ISSN 1007-9327 (print)
ISSN 2219-2840 (online)

World Journal of *Gastroenterology*

World J Gastroenterol 2024 October 7; 30(37): 4083-4167

Published by Baishideng Publishing Group Inc

World Journal of Gastroenterology

Contents

Weekly Volume 30 Number 37 October 7, 2024

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NAME OF JOURNAL
World Journal of Gastroenterology

ISSN
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

LAUNCH DATE
October 1, 1995

FREQUENCY
Weekly

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PUBLICATION DATE
October 7, 2024

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Shanghai Pancreatic Cancer Institute and Pancreatic Cancer Institute, Fudan University
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World J Gastroenterol 2024 October 7; 30(37): 4090-4103

DOI: 10.3748/wjg.v30.i37.4090

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

REVIEW

Effects and mechanisms of *Helicobacter pylori* infection on the occurrence of extra-gastric tumors

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Specialty type: Gastroenterology and hepatology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade A
Novelty: Grade A
Creativity or Innovation: Grade B
Scientific Significance: Grade A

P-Reviewer: Zhang T

Received: April 9, 2024
Revised: August 23, 2024
Accepted: September 12, 2024
Published online: October 7, 2024
Processing time: 170 Days and 6.7 Hours

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Abstract

Helicobacter pylori (*H. pylori*) colonizes the human stomach and many studies have discussed the mechanisms of *H. pylori* infection leading to gastric diseases, including gastric cancer. Additionally, increasing data have shown that the infection of *H. pylori* may contribute to the development of extra-gastric diseases and tumors. Inflammation, systemic immune responses, microbiome disorders, and hypergastrinemia caused by *H. pylori* infection are associated with many extra-gastric malignancies. This review highlights recent discoveries; discusses the relationship between *H. pylori* and various extra-gastric tumors, such as colorectal cancer, lung cancer, cholangiocarcinoma, and gallbladder carcinoma; and explores the mechanisms of extra-gastric carcinogenesis by *H. pylori*. Overall, these findings refine our understanding of the pathogenic processes of *H. pylori*, provide guidance for the clinical treatment and management of *H. pylori*-related extra-gastric tumors, and help improve prognosis.

Key Words: *Helicobacter pylori*; Extra-gastric tumors; Immune system response; Mucosal barrier; Gut microbiome

Core Tip: Apart from gastric diseases, several studies have revealed an association between *Helicobacter pylori* (*H. pylori*) and extra-gastric diseases, including cancers. Inflammation, systemic immune responses, microbiome disorders, and hypergastrinemia caused by *H. pylori* may change the tumor microenvironment and eventually contribute to extra-gastric carcinogenesis. However, the research in this field remains controversial. We summarized the effects of *H. pylori* infection on the occurrence of extra-gastric tumors and their possible mechanisms, hoping to provide insights for clinical treatment and management of *H. pylori*-related extra-gastric tumors, as well as help improve prognosis.

Citation: 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
URL: https://www.wjgnet.com/1007-9327/full/v30/i37/4090.htm
DOI: https://dx.doi.org/10.3748/wjg.v30.i37.4090

INTRODUCTION

Helicobacter pylori (H. pylori) is a gram-negative, helical, microaerophilic, flagellated bacterium that has evolved unique features to survive in the host gastric microenvironment[1]. The infection rate of *H. pylori* varies across different countries and regions[1,2], and recent data show that the global prevalence of *H. pylori* in adults has decreased from 52.6% in 1990 to 43.9% in 2015-2022, which can be attributed to a global public health campaign aimed at decreasing the prevalence of *H. pylori*[3]. Although the global prevalence of *H. pylori* infection in adults has declined over the last three decades, rising antibiotic resistance remains a significant public health concern[4]. *H. pylori* infection is the main cause of gastric mucosal injuries such as chronic non-atrophic gastritis, which can progress to intestinal metaplasia, dysplasia, and finally, gastric cancer[2,5]. As a class I carcinogen identified by the World Health Organization in 1994, *H. pylori* is the primary etiological factor of non-cardia gastric cancer, with approximately nine in 10 cases attributed to *H. pylori* infection[2,6]. In addition to gastric diseases, increasing data have shown that the infection of *H. pylori* may contribute to the development of extra-gastric diseases; including ocular, neurodegenerative, cardiovascular, and obstetric disorders[7-11]. It may also affect the tumor microenvironment and potentially undermine the efficacy of tumor immunotherapies, which have recently become a hot spot[12,13].

In recent years, clinical epidemiology has focused on whether *H. pylori* infection increases the risk of extra-gastric tumors and explored its mechanisms in establishment and progression of extra-gastric tumors, such as colorectal cancer (CRC), pancreatic cancer, and esophageal cancer; however, it remains unclear and divergences exists[14-19]. This review focuses on the effects of *H. pylori* infection on the occurrence of extra-gastric tumors and their possible mechanisms.

