International Journal of Community Medicine and Public Health
Ghamdi KMA et al. Int J Community Med Public Health. 2025 Oct;12(10):4800-4805
http://www.ijcmph.com
pISSN 2394-6032 | eISSN 2394-6040

DOI: https://dx.doi.org/10.18203/2394-6040.ijcmph20252924

Review Article

The role of *Helicobacter* in gastric cancer prevention

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Received: 23 August 2025
Accepted: 08 September 2025

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ABSTRACT

Gastric cancer is one of the most common cancers worldwide. It is associated with high mortality risk. *Helicobacter pylori* (*H. pylori*) is a major significant risk factor for gastric cancer, as its virulence factors significantly contribute to gastric carcinogenesis. *H. pylori* eradication has been associated with reduced incidence of gastric cancer. *H. pylori* mechanisms in achieving long-term and sustained cancer prevention remain unclear. The aim of this review is to explore the effectiveness and mechanisms of *H. pylori* in gastric cancer prevention. *H. pylori* contribute to gastric cancer by molecular mechanisms, such as activating the NF-κB pathway, and cellular mechanisms, such as oxidative stress. Studies have shown that *H. pylori* eradication reduced the incidence of gastric cancer in healthy populations and patients with early gastric cancer undergoing endoscopic mucosal resection. *H. pylori* vaccination can be an effective method in the prevention of *H. pylori* infection, thus preventing gastric cancer. Future studies should develop an integrated approach combining targeted eradication, microbiome management, and innovative vaccination strategies to prevent the occurrence of gastric cancer.

Keywords: *Helicobacter pylori*, *H. pylori*, Gastric Cancer, Prevention, *H. pylori* eradication, *H. pylori* vaccination

INTRODUCTION

Gastric cancer is the fifth most encountered cancer and the fifth leading cause of cancer-related deaths globally.[1] It is predominantly prevalent in East Asia, Eastern Europe, and Latin America, with nearly half of all new cases and associated deaths reported in China.[2] The etiology of gastric cancer is multifactorial, including genetic, environmental, and microbial factors, with *Helicobacter pylori* (*H. pylori*) representing the most significant contributing factor.[3] *H. pylori* bacterium infects more than 40% of the world's population.[4] It has been reported that *H. pylori* infection is responsible for 70% of gastric cancers.[5] In Europe and North America, 87% of non-cardia gastric cancer could be attributed to *H. pylori*, compared with 79% in Asia.[6] While 62% of cardia gastric cancer in Asia could be attributed to *H. pylori* infection.[6]

The contribution of *H. pylori* in the process of gastric carcinogenesis has been established by numerous studies.[7] It leads to chronic inflammation of gastric mucosa and significantly contributes to the development of gastric lesions, inducing gastric carcinogenesis.[8,9] Notably, the International Agency for Research on Cancer (IARC) classified *H. pylori* as a Group 1 carcinogen.10 It was the first bacterium to be included in this classification. In recent years, studies have reported a significant decrease in the incidence of gastric cancer in line with the decrease in the prevalence of *H. pylori* in many countries.[4] These reports suggest that *H. pylori* treatment may decrease the incidence of gastric cancer across populations.

The effectiveness and efficacy of *H. pylori* treatment in preventing gastric cancer in healthy individuals and patients with early gastric cancer undergoing endoscopic mucosal resection have been explored by numerous studies.[11-15] Although the role of *H. pylori* eradication in reducing the incidence of gastric cancer is established, its mechanisms in achieving long-term and sustained cancer prevention remain unclear. This review aims to discuss the mechanisms by which *H. pylori* contribute to gastric cancer, the effectiveness of *H. pylori* eradication in the prevention of gastric cancer, and the systemic consequences of *H. pylori* eradication. Treatment of *H. pylori* infection with antibiotics has shown a significant influence on microbial composition and diversity.

A comprehensive literature search was conducted in Medline (via PubMed), Scopus, and Web of Science databases up to August 12, 2025. Medical Subject Headings (MeSH) and relevant free-text keywords were used to identify synonyms. Boolean operators (AND', OR') were applied to combine search terms in alignment with guidance from the Cochrane Handbook for Systematic Reviews of Interventions. Key search terms included: "*Helicobacter pylori*" OR "*H. pylori*" AND "Gastric Cancer" AND "Prevention". Summaries and duplicates of the found studies were exported and removed by EndNoteX8. Any study that discusses the role of Helicobacter in gastric cancer prevention and published in peer-reviewed journals was included. All languages are included. Full-text articles, case series, and abstracts with the related topics are included. Case reports, comments, and letters were excluded.

