Helicobacter pylori and Gastrointestinal Cancers: Recent Advances and Controversies

Clinical Medicine Insights: Oncology
Volume 18: 1–7

DOI: 10.1177/11795549241234637

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ABSTRACT: *Helicobacter pylori* (*H pylori*), a gastric bacterium, has been extensively studied for its association with gastritis, peptic ulcers, and gastric cancer. However, recent evidence suggests its potential implications beyond the stomach, linking it to other gastrointestinal malignancies, such as esophageal cancer, liver cancer, pancreatic cancer, gallbladder cancer, and colorectal cancer. In light of the expanding research landscape and the increasing interest in exploring *H pylori* broader role in gastrointestinal tumorigenesis, this comprehensive review aims to elucidate the relationship between *H pylori* and gastrointestinal tumors. This review encompasses recent epidemiological studies, research progress, and emerging perspectives, providing a comprehensive assessment of the relationship between *H pylori* and gastrointestinal tumors. The findings highlight the captivating world of *H pylori* and its intricate involvement in gastrointestinal malignancies.

KEYWORDS: *Helicobacter pylori*, gastrointestinal cancers, therapeutic strategies, risk factors

RECEIVED: August 24, 2023. **ACCEPTED:** February 1, 2024.

TYPE: Review

FUNDING: The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the Major Science and Technology Project of the Zhejiang Provincial Department of Science and Technology (grant no. 2020C03030). The funding bodies had no role in writing the article.

DECLARATION OF CONFLICTING INTERESTS: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Introduction

Helicobacter pylori (*H pylori*) is a gram-negative bacterium that colonizes the gastric mucosa of approximately half of the world's population.[1] First discovered and subsequently cultivated by Marshall and Warren in 1982 as Campylobacter pyloridis, it was later reclassified as *H pylori*.[2] Since then, extensive research has been conducted on its association with various gastric diseases, including gastritis, peptic ulcers, and gastric cancer (GC). In 1994, the International Agency for Research on Cancer (IARC) of the World Health Organization unequivocally classified *H pylori* as a Group 1 carcinogen, affirming its role in the development of GC. While the relationship between *H pylori* and GC has been extensively studied, recent evidence suggests that this bacterium's impact extends beyond the stomach. Recently, studies have expanded its impact, revealing links not only to GC but also to other malignancies, including esophageal cancer, liver cancer, pancreatic cancer, gallbladder cancer, and colorectal cancer (CRC), thereby arousing heightened scientific interest. The potential clinical implications of understanding the associations with *H pylori* extend beyond the captivating nature of the subject. This knowledge bears significance in several ways. First, recognizing *H pylori* role in various gastrointestinal cancers could inform targeted screening strategies, especially in regions with high infection rates. Early detection may be improved by considering *H pylori* status. Second, understanding the intricate associations could pave the way for developing novel diagnostics that consider *H pylori* infections as a potential risk factor. In light of the expanding research landscape and the potential clinical implications, this review aims to provide a comprehensive assessment of the relationship between *H pylori* and gastrointestinal tumors. The review will encompass recent epidemiological studies, research progress, and emerging perspectives, shedding light on the captivating world of *H pylori* and its intricate involvement in gastrointestinal malignancies.

H pylori and Esophageal Cancer

Epidemiological evidence increasingly indicates that *H pylori* infection, especially strains carrying the cytotoxin-associated gene A (CagA), is associated with a reduced risk of esophageal or gastroesophageal junction adenocarcinoma.[3–6] Current scientific understanding suggests that *H pylori* infection leads to gastric mucosal atrophy and decreased gastric acid secretion, thereby reducing the incidence of Barrett esophagus (BE) caused by gastroesophageal reflux, consequently lowering the risk of esophageal adenocarcinoma. A comprehensive meta-analysis by Wang et al[7] conducted a meta-analysis including