THE POTENTIAL MECHANISMS OF *H. PYLORI* INFECTION ON THE OCCURRENCE OF EXTRA-GASTRIC TUMORS

In recent years, clinical epidemiology has focused on whether *H. pylori* infection increases the risk of extra-gastric tumors, but the underlying molecular mechanisms are still unclear. One important potential mechanism is the possible involvement of various virulence factors of *H. pylori* in the occurrence and development of extra-gastric tumors by interfering with cell signaling pathways. *H. pylori*-related gastric mucosal diseases are closely related to the pathogenicity of various virulence factors, especially vacuolating cytotoxin A (VacA) and cytotoxin-associated gene A (CagA). These virulence factors alter host cell responses and signaling pathways by causing epithelial cell damage, triggering disorders of cell proliferation and apoptosis, disturbing multiple host cell signaling cascades, and inducing host immune-inflammatory responses[20-22]. In addition, *H. pylori* displays complex tolerance mechanisms to accomplish immune evasion and long-term colonization and then establishes chronic inflammation in the stomach[23,24]. For example, *VacA* can inhibit the activation and proliferation of T cells and B cells, and induce apoptosis in macrophages *via* interferon-β signaling inhibition to significantly lead to immunosuppression[25]. Specific masking mechanisms have been found during *H. pylori* infection, such as lipopolysaccharide (LPS) modifications or flagellin mutations that cannot be detected by toll-like receptor: TLR4[26] and TLR5[27] to evade immune system recognition. In addition, reactive oxygen and nitrogen species produced during *H. pylori* infection can further damage host cells and lead to DNA damage[28]. The long-lasting state of chronic inflammation and oxidative stress induced by *H. pylori* ultimately promotes gastric carcinogenesis. The effects of *H. pylori* virulence factors on the stomach are relatively clear, but how do they produce extra-gastric effects?

Virulence factors in extracellular vesicles, including CagA and VacA, from *H. pylori*-infected cells and *H. pylori* outer membrane vesicles provide theoretical evidence for the possible influence of *H. pylori* virulence factors on extra-gastric tumor development[29,30]. With the secretion of extracellular vesicles into the blood, these extracellular vesicles can be transported to other organs and tissues, where they play a carcinogenic role by interfering with cell signaling pathways; inducing an inflammatory response, and promoting oxidative stress. Extracellular vesicles with *H. pylori* virulence factors found in extra-gastric diseases indicate a potential role of *H. pylori* in the development of extra-gastric tumors[29,31,32].

In addition, the effects of *H. pylori* infection on the host immune system may play a role in extra-gastric tumor development. *H. pylori* infection elicits robust immune responses during its colonization and survival in the gastric mucosa; including immune recognition, innate and adaptive immune responses, and immune tolerance; which are mixtures characterized by T helper (Th): Th1 and Th17, and regulatory T cell (Treg) responses[33,34]. These immunoregulatory effects between *H. pylori* and gastric mucosa maintain the coexistence of *H. pylori* and its host. In summary, in view of the possibility that abnormal regulation of the local immune response may interfere with normal immune surveillance and anti-tumor responses, *H. pylori* infection may increase the risk of extra-gastric tumor development by affecting the tumor immune microenvironment of the host.

Human microbiota consists of a set of dynamic microbial communities that inhabit different parts of the body. The co-evolution of microbiota with the host causes microbiota to play a profound role in promoting human health, and the disturbance of the human microbiota, especially intestinal microbiota, can cause or exacerbate many diseases[35]. The interaction between the intestinal microbiota and the host is related to the occurrence and development of various cancers [36]. *H. pylori* infection can alter the diversity and abundance of the intestinal microbiota[37], and its effects on the intestinal microbiota may be a possible cause for the development of cancers in distant organs and tissues. Therefore, the interaction between *H. pylori* and intestinal microbiota may contribute to the carcinogenic potential of *H. pylori* beyond the stomach.

Moreover, *H. pylori* infection causes hypergastrinemia[38]. Gastrin is a peptide hormone that is synthesized and released by G cells in the gastric antrum. *H. pylori* elevates the pH on the surface of the gastric epithelium by decomposing ammonia produced by urease. This process disrupts the normal feedback regulation of gastrin by gastric acid, resulting in increased release of gastrin. Elevated gastrin levels have been reported to be related to various tumors, underscoring the significant role of *H. pylori* infection in extra-gastric tumors[39]. Given that tumorigenesis is associated with numerous factors, we discussed the combined effects of *H. pylori* infection and other predisposing factors.

THE EFFECTS OF *H. PYLORI* INFECTION ON THE OCCURRENCE OF EXTRA-GASTRIC TUMORS

The virulence factors of *H. pylori* secreted into the bloodstream in the form of extracellular vesicles, regulation of the tumor immune microenvironment by *H. pylori*, hypergastrinemia and gastrointestinal microbiota disturbance caused by *H. pylori* infection suggest that *H. pylori* infection may affect the occurrence and development of extra-gastric tumors. In this section, we summarize the effects of *H. pylori* on the incidence of extra-gastric tumors and investigate the potential mechanisms with the aim of highlighting the comprehensive effects of *H. pylori* on the human body.

CRC

CRC is the third most common cancer worldwide and imposes a huge burden on the imminent future[40]. Given that colorectal adenomas are premalignant lesions that may develop into CRC through the adenoma-to-carcinoma sequence [41], in this section we summarize the potential pathogenesis of *H. pylori* infection in colorectal adenoma and CRC, aiming to provide insights for clinical diagnostic and therapeutic strategies. As previously indicated, *H. pylori* infection is associated with an increased risk of colorectal adenoma and CRC[42-44].