DISCUSSION

Mechanisms of H. pylori in gastric cancer

Molecular mechanisms

The molecular mechanisms through which *H. pylori* contribute to the development of gastric cancer are unclear. Various pathways have been suggested as contributing to gastric carcinogenesis.[16] Signaling pathways that contribute to gastric carcinogenesis when activated include the nuclear factor κB (NF-κB) pathway, the cytokine-stimulated transduction (JAK-STAT) signaling, the Wnt/β-catenin signaling pathway, the PI3K/Akt pathway, the mitogen-activated protein kinase (MAPK) pathway, and the Hippo pathway.[17] The prolonged activation of the STAT3 pathway by *H. pylori* plays a key role in the induction of gastric carcinogenesis. This pathway is associated with increased oncogenic effects such as cell proliferation, differentiation, epithelial-mesenchymal transition (EMT), and inhibition of apoptosis.[18,19] It is mainly regulated by virulence factors such as CagA and other signaling pathways such as Toll-like receptors (TLRs).[20,21]

The NF-κB pathway contributes to gastric carcinogenesis through dysregulating the immune system and directly inducing carcinogenic behaviors of tumor cells.[22] *H. pylori* activates this pathway and induces its translocation into the nucleus by CagA.[23] The NF-κB pathway is also activated by the stimulation of the upstream IKK kinase complex, which upregulates the expression of proinflammatory factors such as IL-1β and TNF-α.[24] Activation of the NF-κB-dependent pathway by *H. pylori* leads to the induction of RASAL2 expression, inducing gastric carcinogenesis through β-catenin signaling.[25] Activation of NF-κB triggers the transcription of genes that promote cell cycle progression, suppress apoptosis, and stimulate angiogenesis, collectively contributing to a tumor-promoting environment.[26] It has been reported that the prolonged activation of the Wnt/β-catenin pathway strongly contributes to the occurrence, progression, and aggressiveness of gastric cancer.[27]

Cellular mechanisms

H. pylori may contribute to gastric carcinogenesis by causing oxidative stress.[28] It leads to the overproduction of reactive oxygen species (ROS) and reactive nitrogen species (RNS) directly through virulence factors like CagA and VacA, which generate ROS within gastric cells, and indirectly through triggering a sustained inflammatory response, inducing the infiltration of neutrophils and macrophages that generate ROS and RNS.[29] *H. pylori* can also inhibit the activity of antioxidants, including superoxide dismutase (SOD), glutathione (GSH), apurinic/apyrimidinic endonuclease 1 (APE1), and thioredoxin (Trx). Furthermore, *H. pylori* can damage DNA by various mechanisms, including oxidative stress, DNA double-strand breaks, ribosomal restriction and digestion damage, and microsatellite instability.[30-34]

H. pylori trigger a sustained inflammatory response by activating innate and adaptive immune responses, resulting in the accumulation of different immune cells in gastric mucosa.[35] These immune cells produce chemical mediators, cytokines, and ROS, damaging gastric epithelial cells and inducing a chronic inflammatory environment, which contribute to gastric carcinogenesis. *H. pylori* trigger an inflammatory response by secreting CagA, which disrupts bile acid metabolism, resulting in *H. pylori*-induced inflammation and gastric carcinogenesis.[36] Additionally, *H. pylori* engage pattern recognition receptors, including NOD1 and NOD2, which in turn amplify inflammatory signaling cascades such as MAPK and NF-κB pathways.[37] These signaling cascades stimulate the overproduction of chemokines, inflammatory cytokines (e.g., IL-8, IL-6), enzymes like COX-2, and adhesion molecules. This results in sustained aggregation and activation of inflammatory cells such as macrophages and neutrophils, triggering a self-sustaining loop of inflammation.