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1308 BE patients, 1388 population-based controls, and 1775 gastroesophageal reflux disease (GERD) individuals. They found that *H pylori* infection was negatively correlated with the risk of BE compared with the population-based controls (odds ratio [OR] = 0.44, 95% confidence interval [CI] = 0.36-0.55), with a stronger negative association observed between individuals with *H pylori* CagA-positive strains and BE ($P = .017$).[7] In the comparison between GERD group and population-based controls, *H pylori* infection was significantly negatively associated with GERD (summary OR = 0.52, 95% CI = 0.35-0.78, $I^2 = 69\%$, $P = .02$). No association was found between *H pylori* and BE when compared with the GERD and BE groups (OR = 0.96, 95% CI = 0.67-1.37, $I^2 = 48\%$). The association between *H pylori* infection and BE is speculated to be mediated by GERD. Barrett esophagus is a recognized precursor lesion of esophageal adenocarcinoma, and the correlation between *H pylori* and BE suggests a possible link with esophageal adenocarcinoma.[7] The incidence rate of GC in East Asia is much higher than in other regions.[8] Surveillance endoscopy for GC after *H pylori* eradication is warranted. The esophagus is also examined for EA and esophageal squamous cell carcinoma (ESCC) during such surveillance. Thus, the benefits of eradicating *H pylori* infection might outweigh the possible increase in EA risk. Regarding the relationship between *H pylori* and ESCC, Gao et al[9] conducted a meta-analysis of *H pylori* and esophageal cancer, showing no significant association between *H pylori* and ESCC, suggesting that *H pylori* is not a risk factor for ESCC.

H pylori and Gastric Cancer

Helicobacter pylori infection affects approximately half of the world's population, with the primary acquisition occurring during childhood. Most infected individuals remain asymptomatic, and once infected, *H pylori* persists, leading to varying outcomes and severity of complications, influenced by bacterial, host, and environmental factors. The occurrence rates of gastric ulcers and gastric adenocarcinoma are approximately 10% to 15% and 1% to 3%, respectively.[10,11] *Helicobacter pylori* infection is recognized as the most potent risk factor for the development of GC, as it can lead to a progressive pathological process, including atrophic long-term gastritis, intestinal metaplasia, and dysplasia.[12,13] Extensive research has been conducted on the pathogenic mechanisms of *H pylori*-induced GC, clinical prevention and control of GC, and the occurrence of metachronous GC following *H pylori* eradication. Screening and eradicating *H pylori* in high-risk areas with a high prevalence of *H pylori* infection and GC may reduce the incidence of GC. A meta-analysis conducted by Ford et al[14] evaluated the efficacy of eradicating *H pylori* in healthy asymptomatic individuals to lower the risk of GC. The analysis found that *H pylori* eradication therapy was superior to placebo or no treatment in preventing subsequent GC (risk ratio [RR] = 0.54, 95% CI = 0.40-0.72, 8323 participants). Further analysis revealed that eradicating *H pylori* could reduce GC mortality compared with placebo or no treatment (RR = 0.61, 95% CI = 0.40-0.92, 6301 participants). This systematic review and meta-analysis provide evidence that eradicating *H pylori* in the general population may serve as a preventive measure against GC.

Helicobacter pylori infection is the main cause of noncardia gastric cancer (NCGC), but its pathogenic role in cardia gastric cancer (CGC) is unclear. A multicenter prospective cohort study of 512 715 Chinese people found that *H pylori* infection accounted for 78.5% of noncardia and 62.1% of cardia stomach cancers.[15]

This extensive prospective case-cohort study has further elucidated the relationship between *H pylori* and GC. It reveals that *H pylori* infection is not only a risk factor for NCGC in Chinese adults but also a significant and potent risk factor for CGC. Zhongxue Han and colleagues conducted a meta-analysis revealing a substantial correlation between *H pylori* infection and NCGC in both East Asia (OR = 4.36, 95% CI = 3.54-5.37) and the West (OR = 4.03, 95% CI = 2.59-6.27). Concerning CGC, a significant association was observed solely in East Asia (OR = 2.86, 95% CI = 2.26-3.63), with no such correlation found in the West (OR = 0.80, 95% CI = 0.61-1.05).[16] These studies have synthesized evidence concerning the association between *H pylori* infection and GC, highlighting regional disparities in the incidence of cardia cancer. Particularly in East Asia, it is imperative to focus on the presence or absence of lesions in the cardia region among patients with *H pylori* infection.

Regarding the impact of eradication after endoscopic submucosal dissection (ESD) of early GC on metachronous GC occurrence, there is still some controversy. Fukase et al[17] assessed the recurrence of metachronous GC in 544 patients with early GC who underwent endoscopic treatment. They were randomly assigned to the *H pylori* eradication group and the noneradication group, and patients underwent endoscopy at 6, 12, 24, and 36 months after randomization, with the main endpoint being the occurrence of newly developed cancer in another part of the stomach. After 3 years of follow-up, 9 patients in the eradication group and 24 patients in the control group developed metachronous GC. The intention-to-treat analysis showed a RR of 0.339 (95% CI = 0.157-0.729, $P = .003$) for metachronous GC, favoring the eradication group.[17] This randomized controlled trial (RCT) study indicates that eradication of *H pylori* in patients with early GC after endoscopic treatment can prevent the occurrence of metachronous GC. Furthermore, a retrospective study of 283 patients with *H pylori* infection undergoing ESD for early GC revealed that persistent *H pylori* infection after failed eradication is an independent risk factor for metachronous GC occurrence,[18] consistent with the findings of Fukase et al.[17] However, Kim et al[19] conducted a retrospective analysis of 433 patients with early GC who underwent ESD to investigate the impact of *H pylori* infection, eradication status, and successful eradication on the occurrence of metachronous GC. The median follow-up time