Intestinal homeostasis encompasses the dynamic equilibrium of the intestinal mucosa, immune barrier, and intestinal environment, which includes intestinal microbiota, nutrients, and metabolites[45]. If the dynamic equilibrium is disrupted, the disturbance of intestinal homeostasis may lead to damage in the mucosal immune barrier and an imbalance in intestinal microbiota. This can result in abnormal intestinal development, function, and even colonic diseases; including inflammation and tumor[46]. A recent study found that *H. pylori* infection promoted colorectal carcinogenesis by altering intestinal homeostasis; including the intestinal mucosa, immune barrier, intestinal microbiota, and metabolites[47].

***H. pylori* infection alters intestinal mucosal barrier:** Integrity of the mucosal barrier is important for the body to resist pathogenic invasion. Research has shown that alterations in tight and adherence junctions in the gastrointestinal epithelium were significantly affected after *in vitro H. pylori* infection, showing decreased expression of a series of junctional molecules and glycosylation of MUC1[48]. In addition, intestinal goblet cells emerge as pivotal regulators of intestinal health, owing to their roles in providing a protective mucus layer that covers the intestine, sensing changes in the local environment, and shaping gut immunity[49]. Recent research has reported that in C57BL/6 and Apc mutant mice, the maturational states of goblet cells were distinctly affected by *H. pylori* infection, with a switch to less differentiated cells. Significantly lower expression of Atoh1 was also found in stem cells of both the small intestine and colon in *H. pylori* infected mice, indicating a skewed differentiation of stem cells into unspecialized colonocytes rather than into goblet cells[47]. *H. pylori* induced pro-carcinogenic signal transducer and activator of transcription-3 signaling of intestinal epithelial cells and the loss of goblet cells[47], all of which demonstrated that *H. pylori* exert a detrimental impact on mucus-producing goblet cells, thereby potentially fostering carcinogenesis.

***H. pylori* infection alters intestinal immune barrier:** The intestinal immune barrier is composed mainly of intestine-associated lymphoids tissue and diffuse immune cells. The immune system of the intestinal mucosa can recognize antigens such as bacteria, viruses, and toxins; induce humoral and cellular immunity to effectively eliminate antigens; resist the invasion of pathogenic microorganisms; resist allergic reactions; and suppress immune responses[50]. *H. pylori* infection induced an *H. pylori*-specific pro-inflammatory immune response in the small intestine and colon of infected mice, which is characterized by the loss of Treg cells and their differentiation into Foxp3$^+$/IL-17$^+$ T cells[47]. Altered T cell homeostasis caused by *H. pylori* in the intestine may be a key event during colorectal carcinogenesis, driving tumor

development and progression. In addition, enhanced indoleamine 2,3-dioxygenase activity and a significantly high rate of kynurenine/tryptophan ratio in patients with *H. pylori* seropositive CRC suggested that *H. pylori* may support immune tolerance, leading to cancer development[51]. In summary, *H. pylori* infection may promote the occurrence and development of CRC by affecting the intestinal immune homeostasis.

***H. pylori* infection alters intestinal microbial barrier:** Intestinal flora mainly includes mucosal and intestinal cavity flora, which forms a multilevel intestinal microbial barrier and plays a pivotal role in the metabolic, physiological, and immunological systems of the human body. *H. pylori* infection can affect the colonic microbiota by interacting with the host's immune system or by altering the local gastric environment where gastric acidity is changed[37,52]. Several studies have demonstrated the compositional changes in the gut microbiota of *H. pylori*-infected patients[52]. Although some results have been inconsistent, this is a possible mechanism. Furthermore, changes in *Akkermansia* spp. and *Ruminococcus* spp. in the gut bacterial community have been reported in mouse models, indicating that *H. pylori* alters the microbiota of the lower gastrointestinal tract, favors the mucus-degrading microbiota, and induces a pro-inflammatory and pro-carcinogenic microbiota signature[47].

The enteric virome is a component of the gut microbiome that interacts with bacteria and other microbial agents[53]. The virome coexists with other components of the microbiota and host in dynamic equilibrium, jointly maintaining intestinal homeostasis and function. Recent studies have demonstrated that alterations in the colonic virome diversity can disrupt intestinal microbial homeostasis, cause intestinal diseases, and promote CRC growth and invasiveness[54,55]. In healthy Western adults, phages or bacteriophages represent the vast majority of enteroviruses, accounting for 97.7%[56]. Recent studies have highlighted the effect of *H. pylori* on intestinal phages in CRC development. Using shotgun viral metagenomic sequencing to characterize the viral community in mice, researchers have discovered a complex phage-bacterial infection network associated with *H. pylori*-promoted CRC. Notably, the relative abundance of temperate phages increased in *H. pylori*-infected $Apc^{+/1638N}$ mice at 12 weeks post-infection, whereas virulent phages became dominant at 24 weeks. The expansion of temperate phages, potentially induced by the activation of prophages triggered by *H. pylori* infection, may contribute to the development of CRC in mice by interacting with the bacterial community[55].