Other mechanisms through which *H. pylori* contributes to gastric cancer include dysregulation of cell apoptosis, cell cycle progression, and autophagy.[38,39]

Impact of H. pylori eradication on gastric cancer risk

Multiple studies have explored the role of *H. pylori* eradication in the prevention of gastric cancer.[11-13,40,41] The Shandong Intervention Trial reported that *H. pylori* treatment significantly decreased gastric cancer incidence in healthy individuals during a follow-up period of 14.7 years (OR = 0.61, 95% CI: 0.38–0.96), and this decrease persisted for 22.3 years of follow-up (OR = 0.48, 95% CI: 0.32–0.71).[2]

Notably, *H. pylori* remarkably reduced gastric cancer mortality (HR = 0.62, 95% CI: 0.39–0.99). Other studies reported positive results for *H. pylori* treatment in preventing gastric cancer in individuals with mild and severe gastric lesions.[40,41] A randomized clinical trial conducted in Fujian Province reported a significant reduction in gastric cancer incidence in a 26.5-year follow-up.42 Furthermore, *H. pylori* eradication in individuals with a family history showed a reduced risk of gastric cancer (HR = 0.45, 95% CI: 0.21–0.94).[13]

A cluster-randomized trial assessed the effectiveness of implementing mass *H. pylori* screening and treatment in China.[27] The study found that the overall successful eradication rate in individuals who received anti-*H. pylori* treatment was 72.9%, while 15.1% of individuals who received symptomatic treatment were *H. pylori* negative after treatment. It also reported a larger reduction in the incidence of gastric cancer in individuals receiving anti-*H. pylori* therapy compared with those receiving symptomatic treatment (HR = 0.86, 95% CI: 0.74–0.99).13 The effect was more pronounced in individuals with successful *H. pylori* eradication (HR = 0.81, 95% CI: 0.69–0.96) compared to those with treatment failure. Successful eradication was remarkably observed in individuals aged 25–45 years.[11] Another study conducted in Hong Kong reported a significant reduction in gastric cancer incidence in individuals aged 60 years and older who received *H. pylori* treatment 10 years or more before (SIR = 0.42, 95% CI: 0.42–0.84).[43] This finding suggests that *H. pylori* eradication leads to a long-term prevention of gastric cancer in older populations.[32] Another study in Taiwan demonstrated that *H. pylori* treatment significantly reduces the incidence of gastric cancer, intestinal metaplasia, and atrophic gastritis (risk reduction=53%, 95% CI: 30%–69%), with no increase in the risk of complications.44 A community-based retrospective study in the United States found that individuals who received *H. pylori* eradication therapy had a significant reduction in the incidence of non-cardia gastric cancer in eight years following treatment (HR=0.37, 95% CI: 0.14–0.97) compared to untreated individuals.[45]

Additionally, *H. pylori* eradication has been associated with reduced incidence of metachronous gastric cancer in patients with early gastric cancer undergoing endoscopic mucosal resection.[14,15,46] Choi et al reported that, in patients with early gastric cancer, *H. pylori* treatment was associated with a reduced risk of metachronous gastric cancer (HR=0.50, 95% CI: 0.26–0.94) and an improvement from baseline in atrophy grade at the lesser curvature of the gastric corpus.46 Another cohort study in Korea found that patients who received endoscopic resection for gastric dysplasia showed decreased gastric cancer and metachronous gastric neoplasm risks (HR=0.88, 95% CI: 0.80–0.96 and HR = 0.76, 95% CI: 0.70–0.82, respectively) following *H. pylori* treatment.[47]

H. pylori eradication systemic effects

Eradication of *H. pylori* can lead to short- and long-term systemic consequences. The treatment of *H. pylori* by antibiotics has shown a significant influence on microbial composition and diversity.[48] It has been reported that successful antibiotic eradication improves gastric microbial richness and evenness, resulting in increased probiotic enrichment and reduced drug-resistant mechanisms.[49] Studies also observed a rise in other genera in the gastric microbiota, such as Neisseria, Prevotella, Neisseria, and Pseudomonadaceae.[2,49] *H. pylori* eradication has also been associated with short-term changes and potentially long-lasting alterations in the balance and the composition of gut microbiota.[50,51] Some studies have shown diversity in gut microbial recovery, while others reported persistent alterations.[53] These disturbances may impair infection resistance, metabolism, and immune homeostasis and promote resistant strains, warranting strategies such as probiotics and long-term ecological monitoring.[52,2]

