Cag PAI: cytotoxin-associated gene

pathogenicity island;

VacA: vacuolating cytotoxin A;

TNF- α : tumor necrosis factor-alpha;

T4SS: type IV secretion system;

SabA: Sialic acid-binding adhesin;

COX-2: Cyclooxygenase-2;

PGE2: prostaglandin E2;

AP-2: activator protein 2;

HDM2: human double minute 2;

IM: intestinal metaplasia;

DYS: dysplasia.

Rezumat

Rolul infecției cu Helicobacter pylori în apariția cancerului gastric – revizie a literaturii

Helicobacter pylori (*H. pylori*) clasificat ca un carcinogen de Grupul 1 de către Agenția Internațională pentru Cercetarea Cancerului (IARC) prezintă o strânsă legătură cu cancerul gastric. Progresia de la atrofie la metaplazie, displazie și carcinom, constituie modalitatea de apariție a neoplasmului gastric, iar infecția cu *H. pylori* crește semnificativ riscul de a dezvolta cancer gastric, în special la indivizii cu gastrită atrofică. Factorii de virulență precum CagA și VacA, perturbă căile de semnalizare ale gazdei, contribuind la inflamația cronică și carcinogeneză. Citokinele proinflamatorii și genele supresoare tumorale disfuncționale alimentează în continuare acest proces. Eradicarea infecției cu *H. pylori* reduce incidența cancerului gastric în special la pacienții cu gastrită atrofică și/sau metaplazie intestinală. Cu toate acestea, aceasta nu poate preveni apariția neoplasmului la cei cu leziuni pre-neoplazice avansate. Detectarea și gestionarea precoce a infecției cu *H. pylori* sunt cruciale în diminuarea riscului de cancer gastric, oferind beneficii semnificative.

Cuvinte cheie: *H. pylori*, cancer gastric, adenocarcinom gastric, meta-analiză, MAPS II, eradicare *H. pylori*

Abstract

Helicobacter pylori (*H. pylori*), classified as a Group 1 carcinogen by the International Agency for Research on Cancer (IARC), is

Received: 19.02.2024

Accepted: 16.04.2024

linked to gastric cancer. The progression from atrophy to metaplasia, dysplasia, and carcinoma constitutes the pathway for intestinal-type gastric carcinoma development. *H. pylori* infection significantly increases gastric cancer risk, particularly in individuals with atrophic gastritis. Virulence factors like CagA and VacA disrupt host signaling pathways, contributing to chronic inflammation and carcinogenesis. Pro-inflammatory cytokines and dysregulated tumor suppressor genes further fuel this process. Eradicating *H. pylori* reduces gastric cancer incidence, especially in patients with atrophic gastritis and/or intestinal metaplasia. However, it may not prevent cancer in those with advanced pre-neoplastic lesions. Early detection and management of *H. pylori* infection are crucial in mitigating gastric cancer risk, offering significant benefits.

Key words: *H. pylori*, gastric cancer, gastric adenocarcinoma, meta-analysis, MAPS II, eradication *H. pylori*

Introduction

Helicobacter pylori Infection

Helicobacter pylori (*H. pylori*) is a widely encountered pathogen among the general population, colonizing approximately 50% of individuals (1). Despite over 90% of infected individuals being asymptomatic, *H. pylori* infection poses significant risks and a high social burden. *H. pylori* is a Gram-negative bacterial pathogen that selectively colonizes the gastric epithelium. Infected individuals have a risk of 1-10% to develop gastric or duodenal ulcers. Additionally, *H. pylori* has been categorized as a Group 1 carcinogen by the World Health Organization, offering a risk of 0.1-3% to develop gastric cancer and 0.01% to develop mucosa-associated lymphoid tissue lymphoma. It is estimated that *H. pylori* is the causative agent in 6.2% of all diagnosed cancers worldwide (2). There are several diagnostic models for detecting *H. pylori* infection, such as the stool antigen test (SAT), which demonstrates good sensitivity. According to a recent meta-analysis of 45 studies, the pooled sensitivity and specificity of *H. pylori* SATs in children were reported to be 92.1% and 94.1%, respectively. The urea breath test (UBT) is a highly efficient non-invasive method that is widely used. Despite

recent recommendations from experts, serologic testing remains the most commonly prescribed diagnostic test in the USA. Endoscopy, although invasive, is another method for the *H. pylori* infection diagnosis, involving the observation of typical bacteria associated with inflammatory reactions in tissue slides (3,4). Current guidelines and a network meta-analysis recommend vonoprazan-based triple therapy for 7 days and non-bismuth therapies for 10-14 days as effective for eradicating the infection. These regimens demonstrate good eradication rates of approximately 90%, even in areas with high antimicrobial-resistant strains (5).