***H. pylori* infection affects intestinal metabolism:** (1) *H. pylori*-induced hypergastrinemia may contribute to the development of CRC: Increased gastrin release has been reported to potentiate the carcinogenic effects of colorectal adenoma and CRC by overexpressing proinflammatory and growth factors[57]. The proliferative effect of chronic hypergastrinemia may further increase mutation susceptibility and result in the development of adenomas[58]. Gastrin precursors, known to promote colon epithelial cell proliferation and survival, have been reported to contribute to angiogenesis by stimulating the expression of the proangiogenic factor and vascular endothelial growth factor (VEGF) *via* the PI3K/AKT pathway[59]. Similarly, the induction of VEGF-A transcription and translation may play a role in the carcinogenic effects of gastrin[60]. Furthermore, studies have shown feed-forward mechanisms, whereby gastrin and cholecystokinin-2 receptor expression were upregulated during inflammation. Gastrin increases the expression of inflammatory mediators such as COX-2 and IL-8 *via* multiple pathways, thus strengthening the pro-inflammatory function of immunocytes[57,61].

H. pylori infection is an important cause of hypergastrinemia[62], which suggests that *H. pylori* may promote hypergastrinemia to the occurrence and development of CRC by promoting gastrin secretion. And it has been reported that *H. pylori* commonly infects patients with CRC and leads to hypergastrinemia and COX-2 expression, both of which are probably responsible for the initiation and promotion of CRC[39]. These findings suggest that *H. pylori*-induced alterations in gastrin and its precursors and derivatives may contribute to the development of CRC;

And (2) *H. pylori* acts synergistically with metabolic disease to promote CRC development: Interestingly, one perspective suggests that *H. pylori* may be linked to metabolic diseases, which are also associated with the risk of CRC[63,64]. The combination of *H. pylori* infection and elevated hemoglobin A1c (HbA1c) levels or the prevalence of diabetes mellitus affects the risk of colorectal adenoma[41,65]. Data show that the odds ratio (OR) for adenoma was 1.437 (95%CI: 1.197-1.726) (if *H. pylori* was present) and 1.629 (95%CI: 1.239-2.14) (if HbA1c ≥ 6.5). When combining these two factors, the OR increased to 4.712 (95%CI: 3.189-6.963), suggesting that these two factors may have a synergistic effect on colorectal adenoma. Hyperglycemic conditions affected gastrointestinal morphology and function, resulted in the impairment of the gut barrier and alterations in intestinal mucosal permeability. These disruptions can initiate a robust inflammatory process, activate signal transducers and activators, promote cellular proliferation and survival, and ultimately contribute to tumorigenesis[41].

In conclusion, a growing body of evidence suggests that *H. pylori* infection may increase the risk of CRC. However, the relationship between *H. pylori* infection and CRC is complex and variable, and the exact underlying mechanisms are not fully understood. Further clinical and experimental studies are required to elucidate the underlying mechanisms and their associations.

Lung cancer

Lung cancer was the second most commonly diagnosed cancer and the leading cause of cancer-related mortality in 2020 [66]. An increasing number of studies have revealed an association between *H. pylori* infection and respiratory diseases and lung cancer. The seroprevalence of *H. pylori*, especially CagA expression, was significantly higher in patients with lung cancer than in healthy controls[67]. In fact, *H. pylori* has been detected in the bronchoalveolar lavage of patients with lung cancer using real-time polymerase chain reaction[68]. Specific *H. pylori* biomarkers, such as CagA, VacA, HP1564 and Catalase, are significantly associated with an increased risk of lung cancer; whereas not all *H. pylori* strains are associated with it, indicating the role of specific antigens or virulence factors in lung carcinogenesis[69].

H. pylori infection increases the risks of lung damage and inflammation. The oral cavity is a reservoir for *H. pylori*[70] and gastroesophageal reflux plays a role in the transmission of *H. pylori* to the lungs. The gastroesophageal reflux of *H. pylori* urease proteins may provide an antigenic trigger for the initiation of pulmonary granuloma[71]. In addition, *H. pylori* VacA has been detected in the human lung, where it exhibited cytotoxic effects and stimulated the secretion of IL-8 and IL-6 in targeted airway epithelial cells, suggesting its role in the pathogenesis of lung inflammation[72]. Another study has found an increasing secretion of the inflammatory factors like tumor necrosis factor α, IL-1β, IL-6, and IL-8, as well as an increasing p65 nuclear factor-kappa B (NF-κB) protein expression both in mice and *in vitro* with *H. pylori* infection and VacA treatment. This indicated that *H. pylori* infection promotes inflammatory factor secretion and induces lung injury through the activation of NF-κB signaling *via* VacA exotoxin[73]. Additionally, chronic and subclinical tracheobronchial aspiration in *H. pylori* infected individuals, together with the effects of smoking and air pollution, may synergistically initiate and sustain an inflammatory response within the lung epithelium. This inflammatory state could potentially facilitate malignant transformation and tumor growth[74].