after ESD was 30 months. Among the 11 patients in the *H pylori* testing group, metachronous GC occurred during the follow-up period, with 7 cases in the *H pylori*-negative group, 3 cases in the *H pylori* eradication group, and 1 case in the persistent *H pylori* group ($P > .05$). Kim et al[19] concluded that *H pylori* eradication and infection status do not seem to have a preventive effect on the occurrence of metachronous GC after ESD for early GC, and endoscopic mucosal atrophy and intestinal metaplasia are risk factors for metachronous GC. Considering the limitations of retrospective analysis and the follow-up time in this study, in combination with previous research,[20,21] it is important to monitor and manage *H pylori* infection. Eradication in *H pylori*-infected individuals before progressing to atrophic gastritis achieves the best results and maximizes the restoration of the gastric microenvironment's stability. Patients with early GC who already have gastric mucosal atrophy or intestinal metaplasia have a higher risk of developing metachronous GC. *H pylori* eradication may potentially prolong this process, and a strategy of regular endoscopic follow-up is necessary.

H pylori and Mucosa-Associated Lymphoid Tissue Lymphoma

The intricate relationship between mucosa-associated lymphoid tissue (MALT) lymphoma and *H pylori* has emerged as a paradigm-shifting aspect in the understanding and management of this unique subtype of non-Hodgkin lymphoma.[22-24] Successful eradication of *H pylori* often results in disease regression, emphasizing the importance of accurate detection and targeted antibiotic therapy. Endoscopic evaluation, histopathologic examination, and molecular testing for *H pylori* are crucial components of the diagnostic workup. Regarding the treatment of MALT lymphoma, most European guidelines include *H pylori* eradication as first-line therapy.[25-27] In a study conducted by Gong et al involving 345 patients diagnosed with gastric MALT lymphoma, the researchers observed that 91.9% of the patients tested positive for *H pylori* infection. Following *H pylori* eradication treatment, the overall complete remission rate was determined to be 82.3%, with a specific breakdown indicating a complete remission rate of 84.5% for *H pylori*-positive patients and 57.1% for those who tested negative for *H pylori*.[28] This indicates that eradication therapy is worthwhile even for *H pylori*-negative MALT lymphoma patients. Possible explanations include the occurrence of false-negative results in *H pylori* testing among MALT lymphoma patients or the potential involvement of other bacteria sensitive to antibiotic treatment in the initiation and progression of MALT lymphoma.