Gastric Cancer

Although the incidence of gastric cancer has significantly decreased in the USA and Western Europe, it still ranks as the fifth most common cancer and the third leading cause of cancer-related death globally. Over 95% of gastric cancers are adenocarcinomas, and these are classified according to location (cardia/proximal or noncardia/distal) and histologic type (diffuse or intestinal) (6,7). A family history of GC is one of the most important risk factors, however they are mostly sporadic only 10% of gastric cancers show familial aggregation. Other risk factors

such as *Helicobacter pylori* infection, tobacco smoking, high salt intake and other dietary factors are associated with intestinal type gastric cancer. The primary prevention of gastric cancer encompasses two main strategies: improvement of dietary habits and reduction of *H. pylori* infection. Secondary prevention focuses on early detection, with endoscopy being the gold standard method (8). From a treatment standpoint, significant progress has been made in increasing the 5-year survival rate for stage IA and IB tumors treated surgically by over 60%. However, patients with stage III tumors undergoing surgery still experience a poor survival rate. Presently, there exist numerous treatment modalities, including surgery, chemotherapy, radiation therapy, targeted therapy, and immunotherapy for advanced and metastatic gastric cancer. While there are currently limited therapies that provide significant benefits, numerous treatments are undergoing rigorous study and clinical trials. These investigational therapies hold promise for potentially improving survival rates in the future (9).

Methods to Literature Search

The research methodology encompassed extensive exploration across prominent computerized databases from July 1999 to August 2023, including but not limited to Medline, PubMed, Medscape, ESGE guidelines, Springer, Sciondirect, and Google Scholar. Various combinations of keywords such as *H. pylori*, gastric cancer, gastric adenocarcinoma, meta-analysis, MAPS II, eradication *H. pylori*, systematic review, and narrative review were utilized to ensure comprehensive coverage. Language limitations were not imposed during the literature search process.

Results

H. pylori - The International Agency for Research on Cancer (IARC), a branch of the World Health Organization, has categorized *H. pylori* as a Group 1 carcinogen, definitively

linked to gastric cancer. The progression from atrophy to metaplasia, then dysplasia, and finally carcinoma is believed to be the pathway through which intestinal-type gastric carcinoma develops. Evidence supporting the association between *H. pylori* infection and gastric cancer stems from various sources: epidemiological studies comparing prevalence rates of gastric cancer and *H. pylori* infection, cross-sectional studies examining *H. pylori* infection in patients with gastric cancer, prospective studies linking *H. pylori* infection with gastric cancer, and clinical trials demonstrating a marked decrease in gastric cancer incidence following *H. pylori* eradication (10).

A systematic review and meta-analysis evaluating the global prevalence of Gastric Cancer (GC) in *H. pylori* infected individuals revealed regional variability in *H. pylori* infection among GC patients, particularly noting a significant correlation between high GC rates and *H. pylori* presence in developed countries (11).

Prevalence of Gastric Cancer in Patients Infected with H. pylori

In a recent investigation involving 114 cases of histologically-confirmed gastric cancer from Eastern Libya, the overall prevalence of *H. pylori* infection was 63.2%. Notably, the infection was more prevalent in cases of intestinal type gastric adenocarcinoma (71.7%) and malignant lymphoma (66.6%) compared to diffuse adenocarcinoma (55.3%) (12).

In a cross-sectional study, the initial prevalence estimates of gastric cancer among subjects positive for *H. pylori* infection were determined to be 19.46%. (95% CI: 18.34–20.57) (N=69; I²=98.59%). Thus, among 1000 *H. pylori* positive patients, an estimated 183 to 206 individuals are susceptible to GC (11).