H. pylori can promote lung cancer by affecting the gut microbiome. Research has found that disorders of the gut microbiome had an impact on the progression of lung cancer and that the interconnection between the lung and gut microbiomes is particularly important. This interrelation between the two organ systems called the gut-lung axis[75,76]. Dysregulation of the gut microbiome caused by *H. pylori* infection is associated with the exacerbation of chronic respiratory diseases such as chronic obstructive pulmonary disease, suggesting that *H. pylori* has a negative effect on lung growth[77]. However, *H. pylori*-specific effects on the lung microbiome remain unclear, and whether it plays a role in increasing susceptibility to lung cancer through microbiome disorders remains to be elucidated.

In conclusion, the correlation between *H. pylori* and lung cancer, as well as its underlying mechanisms, remain to be precisely elucidated, and the relevant explanation remains controversial. Few studies have investigated the association between *H. pylori* and lung cancer. However, there are opposing conclusions from these studies[78]. Considering the small sample size, the fact that existing studies are all retrospective, and mixed factors such as smoking habits and air pollution, the association between *H. pylori* infection and lung cancer should be interpreted cautiously[78]. Hence, a more comprehensive investigation of the precise relationship between *H. pylori* infection and lung cancer is warranted. Such research would provide insights into the prevention and treatment strategies of lung cancer.

Cholangiocarcinoma and gallbladder carcinoma

H. pylori may be associated with Cholangiocarcinoma (CCA) carcinogenesis through the induction of biliary epithelial cell inflammation and proliferation[79]. *H. pylori* CagA-positive ($CagA^+$) strain DNA was detected more frequently in bile samples of CCA patients than in cholelithiasis patients, and was not detected in the control group. Moreover, patients with CCA and *H. pylori*-PCR-positive liver tissue presented with a significantly higher inflammatory grade and change in the proliferation of biliary cells in the portal zone around the bile ducts than patients with a non-infected liver[79], suggesting that *H. pylori* infection may be involved in the severity of hepatobiliary diseases. In addition, another study found that *H. pylori* infection induced CCA development *via* inflammation-mediated DNA damage. Specifically, elevated high-mobility group box 1, proliferating cell nuclear antigen levels and increased IL-8 mRNA expression were observed in the liver tissues of *H. pylori*-infected hamsters, indicating that *H. pylori* infection may contribute to CCA development, particularly when combined with other carcinogenic agents[80].

H. pylori may also be involved in gallbladder carcinoma (GBC) development. *H. pylori* isolated from the gallbladder damages human gallbladder epithelial cells *in vitro*, specifically causing obvious vacuoles, cell rupture necrosis, and even cell death[81]. Moreover, it is interesting to note that *H. pylori* may act as a gallstone disease lithogenic factor[82] and there is a higher presence of *H. pylori* in patients with cholelithiasis than non-infected group[83]. Confirmed by histopathological data, *H. pylori* infection in patients with CCA and GBC implies an association with bile duct stone formation[84,85], which provides new insights into the effects of *H. pylori* infection in liver diseases. Moreover, it is noted that the co-infection of *H. pylori* with other bacteria like *Helicobacter bilis* and *Helicobacter hepaticus* resulted in more aggressive inflammation in gallbladder mucosa[79,83].

Hepatocellular carcinoma

H. pylori may be associated with the carcinogenesis of hepatocellular carcinoma (HCC) through the induction of epithelial cell inflammation, proliferation, and apoptosis. Research has shown that *H. pylori* affects the replication of hepatocytes primarily by inducing apoptosis with a compensatory increase in DNA synthesis to maintain the balance of cell loss[86]. Analogously, *H. pylori* infection might also increase the risk of transforming growth factor-β1-mediated tumorigenesis by disturbing the balance between apoptosis and proliferation of hepatocytes[87]. In addition, portal vein thrombosis and HCC development were found to increase with *H. pylori* infection through increased inflammatory markers and vascular mediators such as nitric oxide and VEGF, which may lead to HCC development[88].

In terms of the combination of the role of bacteria and viruses, there is a significantly higher risk of developing HCC and hepatic fibrosis in the presence of hepatitis C virus infection along with *H. pylori*[89,90], and similar results were reported in studies of patients infected with hepatitis B virus[91], indicating the role of co-infection with *H. pylori* and virus in the development of HCC. Thus, it is meaningful to elucidate the relationship between chronic liver disease and *H. pylori* infection; and whether there is a link to the development of cancer, especially in patients at high risk of severe hepatic impairment.

An increasing number of clinical and experimental studies have found associations between *H. pylori* and liver diseases, such as nonalcoholic fatty liver disease and HCC[90,92-95]. However, no correlations were identified[96-98]. Histidine-rich protein (Hpn), a nickel-affinity protein from *H. pylori*, was found to suppress cell growth and induce apoptosis in HCC by suppressing ubiquitin-specific peptidase 5 expression and activating $P14^{ARF}$-P53 signaling, suggesting an anti-HCC role for Hpn[99]. Thus, despite increasing evidence on the correlation between *H. pylori* infection

and the pathogenesis of liver diseases, definitive conclusions cannot be drawn.

Esophageal cancer

Esophageal cancer is the eighth most commonly diagnosed cancer and the sixth most common cause of cancer-related deaths globally, and squamous cell carcinoma is a major burden[100]. The controversy surrounding the role of *H. pylori* in Barrett's esophagus (BE), esophageal adenocarcinoma (EAC) and esophageal squamous cell carcinoma (ESCC) persists, suggesting that *H. pylori* acts as a protective agent or contributes to these diseases. This contention arises partly because of the considerable heterogeneity and improper handling of potential confounding factors[101-103].