H pylori and Pancreatic Cancer

Pancreatic cancer is the seventh leading cause of cancer-related deaths globally, and it often remains asymptomatic in its early stages, leading to late diagnosis with a dismal 5-year survival rate of only 9%. It is one of the most malignant tumors.[29] The cause of pancreatic cancer remains unclear, and certain factors such as smoking, diabetes, obesity, dietary factors, alcohol consumption, age, race, family history, genetic factors, *H pylori*, non-O blood type, and long-term pancreatitis are considered risk factors for pancreatic cancer. Notably, recent research has found a correlation between the colonization of *H pylori* in the stomach, a widely studied bacterium, and an increased risk of pancreatic cancer. A nested case-control study involving 29 133 Finnish male smokers aged 50 to 69 found a statistically significant increase in the risk of pancreatic cancer for individuals infected with *H pylori* or carrying CagA-positive strains compared with *H pylori*-negative subjects (OR = 1.87, 95% CI = 1.05-3.34; OR = 2.01, 95% CI = 1.09-3.70, respectively), suggesting a potential role of *H pylori* in pancreatic cancer development.[30] However, Risch et al conducted a population-based case-control study examining the association between blood type, *H pylori* serum positivity, and the virulence factor CagA, and found that CagA serum positivity was not associated with an increased risk of pancreatic cancer, while CagA-negative *H pylori* serum positivity showed a significant association (OR = 1.68, 95% CI = 1.07-2.66).[31] Their meta-analysis of 6 previous studies further supported a statistically significant association between *H pylori* and pancreatic cancer. Subsequent reviews and meta-analyses have also highlighted the relevance of *H pylori* infection as a risk factor for pancreatic cancer, estimating population attributable fractions ranging from 4% to 25%.[32] The mechanism by which *H pylori* increases the risk of pancreatic cancer remains unclear, but several hypotheses have been proposed. One hypothesis suggests that *H pylori* infection may enhance the pancreatic carcinogenic effect of N-nitrosamines from smoking or diet through various toxicities and characteristics of the bacterium and host-bacterium interactions.[33] Another hypothesis is that *H pylori* stimulates long-term inflammation, which in turn promotes cell proliferation, mutagenesis, activation of oncogenes, and angiogenesis, thereby increasing the risk of carcinogenesis. It is also suggested that the bacterium may affect cancer development by activating nuclear factor-κB (NF-κB) and inhibiting apoptosis.[34] However, some studies have not observed a correlation between *H pylori* infection and the incidence of pancreatic cancer, thus not supporting a causative role of *H pylori* in pancreatic cancer cause.[35-38] Currently, the research findings regarding the relationship between *H pylori* infection and pancreatic cancer show some inconsistencies. Therefore, large-scale prospective studies are needed in the future to further analyze the role of *H pylori* infection in pancreatic cancer.

H pylori and Gallbladder Cancer

Gallbladder cancer is a rare disease believed to be associated with gallstones and long-term gallbladder inflammation.[39] Prolonged long-term inflammation is a significant driving factor for gallbladder cancer. Since the discovery of *H pylori* in gallbladder mucosa from patients undergoing cholecystectomy

for gallstones and cholecystitis in 1996 by Kawaguchi et al,[40] an increasing number of researchers[41,42] have detected various Helicobacter species in gallbladder tissues, gallstones, and bile, including *H pylori, H bilis, H hepaticus, H pullorum, and H ganmani*, with *H pylori* being the most common type.[43] Wang et al[43] conducted a meta-analysis on *H pylori* and gallbladder inflammation. The analysis included 20 studies involving 1735 participants with long-term cholecystitis or gallstones. The results showed that gallbladder *H pylori* infection was positively associated with an increased risk of long-term cholecystitis and gallstones (OR = 3.05, 95% CI = 1.81-5.14, I^2 = 23.5%). This provides evidence for the association between gallbladder *H pylori* infection and an increased risk of long-term cholecystitis and gallstones. *H pylori* infection may contribute to an increased risk of gallbladder stones and cholecystitis through several potential mechanisms. First, *H pylori* can induce oxidative stress and free radical reactions through the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS), leading to DNA damage in epithelial cells.[44,45] In addition, it releases a large amount of pro-inflammatory and vasoactive substances, such as interleukin (IL)-1, IL-6, IL-1β, and tumor necrosis factor alpha (TNF-α),[46] which are associated with the mechanism of long-term inflammation in the gallbladder. Moreover, *H pylori* has been found to deplete cholesterol in gastric glands to prevent interferon-gamma signaling and escape the inflammatory response,[47] which is relevant to the mechanism of long-term inflammation in the gallbladder. Furthermore, as a part of the gut microbiota, *H pylori* colonization in the biliary tract may promote the formation of cholesterol gallstones.[48] Finally, *H pylori* colonization may have adverse effects on bile acid metabolism, glucose, and cholesterol balance, leading to gallstone development.[49] Given the relationship between *H pylori* infection and cholecystitis or gallbladder stones, further analysis of the risk of *H pylori* infection in gallbladder cancer is necessary. Murphy et al[50] conducted a nested case-control study and found that the positivity rate of *H pylori* protein in baseline serum was associated with an increased risk of biliary tract cancer. Specifically, individuals with positive serum for 4 or more *H pylori* antigens had a significantly increased risk of biliary tract cancer, with an OR of 7.01 (95% CI = 0.79-62.33). Moreover, the study also found that the infection rate of *H pylori* was as high as 100% in gallbladder cancer patients, and other biliary tract cancers also had a high infection rate. These research findings suggest that *H pylori* infection may be a risk factor for gallbladder cancer. However, Kornerup et al[51] conducted a cohort study that included 53 220 Danish residents, with an overall *H pylori* infection rate of 19.7%. During the follow-up period with a median of 4.6 years, 5 *H pylori*-positive patients were diagnosed with hepatobiliary cancer, while 59 *H pylori*-negative patients were diagnosed with hepatobiliary cancer. Therefore, *H pylori* infection was associated with a lower risk of hepatobiliary cancer (HR = 0.27, 95% CI = 0.11-0.68). Considering previous conflicting studies on *H pylori* in hepatobiliary tumors, some limitations should be taken into account, such as potential confounding factors that need correction and varying research designs exploring the effect of *H pylori* infection on hepatobiliary tumors. Future research on *H pylori* in the hepatobiliary region is necessary to clarify its relationship with hepatobiliary tumors and guide clinical practices, potentially offering new avenues and strategies for early diagnosis and treatment of gallbladder cancer.