Other studies describe a lower prevalence rate of gastric cancer among patients positive for *H. pylori* infection thus employing a random-effects model, another study determined a pooled prevalence of GC among *H. pylori* positive patients at 8.97% (95% CI:

8.62–9.33) (N=149; I2=98.68%). Hence, within a cohort of 1000 *H. pylori* positive patients, an estimated 8.62 to 9.33 individuals are susceptible to GC. The prevalence of *H. pylori* infection among individuals under 50 years old was reported at 41.9%. The findings underscore that *H. pylori* infection in isolation (non-atrophic *H. pylori* gastritis) presents a distinct risk factor for GC, echoing assertions made by the IARC/WHO statement in 1994. A study conducted by Vohlonen et al. highlighted a risk ratio (RR) of 5.8 (95%CI: 2.7–15.3) for stomach cancer among individuals with *H. pylori* infection compared to those with healthy stomach, escalating to 9.1 (95% CI: 2.9–30.0) in men with atrophic gastritis (13).

An analysis predating 1998, encompassing approximately 800 GC cases, revealed a risk ratio of 2.5 (95% CI: 1.9–3.4) for GC in *H. pylori* seropositive individuals (14).

Additionally, another study showed a risk ratio of 3.1 (95%CI: 1.97–4.95) between *H. pylori* infected and non-infected individuals. The findings of this research suggest that while elevated levels of *H. pylori* IgA and IgG antibodies, as well as low pepsinogen I (PG I) levels, can independently predict the onset of noncardia gastric cancer, their predictive efficacy fluctuates depending on the duration and stage of the follow-up period. However, when used together, their predictive power increases. Individuals exhibiting elevated levels of both IgA and IgG antibodies and low PG I are at the highest risk, with a risk exceeding 10-fold for developing the disease (15).

Virulence Factors

H. pylori secretes numerous virulence factors that have the potential to disrupt host intracellular signaling pathways, thereby facilitating the onset of neoplastic transformation. Among these factors, CagA (cytotoxin-associated gene A) and its associated pathogenicity island (Cag PAI), along with VacA (vacuolating cytotoxin A), are recognized as the primary contributors to pathogenesis. The ensuing chronic inflammation in the gastric

mucosa, resulting from *H. pylori* infection, plays a significant role in initiating and advancing gastric cancer (GC)(16).

In an analysis, data from both the ESTHER and VERDI studies were amalgamated. The presence of *H. pylori* infection was evaluated using a commercial ELISA to detect IgG antibodies against *H. pylori*. A novel *H. pylori* multiplex serology method was employed to ascertain the serostatus of 15 specific *H. pylori* antigens. Among these antigens, seropositivity for 7 out of 15 *H. pylori* specific antibodies, as measured by multiplex serology, showed significant associations with GC within this study population, with stronger associations noted for noncardia GC. Notably, CagA and GroEL emerged as independent predictors of GC risk. The higher risk of Gastric Cancer associated with CagA seropositivity compared to screening ELISA presents two plausible explanations. Firstly, the notable disparity in CagA seropositivity (75.6%) versus screening ELISA (66.1%) among GC cases suggests that CagA might exhibit stronger antigenicity compared to other immunogenic proteins, leading to a prolonged presence of CagA antibodies post-clearance of infection. Secondly, lower proportions of CagA-positive strains were observed among *H. pylori* infected controls compared to *H. pylori* infected GC cases, aligning with previous indications of CagA's role as a virulence factor predisposing individuals to gastric diseases (17).

H. pylori triggers an inflammatory reaction in both gastric epithelial cells and recruited circulating immune cells via diverse pathways. Research indicates that *H. pylori* infection can elevate numerous pro-inflammatory cytokines, including interleukin (IL)-1, IL-6, IL-8, TNF- α , NF- κ B, and regulated on activation normal T cell expressed and secreted (RANTES). The activation of NF- κ B and the increased expression of IL-8 in gastric epithelial cells are proposed as crucial mechanisms underlying *H. pylori* induced chronic inflammation and gastric carcinogenesis. Additionally, *H. pylori* can activate NF- κ B in immune cells (e.g., B lymphocytes)

through classical and alternative pathways. P53, a vital tumor suppressor gene, is implicated in various solid tumor developments such as liver and gastric cancer due to its dysfunction, including mutations. Mutation-induced inactivation of p53 is observed in around 40% of gastric cancers, with higher incidence notably seen in individuals infected with CagA-positive strains of *H. pylori* (16).

Another study observed that Cytotoxin-Associated Gene (CagA), Vacuolation Cytotoxin A (VacA), Interleukin-1 β (IL-1 β), Interleukin 8 (IL-8), Interleukin 10 (IL-10) have an association in the pathogenesis of gastric cancer development on *H. pylori* infection (18).