H. pylori infection may offer protection against gastroesophageal reflux disease (GERD) and its associated neoplastic complications such as BE and EAC. This protective effect may be associated with *H. pylori*-induced gastritis and the subsequent reduction in stomach acidity[104]. A meta-analysis of 72 studies indicated that *H. pylori* infection was associated with a lower risk of BE, while another study indicated that the correlation was stronger in the $CagA^+$ subgroup [102,105]. In addition, *H. pylori* preferentially induces apoptosis in Barrett's-derived cancer cells compared to normal cells, suggesting that *H. pylori* may protect against the development of dysplasia in the Barrett's epithelium in patients with GERD[106]. Whether *H. pylori* actually protects against these esophageal diseases is still under debate. Some studies indicated that neither *H. pylori* infection nor *H. pylori* infection by $CagA^+$ strains reduce the risk of BE[107] and that no significant correlation between *H. pylori* infection and ESCC in the general population has been observed[103]. Studies on the mechanisms of *H. pylori* infection and esophageal cancer suggest that this protective effect may be overemphasized [101].

Gastrin induced by *H. pylori* infection, especially amidated gastrin, plays an important role in the neoplastic progression of BE *via* the activation of several signaling pathways to maintain chronic inflammation, and certain molecular alterations support the pathophysiology of *H. pylori*-related GERD-BE-EAC sequence[108,109]. In addition, cytokine IL-8 release was significantly increased *via* the p38 mitogen-activated protein kinase (MAPK) signaling pathway, and the expression of Src homology-2 domain-containing phosphatase mRNA declined sharply in the $CagA^+$ *H. pylori* group, indicating that $CagA^+$ *H. pylori* filtrates could induce the proliferation of Ec109 cells *in vitro*[110]. In another study, researchers also observed that LPS-TLR4 signaling was associated with the activation of extracellular regulated protein kinase and p38 MAPK signaling pathways[111], indicating that *H. pylori* may play a role in the LPS-induced development of ESCC. Moreover, it is interesting to find that *H. pylori* infection may cause changes in the esophageal microbiota, and research in this area is considered imperative[37].

Prostate cancer

Several studies have focused on the relationship between the microbiome composition and prostate cancer (PCa) risk, demonstrating that certain bacteria may be associated with cancer development and altered responses to treatment[112]. A study provides molecular evidence for the presence of *H. pylori* DNA in the prostate tissue of patients with benign prostatic hyperplasia and PCa[113]. More importantly, research has found a marked increase in the integration of viral and microbial sequences in prostate tumor DNA; in particular, *H. pylori* CagA gene integration in the PPP1R9A and NCAM1 genes was found, which may be a contributing factor to prostate tumorigenesis[114]. There is still a dearth of coverage on this theme; conversely, we have noticed that *H. pylori* infection is associated with a reduced risk of mortality in patients with PCa receiving androgen deprivation therapy[115]. Therefore, relevant research is warranted.

Urinary bladder carcinoma

Inflammation in the urinary bladder and pelvis was observed when *H. pylori* was transurethrally inoculated into the mouse urinary tract[116] and the disappearance of mucosa-associated lymphoid tissue lymphoma of the urinary bladder after treatment for *H. pylori* was found as well[117], indicating that chronic antigenic stimulation of infectious agents might be associated with the development of this malignancy. However, direct evidence for this correlation is lacking. Further studies are required to confirm the role of *H. pylori* infection in urinary bladder carcinogenesis.

DISCUSSION

In this review, we discuss the relationship between *H. pylori* infection and the development of extra-gastric tumors, as shown in Figure 1 and Table 1. Through exosomes or other forms, *H. pylori* virulence factors play an important role in promoting inflammation, regulating host immune responses, inducing abnormal proliferation and apoptosis[1] and may finally contribute to the onset of extra-gastric tumors. Currently, it has been reported that *H. pylori* affects the occurrence and development of some inflammatory diseases through exosomes, such as atherosclerosis, liver fibrosis, and Alzheimer's disease[30]; but in fact; there is no literature directly reporting that *H. pylori* affects the occurrence and development of extra-gastric tumors through exosomes. This may be because studies on exosomes of *H. pylori* infected cells are relatively new and limited. For the study of extra-gastric cancer caused by *H. pylori* exosomes, *in vivo* experiments in mice may require a longer period and a larger exosome; and the dose and experimental details, such as how to measure the role of key exosome molecules; need to be explored. In addition, it puts forward higher requirements for manpower, material resources, experimental technology, operating conditions, and determination of experimental endpoints. These may be the main reasons for the lack of research on extra-gastric tumors caused by *H. pylori* exosomes.