H pylori and Hepatocarcinoma

Hepatocellular carcinoma (HCC) is a primary malignant tumor of the liver, and its pathogenesis involves a complex interplay of various risk factors. Among these, liver parenchymal damage leading to cirrhosis serves as a common underlying factor for most HCC cases. Notably, long-term hepatitis B virus (HBV) or hepatitis C virus (HCV) infections and exposure to aflatoxin have been identified as major contributors to the development of HCC.[52,53] However, the complete spectrum of risk factors influencing HCC remains incompletely understood, and there is an ongoing debate regarding the potential role of *H pylori* in HCC development. Avenaud et al[54] have conducted research where they detected the presence of *H pylori* in liver tissues of liver cancer patients, raising intriguing questions about its possible involvement in the pathogenesis of HCC. These findings have sparked interest in understanding whether *H pylori* infection might play a part in the complex cascade of events leading to HCC development. However, it is essential to note that the mere presence of *H pylori* in liver tissues does not conclusively establish a causal relationship with HCC. Xuan et al[55] conducted a comprehensive meta-analysis of 53 case-control studies and 3 retrospective cross-sectional studies to further explore the potential association between *H pylori* infection and the risk of HCC. Their results showed a significant positive correlation, with an OR of 13.63 (95% CI = 7.90-23.49), indicating that *H pylori* infection might indeed influence the development of HCC. Nevertheless, these observational findings solely demonstrate an association and do not confirm a causal link between *H pylori* and HCC Intriguingly, HCC often develops in the context of liver fibrosis, which can lead to alterations in intrahepatic immune responses and hemodynamics. Such changes might create a permissive microenvironment, allowing *H pylori* to colonize the liver and potentially evade hepatic immune surveillance.[56] This hypothesis warrants further investigation to elucidate the exact mechanisms through which *H pylori* might contribute to the pathogenesis of HCC. In light of these varying findings, García et al[57] conducted an animal study using HCV transgenic mice to examine the impact of *H pylori* infection on liver cell tumor development. Surprisingly, their results indicated that *H pylori* infection did not promote the occurrence of liver cell tumors in this particular mouse model. While this research sheds some light on the potential role of *H pylori* in HCC, it

also highlights the complexity of the relationship and the need for additional studies to decipher the precise interactions between *H pylori* and HCC development. In conclusion, the role of *H pylori* in the pathogenesis of HCC remains a subject of debate and warrants further investigation through large-scale prospective studies. Understanding the potential contributions of *H pylori* to the development of HCC could offer new insights into the prevention, early diagnosis, and treatment of this deadly liver cancer. Nonetheless, it is crucial to interpret the findings cautiously and recognize that HCC is a multifactorial disease with multiple interacting risk factors.

H pylori and Colorectal Cancer

Colorectal cancer has been confirmed to be positively associated with *H pylori* infection. In a nationwide population-based cohort study, 3936 newly diagnosed *H pylori*-infected individuals (the *H pylori* infection cohort) and 15 744 age- and sex-matched controls were included. The study revealed that the cumulative incidence of *CRC* was higher in the *H pylori* infection cohort compared with the control cohort ($P < .001$). After adjusting for potential confounding factors, *H pylori* infection was significantly associated with an increased risk of *CRC* (HR = 1.87, 95% CI = 1.37-2.57).[58] Indeed, this finding aligns with research conducted on populations in Western countries. The seropositivity of *H pylori* antibodies has been consistently associated with an increased risk of *CRC*.[59-61] In 2020, Choi et al conducted a comprehensive meta-analysis to explore the association between *H pylori* infection and the risk of *CRC*. This meta-analysis incorporated data from 48 studies, comprising a total of 171 045 participants, with 31 of these studies reporting on the relationship between *H pylori* infection and cancer risk. The results of this meta-analysis revealed a significant positive correlation between *H pylori* infection and an increased risk of developing *CRC* (OR = 1.44, 95% CI = 1.26-1.65).[62] These findings provide substantial evidence supporting the notion that *H pylori* infection may play a role in promoting the occurrence of *CRC*, reinforcing the importance of further research in understanding the underlying mechanisms and potential preventive strategies.