Several studies have investigated the impact of *H. pylori* infection on the dysregulation of miRNA expression patterns. Li et al. (2012) demonstrated that interleukin (IL)-8, IL-1 β , and tumor necrosis factor- α (TNF- α) could induce miR-146a expression in the HGC-27 cell line ($p < 0.01$) in an NF- κ B-dependent manner. However, the upregulation of miR-146a upon *H. pylori* infection appeared to be independent of these pro-inflammatory cytokines. Numerous investigations have explored the relationship between miRNAs and *H. pylori* in gastrointestinal disorders, particularly gastric cancer (GC), suggesting the potential utility of this relationship in early interventions and therapies for conditions such as GC, gastritis, intestinal metaplasia, and other gastrointestinal ailments. This review underscores the importance of elucidating the connection between *H. pylori* and gastrointestinal disorders within the context of the miRNA-pathogen interaction network. Furthermore, analysis of this interaction network sheds light on the precise mechanisms underlying *H. pylori* infection in various human gastrointestinal conditions (19).

Outer inflammatory protein A (OipA), encoded by the HopH gene, is an outer membrane protein associated with inflammation. *H. pylori* strains positive for OipA elicit a more pronounced inflammatory response compared to OipA-negative strains, conse-

quently heightening the risk of gastric carcinoma and gastric ulcer disease. OipA expression is more prevalent in gastric biopsy samples obtained from patients with precancerous lesions than those with gastritis alone. OipA promotes the secretion of pro-inflammatory cytokines such as IL-1, IL-6, and IL-8 while inhibiting IL-10 release and dendritic cell maturation, thereby increasing the susceptibility to gastric carcinoma. Tumor necrosis factor- α (TNF- α) plays a pivotal role in gastric carcinoma development by activating the Wnt/ β -catenin signaling pathway. Elevated nuclear accumulation of β -catenin has been linked to macrophage infiltration in the gastric mucosa, which is triggered by *H. pylori* infection-induced inflammatory reactions. Macrophages release TNF- α , promoting Wnt/ β -catenin signaling upregulation and contributing to gastric carcinoma pathogenesis (20).

The findings concerning GroEL are particularly intriguing, given the higher seropositivity for this protein, which is widely expressed in most *H. pylori* strains, compared to CagA. GroEL, a member of the molecular chaperone family essential for the proper folding of numerous bacterial proteins, was found to exhibit an even higher seropositivity than CagA. Moreover, GroEL has been implicated in gastrointestinal homeostasis due to its ability to interact with gastrointestinal mucosa components and aggregate *H. pylori*. Interestingly, while similar seropositivity rates were observed between screening ELISA and GroEL in controls, a significantly higher GroEL positivity (83.7%) was noted in GC cases compared to screening ELISA (66.1%). These findings suggest that GroEL antibodies may persist longer post-disease-related clearance of *H. pylori* infection, making GroEL a potentially valuable marker for current or past infection and mitigating the underestimation of *H. pylori* related GC risk associated with disease-related clearance of infection (17).

In a review, the different elements contributing to the infectious mechanism of *H. pylori* and their role in advancing the

infection towards gastric carcinoma were examined (18).

Blood group antigen-binding adhesin (BabA) is an outer membrane protein of *H. pylori* that specifically binds to Lewis b blood group antigens (Leb) located on the surface of host gastric epithelial cells. *H. pylori* strains expressing BabA demonstrate increased virulence and exhibit higher colonization capability. The translocation of CagA into host cells via the type IV secretion system (T4SS) is facilitated by the binding of BabA to host epithelial cells. The severity of *H. pylori* associated complications is exacerbated by the presence of CagA, VacA, and BabA2, as these virulence factors act synergistically, resulting in heightened inflammation and an elevated risk of gastric carcinoma. Sialic acid-binding adhesin (SabA) is another adhesin protein of *H. pylori* that interacts with the Sialyl-Lewis X antigen present on the gastric epithelium. The expression of Sialyl-Lewis X is upregulated during host inflammatory responses, promoting increased adherence of *H. pylori* to the gastric mucosa through SabA. SabA has been implicated in the progression of gastric diseases, including gastric atrophy and carcinoma (20).