Epithelial cells, immune cells, and microbiota constitute the mucosal, immune, and microbial barriers in some organs and tissues, such as the stomach, intestine, and lungs. These barriers jointly maintain homeostasis of these organs and the host body. Notably, damage to the dynamic equilibrium by *H. pylori* infection leads to the breakdown of homeostasis,

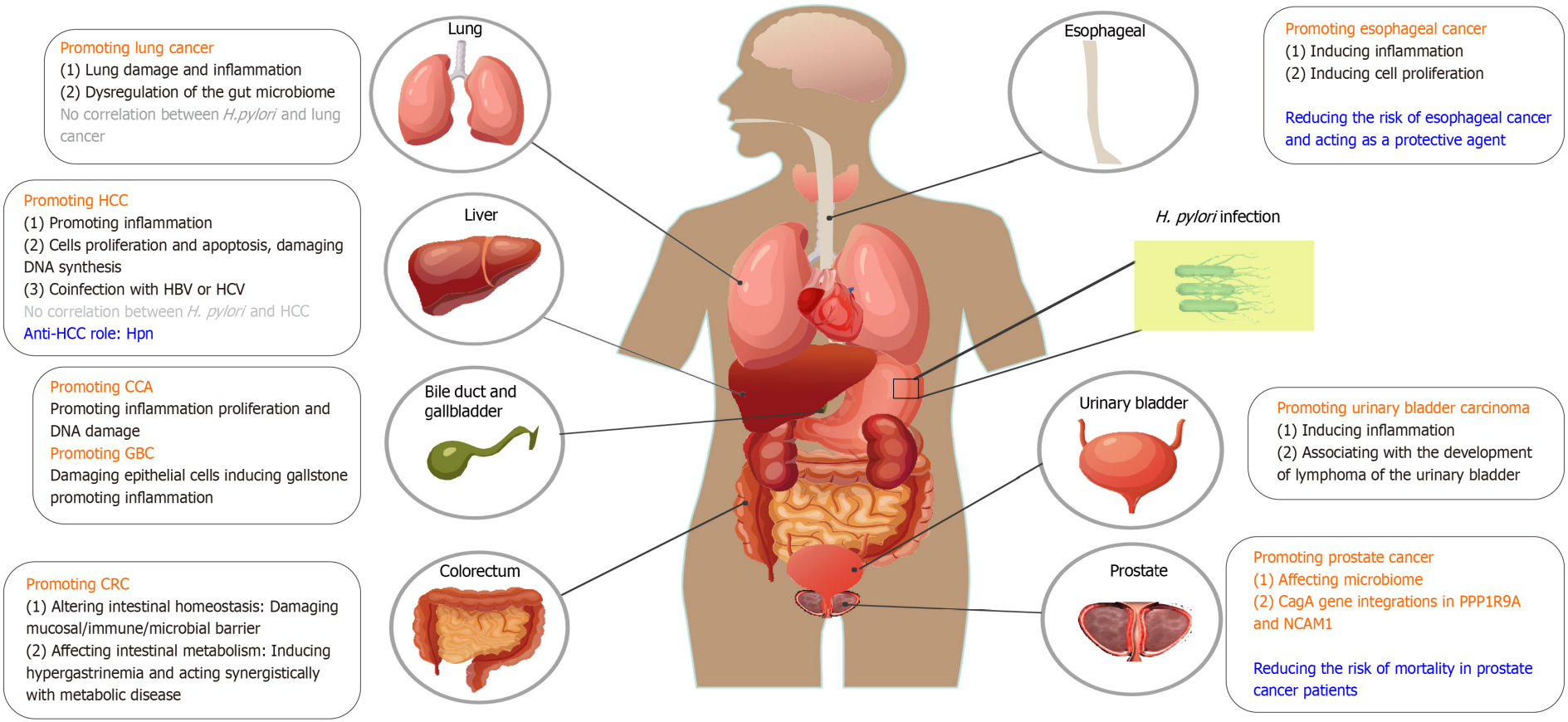

Figure 1 Summary schematic of the effects and mechanisms of *Helicobacter pylori* infection on the occurrence of extra-gastric tumors. The orange indicates that *Helicobacter pylori* infection has a promoting effect on cancer progression and occurrence, the gray indicates no significant effect on cancer progression and occurrence, and the blue indicates an inhibiting effect on cancer progression and occurrence. HCC: Hepatocellular carcinoma; HBV: Hepatitis B virus; HCV: Hepatitis C virus; CCA: Cholangiocarcinoma; GBC: Gallbladder carcinoma; CRC: Colorectal cancer; *H. pylori: Helicobacter pylori*; Hpn: Histidine-rich protein; CagA: Cytotoxin-associated gene A.

which induces diseases and cancers in related organs and tissues. Disturbances in the microbiome are frequently observed in patients with cancer, especially colorectal and PCas. This phenomenon may be attributed to an increased systemic inflammatory response or the ability of certain bacteria to alter the host immune response, making it more favorable for tumor growth[1,55,118,119]. There is growing evidence of the impact of *H. pylori* infection on the host microbiota, including bacteria and viruses that play a direct or indirect role in the progression of extra-gastric diseases. However, there remains a lack of data depicting the functional profiles of host microbial species and revealing the specific mechanisms by which microbes support cancer development[120]. With advances in technology, the integration of spatial transcriptomics with viral metagenomics is promising for studying the spatial distribution of viruses and virus-host cell

Table 1 The mechanisms of *Helicobacter pylori* infection on the occurrence of extra-gastric tumors