While the aforementioned study elucidates the elevated risk of *CRC* being associated with *H pylori* infection, the underlying mechanisms explaining this increased risk remain unclear. The direct causal relationship between *H pylori* infection and *CRC* has yet to be established definitively. In an animal study conducted by Ralser et al,[63] they explored the potential mechanisms underlying the promotion of lower digestive tract tumors by *H pylori* infection. To determine whether *H pylori* infection enhances the development of gastrointestinal tumors, they infected Apc+$^{/min}$ and Apc+$^{/1638N}$ mice with *H pylori* at different time points. Apc+$^{/min}$ mice were highly susceptible to infection, with only 60% of the mice surviving after 12 weeks of *H pylori* infection. Compared with the uninfected control group, the tumor burden in the small intestine and colon of infected Apc+$^{/min}$ mice increased. Similar results were observed in Apc+$^{/1638N}$ mice, with the number of tumors doubling after infection, and larger tumors observed in the small intestine. Interestingly, in these mice, colon tumors were only detected in those infected with *H pylori*. These observations suggest that even though *H pylori* only infects the stomach of these mice, it promotes the development of tumors in the intestinal tract and colon of susceptible mice. According to the findings by Ralser et al,[63] *H pylori* promotion of *CRC* development may be associated with the following mechanisms in *H pylori*-infected mice's small intestine and colon:

1. Induction of *H pylori*-specific pro-inflammatory immune response: The infection leads to the loss of Treg cells, which then differentiate into Foxp3 IL-17A T cells.
2. Activation of oncogenic signaling pathways and loss of goblet cells: Overactivation of the activator of transcription 3 (STAT3) pathway occurs, and the number of mucin-producing cells decreases in *H pylori*-infected mice. Goblet cells show distinct changes in their maturation status, transforming into less differentiated goblet cells.
3. Favorable conditions for mucin-degrading microbial communities: *H pylori* infection alters the microbial community in the lower digestive tract, favoring the survival of mucin-degrading microbial communities in both wild-type C57BL/6 mice (WT) and Apc-mutant mice. This disruption in the colonic environment induces pro-inflammatory and procarcinogenic microbial characteristics.

These mechanisms shed light on how *H pylori* infection may promote the development of *CRC* in the mice studied and further highlight the importance of understanding these pathways for potential preventive and therapeutic strategies. Guo et al[64] conducted a retrospective cohort study in a population-based setting and discovered that the eradication of *H pylori* may potentially reduce the incidence of *CRC* in the long term. This finding further emphasizes the potential additional benefits of eradicating *H pylori*.

The mounting evidence supports the positive correlation between *H pylori* infection and *CRC* risk, as well as its association with other gastrointestinal cancers. In the cancers demonstrating a positive association with *H pylori*, commonalities exist that may serve as potential links and contribute to a comprehensive pathophysiologic explanation. First, many of these cancers arise from epithelial tissues lining the digestive tract, suggesting a shared anatomical origin. In addition, the presence of long-term inflammation, a known consequence of *H pylori* infection, appears to be a unifying factor across these cancers. This long-term inflammatory state may create an environment conducive to the development and progression of malignancies. Finally, the role of microbiome in gastrointestinal cancer should not be ignored. The microbiome's role in gastrointestinal cancers, especially in the context of *H pylori* infection, is a crucial

area of inquiry. The impact of microbiome on immune response and tumor microenvironment is complex and needs further exploration.

In conclusion, the comprehensive review presented here delves into the intricate relationship between *H pylori* and various gastrointestinal cancers, shedding light on recent advances, controversies, and potential therapeutic strategies. The expanding research landscape has revealed *H pylori* implications beyond gastric diseases, linking it to esophageal cancer, liver cancer, pancreatic cancer, gallbladder cancer, and CRC. Despite the wealth of evidence supporting the association between *H pylori* infection and an increased risk of gastrointestinal malignancies, certain contradictions and complexities persist in the data, necessitating further exploration.

Author Contributions

CZ and YC summarized the articles and wrote the article. YL, HZ, JJ, and WP helped for article selection and gave valuable advice to the article. WP approved the version to be published. All authors have read and approved the final article. CZ and YC contributed equally.

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