Cyclooxygenase-2 (COX-2) is implicated in gastric carcinoma development by inhibiting apoptosis, stimulating cell proliferation, angiogenesis, invasion, and metastasis. Upregulation of COX-2 is an inflammatory response to *H. pylori* presence, leading to increased prostaglandin E2 (PGE2) production. COX-2 possesses activator protein 2 (AP-2) and NFkB binding sites, further exacerbating inflammation and tumor progression. P53, a tumor suppressor gene regulating the cell cycle, plays a critical role in tumor suppression. Inactivation of P53, observed in approximately 40% of gastric tumors, is mediated by human double minute 2 (HDM2) protein. *H. pylori* infection triggers the activation of serine/threonine kinase (AKT kinase) in gastric cells, which phosphorylates HDM2, thereby reducing P53 levels in the gastric mucosa and promoting gastric carcinoma development (18).

Pathogenic Modifications

GC is a major leading cause of cancer deaths worldwide and is associated with high morbidity. Numerous studies have shown that GC is strongly associated with atrophic gastritis from *H. pylori* infection (21).

This infection has been linked to a roughly sixfold increase in the risk of adenocarcinomas distal to the cardia, encompassing both intestinal and diffuse types (10).

H. pylori colonization of the human stomach contributes to bacterial pathogenesis within the gastric system. This process leads to the development of chronic atrophic gastritis, intestinal metaplasia, and ultimately, gastric cancer. The inflammation induced by *H. pylori* in stomach tissues can result in life-long or chronic infection if not appropriately managed. Various mechanisms support the survival of *H. pylori* in the gastric environment. Precancerous lesions in the stomach represent abnormal histopathological conditions associated with the risk of gastric cancer, often stemming from long-term mucosal infections with *H. pylori*. The progression of this infection involves distinct stages, each marked by increasing damage to the gastrointestinal tract. These precancerous conditions typically progress through five stages: active nonatrophic gastritis (resulting from the inflammatory response to *H. pylori*), multifocal atrophic gastritis (characterized by permanent damage to epithelial cells and gastric glands due to prolonged inflammation), intestinal metaplasia (either complete or incomplete), dysplasia (involving cytological abnormalities of the epithelium), and ultimately, invasive carcinoma(22).

H. pylori infection serves as a crucial trigger, initiating a series of events referred to as Correa's cascade. This cascade commences with an inflammatory phase that inflicts damage upon the gastric mucosa. If left unmanaged, inflammation induced by *H. pylori* in stomach tissues can lead to persistent or lifelong infection. Various mechanisms support the survival of *H. pylori* in the gastric environment.

Effective primary prevention strategies for this phase include eradicating *H. pylori*, reducing inflammation, and promoting mucosal repair. Precancerous lesions in the stomach denote abnormal histopathological conditions associated with an elevated risk of gastric cancer, often stemming from prolonged mucosal infections with *H. pylori*. These precancerous conditions typically progress through five stages: active nonatrophic gastritis (resulting from the inflammatory response to *H. pylori*), multifocal atrophic gastritis (characterized by permanent damage to epithelial cells and gastric glands due to prolonged inflammation), intestinal metaplasia (either complete or incomplete), dysplasia (involving cytological abnormalities of the epithelium), and ultimately, invasive carcinoma (22,23).

According to the latest MAPS II guidelines, the association between gastric atrophy induced by *H. pylori* infection and the increased risk of gastric cancer is acknowledged (24):

- "Patients with advanced stages of gastritis, that is, atrophy and/or intestinal metaplasia affecting both antral and corpus mucosa, should be identified as they are considered to be at higher risk for gastric adenocarcinoma";
- "High grade dysplasia and invasive carcinoma should be regarded as the outcomes to be prevented when patients with chronic atrophic gastritis or intestinal metaplasia are managed" (24).

Furthermore, the MAPS II guidelines recommend for adequate staging of gastric precancerous conditions endoscopic biopsy sampling according to the Sydney system: at least five biopsies, comprising two from the antrum, one from the incisura, and two from the body.