H. pylori infection has been linked to significant metabolic abnormalities due to its disruptive effects on gastrointestinal flora.[54] These effects include stimulating the production of pro-inflammatory cytokines such as C-reactive protein, tumor necrosis factor-α, and interleukin-6, impairing insulin signaling and lipid metabolism.[55,56] Thus, treatment of *H. pylori* can mitigate inflammation, enhance insulin sensitivity, and improve dyslipidemia. Multiple studies evaluated the effects of *H. pylori* eradication on metabolic profiles and reported a reduction in trimethylamine N-oxide and creatine levels and an elevation in lactate and low-density/very low-density lipoprotein levels after treatment. These findings highlight a significant impact of *H. pylori* on metabolic profiles related to energy, amino acid, lipid, and microbial metabolism.[57]

H. pylori vaccination

Recently, prevention of gastric cancer by *H. pylori* vaccination has been emerging.[58] However, developing an effective vaccine for *H. pylori* is challenging due to the genetic diversity of *H. pylori* strains. Current available vaccines target a range of *H. pylori* antigens and have shown positive impact on host immunity regardless of vaccine composition (primarily peptide vaccines and RNA vaccines) and the delivery route (oral, subcutaneous, or intranasal mucosal injection).[59] Nevertheless, these vaccines did not result in long-term protection against *H. pylori* infection.

The currently available *H. pylori* vaccines are mainly based on subunit oral vaccines, which function by eliciting mucosal responses. These vaccines, composed of single, highly specific peptides and free from toxic components, are theoretically unlikely to trigger prolonged, intense inflammatory responses. A recent study assessed the effectiveness of a multi-epitope oral vaccine, which involves four *H. pylori* virulence factors (NAP, Urease, HpaA, and HSP60), in murine models. The vaccine resulted in strong systemic and mucosal immune responses, demonstrating promising results.[60]

A randomized phase 1/2 clinical trial evaluated an oral vaccine composed of three recombinant *H. pylori* antigens: CagA, VacA, and NAP. Although the vaccination group showed higher levels of specific antibodies for *H. pylori* compared to the control group, the vaccine was unable to achieve superior infection prevention.[59] Vaccines based on nucleic acids are a promising approach in the field of *H. pylori* vaccination, leading to a robust cellular and humoral immunity against multiple *H. pylori* subtypes.[58] This technology overcomes key obstacles to oral vaccine delivery, including gastric acidity and the complexities of inducing mucosal immunity, offering a promising direction for future research.

CHALLENGES AND RECOMMENDATIONS

Despite the proven role of *H. pylori* eradication in gastric cancer prevention, challenges remain. Many infected individuals never develop gastric cancer, while some with successful eradication still do, reflecting the interplay of genetic, environmental, and microbial factors. The overuse of antibiotics raises societal concerns, demanding novel antimicrobials, noninvasive susceptibility testing, and advanced resistance surveillance using NGS. Addressing these issues is essential to optimize prevention strategies, improve eradication outcomes, and minimize unintended consequences.

Duan et al recommend that future research should aim to elucidate the roles of *H. pylori* virulence factors in gastric carcinogenesis, investigate how different bacterial genotypes influence disease progression and treatment outcomes, develop novel therapeutic targets and immunotherapies based on the molecular pathways altered by *H. pylori*, and establish improved prevention approaches, including more effective eradication regimens and vaccination strategies, to lessen the global burden of *H. pylori*–associated gastric cancer.[16]

CONCLUSION

H. pylori infection plays a central role in gastric carcinogenesis through complex molecular, cellular, and inflammatory mechanisms. While *H. pylori* eradication offers substantial preventive benefits, it may also induce alterations in the gastrointestinal microbiota and metabolic profiles, warranting careful monitoring. An integrated approach combining targeted eradication, microbiome management, and innovative vaccination strategies may offer the most effective path toward reducing the global burden of gastric cancer

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Ghamdi KMA, Bawareth RL, Kankouni MW, Alaidarous HA, Almutairi SM, Almalki WM, et al. The role of *Helicobacter* in gastric cancer prevention. Int J Community Med Public Health 2025;12:4800-5.