Eradication of H. pylori Infection and Reduction of Gastric Cancer Incidence

The association between *H. pylori* and gastric cancer has been also demonstrated through the eradication of the infection, which has concomitantly led to a decrease in the

incidence of gastric cancer, as observed in various studies

In a study conducted, 1838 individuals diagnosed with *H. pylori* infection were divided into two groups through a random selection process. One group received a treatment regimen comprising lansoprazole (30 mg), amoxicillin (1000 mg), and clarithromycin (500 mg), each taken twice daily for 7 days, while the other group received a placebo. The primary objective of the study was to monitor the occurrence of gastric cancer. Additionally, a predetermined secondary objective was to evaluate the incidence of gastric cancer based on the eradication status of *H. pylori* during the follow-up period. The study revealed a 55% reduction in the risk of gastric cancer among participants who underwent *H. pylori* eradication therapy compared to those who received the placebo over a median follow-up period of 9.2 years. It is noteworthy that individuals who achieved successful *H. pylori* eradication experienced a 73% lower risk of gastric cancer compared to those with persistent infection (25).

A systematic review and meta-analysis indicates that identifying and eliminating *H. pylori* infection decreases the subsequent occurrence of gastric cancer in asymptomatic healthy individuals who are infected. The findings remained consistent across the majority of sensitivity analyses conducted. The number needed to treat differed based on the cancer risk within the studied population; however, the estimation suggests it could be as low as 15 for *H. pylori* positive men residing in high-risk regions for gastric cancer, such as China or Japan, compared to nearly 250 for infected women in low-risk regions like the US (26).

Two meta-analyses examining the risk of gastric cancer post *H. pylori* eradication reached the consensus that eradication significantly reduces the risk of gastric cancer in patients with chronic atrophic or non-atrophic gastritis [pooled relative risk (RR) 0.64, 95%CI 0.48–0.85], whereas no significant reduction was observed in patients with

IM or dysplasia (RR 0.88, 95%CI 0.59–1.31) (27,28).

First meta-analysis demonstrated that eradicating *H. pylori* significantly diminishes the risk of GC development compared to non-eradication. This finding remained robust across various sensitivity analyses. Furthermore, these findings corroborate earlier meta-analyses. Eradicating *H. pylori* stands as a fundamental preventive measure for individuals with non-atrophic or atrophic gastritis. However, eradication of *H. pylori* in patients already exhibiting advanced pre-neoplastic lesions, such as intestinal metaplasia or dysplasia, does not preclude the development of GC (27).

Another meta-analyses observed the impact of *H. pylori* eradication on both primary and secondary prevention. Additionally, their results indicated that individuals with intestinal metaplasia (IM) or dysplasia (DYS) might not experience reduced gastric cancer risk from *H. pylori* treatment. It is advisable for such patients to undergo regular endoscopic surveillance and consider early intervention.

Although these meta-analyses had a shorter follow-up period for the study subjects, there are other studies in the literature that have presented a longer follow-up period.

In a separate extensive study known as the Shandong Intervention Trial, which included 2258 participants, it was observed that the risk of gastric cancer was reduced by 39% with *H. pylori* treatment compared to placebo during a prolonged follow-up period spanning 15 years (29).

The outcomes from an extended follow-up period of 22 years within the same study indicated a greater disparity in risk, with a 52% lower incidence observed in the treatment group (30).

Surveillance

Virtual CE can assist in directing biopsies for staging atrophic and metaplastic alterations and targeting neoplastic lesions. There is no evidence supporting surveillance for patients with mild to moderate antral atrophy only.

However, in patients with intestinal metaplasia (IM) at a single site and additional risk factors such as a family history of gastric cancer, incomplete IM, or persistent *H. pylori* gastritis, endoscopic surveillance with CE and guided biopsies may be considered every 3 years. Those with advanced stages of atrophic gastritis should undergo high-quality endoscopy every 3 years. If dysplasia is detected without an endoscopically visible lesion, immediate reassessment with high-quality endoscopy and CE is recommended.

Discussion

H. pylori, classified as a Group 1 carcinogen by the International Agency for Research on Cancer (IARC), is definitively linked to gastric cancer. The progression from atrophy to metaplasia, then dysplasia, and finally carcinoma is believed to be the pathway through which intestinal-type gastric carcinoma develops.

The variability in gastric cancer prevalence among individuals infected with *H. pylori* is noteworthy. While one study reported an initial prevalence of 19.46% among *H. pylori* positive subjects, significantly lower estimates around 8.97% have also been observed. Furthermore, *H. pylori* infection emerges as a significant risk factor for gastric cancer, with a notably high risk ratio compared to healthy individuals. For instance, one study highlighted a risk ratio of 5.8 for gastric cancer among *H. pylori* infected individuals, escalating to 9.1 in men with atrophic gastritis. These findings suggest that *H. pylori* infection and associated biological markers may serve as valuable tools in identifying individuals at heightened risk for gastric cancer.

H. pylori's virulence factors, particularly CagA and VacA, disrupt host signaling pathways, contributing to gastric cancer initiation and progression via chronic inflammation. Analysis of ESTHER and VERDI study data reveals significant associations between *H. pylori* specific antibodies, like CagA and GroEL, and gastric cancer risk, indicating their potential as independent predictors.

Studies highlight the role of pro-inflamma-

tory cytokines like IL-1, IL-6, and TNF- α in *H. pylori* induced chronic inflammation, fostering gastric carcinogenesis, alongside dysregulation of tumor suppressor genes like p53 and miRNAs. GroEL, with higher seropositivity than CagA, emerges as a potential marker for *H. pylori* related gastric cancer risk, persisting post-clearance of infection, thus mitigating underestimation. Various *H. pylori* virulence factors, including BabA, SabA, and COX-2, synergistically exacerbate inflammation and elevate the risk of gastric carcinoma through mechanisms like increased colonization capability and inflammatory responses. Understanding the intricate mechanisms of *H. pylori* infection and its role in gastric carcinoma progression underscores the importance of developing targeted interventions and therapies for gastrointestinal disorders.

GC ranks among the leading causes of cancer-related deaths globally and is strongly associated with atrophic gastritis resulting from *H. pylori* infection. *H. pylori* infection increases the risk of distal adenocarcinomas, including both intestinal and diffuse types, by approximately sixfold. Colonization of the human stomach by *H. pylori* contributes to the development of chronic atrophic gastritis, intestinal metaplasia, and ultimately, gastric cancer. The progression from *H. pylori* induced inflammation to precancerous lesions and ultimately invasive carcinoma involves distinct stages, highlighting the importance of early detection and management of *H. pylori* infection in mitigating the risk of gastric cancer.

H. pylori infection initiates Correa's cascade, beginning with gastric mucosal inflammation, which can lead to persistent infection if left untreated.

Effective primary prevention strategies involve eradicating *H. pylori*, reducing inflammation, and promoting mucosal repair to prevent progression to gastric cancer.

Precancerous lesions in the stomach, stemming from prolonged *H. pylori* infection, progress through stages including nonatrophic gastritis, multifocal atrophic gastritis,

intestinal metaplasia, dysplasia, and ultimately, invasive carcinoma.

According to the latest MAPS II guidelines, advanced stages of gastritis with atrophy and/or intestinal metaplasia are associated with a higher risk of gastric adenocarcinoma, emphasizing the need for identification and management of high-risk patients.

Adequate staging of gastric precancerous conditions involves endoscopic biopsy sampling according to the Sydney system, with at least five biopsies taken from specific locations in the stomach.

Studies demonstrate a decrease in gastric cancer incidence following eradication of *H. pylori* infection, with a 55% reduction observed over a median follow-up of 9.2 years. Meta-analyses reaffirm the preventive effect of *H. pylori* eradication, particularly in individuals with non-atrophic or atrophic gastritis, showing a significant reduction in gastric cancer risk. However, eradication may not prevent gastric cancer development in patients with advanced pre-neoplastic lesions like intestinal metaplasia or dysplasia. Prolonged follow-up studies, such as the Shandong Intervention Trial, spanning up to 22 years, further support the significant risk reduction (39% to 52%) associated with *H. pylori* treatment in preventing gastric cancer.

Conclusions

H. pylori infection, recognized as a Group 1 carcinogen, is unequivocally linked to gastric cancer development, with a sixfold increase in risk observed in individuals colonized by the bacterium, underlining its significance in gastric carcinogenesis. The progression from *H. pylori* induced inflammation to precancerous lesions and eventually invasive carcinoma, as outlined in Correa's cascade, underscores the critical importance of early detection and management of *H. pylori* infection to mitigate the risk of gastric cancer. In conclusion, substantial evidence indicates that eradicating *H. pylori* provides significant benefits for individuals with chronic non-

atrophic and atrophic gastritis, both histologically and in terms of lowering the risk of gastric cancer.

Conflicts of Interests

The authors declared no potential conflicts of interest.

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