Cancers affected by *H .pylori*	Roles of *H.pylori*	Effects and mechanisms of *H. pylori* infection	Results
CRC	Damaging mucosal barrier	Decreased expression of junctional molecules and the glycosylation of MUC1 in gastrointestinal epithelium [48]	Affecting the assembly and function of the adherent junctions and breaking the mucosal barrier that protects the epithelial cells from the degradative enzymes
		Inducing goblet cells switch to less differentiated ones and a lower expression of Atoh[49]	A loss of goblet cells
	Damaging immune barrier	Inducing loss of Treg cells and their differentiation into Foxp3+ IL-17A+ T cells[47]	Inducing a pro-inflammatory immune response
		Enhanced indoleamine 2,3-dioxygenase activity and increased ratio of the kynurenine to tryptophan low serum nitrite levels[51]	Enhancing systemic immune tolerance
	Damaging microbial barrier	Increasing *Akkermansia* spp and *Ruminococcus* spp[47]	Altering the microbiota of the lower gastrointestinal tract, favoring mucus-degrading microbiota and inducing a pro-inflammatory and pro-carcinogenic microbiota signature
		Elevating relative abundance of temperate phages[55]	Expanding virulence by phage-mediated horizontal gene transfer and contributing to the development of CRC
	Inducing hypergastrinemia	Promoting the secretion of gastrin and COX-2 expression[39]	Contribute to the initiation and promotion of CRC
	Acting synergistically with metabolic disease	Combination with elevated HbA1c or diabetes mellitus[63,64]	Increasing the risk of colorectal adenoma
Lung cancer	Promoting lung cancer	Gastroesophageal reflux of *H. pylori* urease may trigger for the initiation of pulmonary granuloma[71]	Inducing the risk of lung damage and inflammation
		Promoting inflammatory factor secretion and inducing lung injury through the activation of NF-κB signaling *via* VacA exotoxin[72]	
		Acting synergically with the effects of smoking or air-pollution to establish and perpetuate an inflammatory reaction[74]	
		Inducing dysregulation of the gut microbiome[77]	May increase susceptibility to lung cancer
	No clear evidence of a causal association between *H. pylori* infection and respiratory diseases	A limited number of underpowered studies reporting contrasting results[78]	The correlation between *H. pylori* and lung cancer as well as its underlying mechanisms, remains to be elucidated with precision
CCA and GBC	Associating with the carcinogenesis of CCA	Enhancing inflammation, promoting proliferation of biliary cells, inducing inflammation-mediated DNA damage[79]	Contributing to the development of CCA
	Involving in GBC development	Damaging human gallbladder epithelial cells[81]	Contributing to the development of GBC
		Acting as a gallstone disease lithogenic factor[82]	
		inducing more aggressive inflammation in in gallbladder mucosa with other bacteria[79,83]	
HCC	The relationship between *H. pylori* infection and risk of HCC is still controversial	Inducing epithelial cell inflammation, proliferation and disturbance of apoptosis and DNA synthesis[86]	Leading to HCC development
		Coinfection with HBV or HCV[86]	
		No associations between *H. pylori* and liver diseases [96-98]	No correlations with HCC or playing an anti-HCC role
		Hpn, a nickel-affinity protein from *H. pylori* can suppress cell growth and induce apoptosis of HCC [99]	
Esophageal cancer	The relationship between *H. pylori* infection and risk of Esophageal cancer is still	Gastrin maintains chronic inflammation and certain pathophysiology molecular alterations[108,109]	May contribute to esophageal cancer development

	controversial		
		Increased IL-8 *via* p38 MAPK pathway and the declined expression of SHP-2 mRNA to induce cell proliferation[110], LPS-TLR4 signaling associating with the activation of ERK and p38 MAPK pathways [110]	
		Heterogeneity and improper handling of potential confounding factors[101-103]	Arguing that whether *H. pylori* is a protective agent or a cause of esophageal cancer
PCa	The relationship between *H. pylori* infection and risk of prostate cancer is still controversial	Affecting human microbiome[112]	May contribute to the development of prostate cancer
		CagA gene integrations in PPP1R9A and NCAM1 genes[113]	
		Associating with a reduced risk of mortality in PCa patients receiving androgen deprivation therapy[113]	Negative correlations with prostate cancer
Urinary bladder carcinoma	Associating with the development of urinary bladder carcinoma	Inducing inflammation in the urinary bladder and pelvis[116], associating with the development of mucosa-associated lymphoid tissue lymphoma of the urinary bladder[116]	May contribute to urinary bladder carcinoma but lacking of direct evidence and further studies are needed to confirm

H. pylori: Helicobacter pylori; PCa: Prostate cancer; CRC: Colorectal cancer; Treg: Regulatory T cell; HbA1c: Hemoglobin A1c; NF-κB: Nuclear factor-kappa B; VacA: Vacuolating cytotoxin A; CCA: Cholangiocarcinoma; GBC: Gallbladder carcinoma; HCC: Hepatocellular carcinoma; HBV: Hepatitis B virus; HCV: Hepatitis C virus; CagA: Cytotoxin-associated gene A; Hpn: Histidine-rich protein.

interactions[54].

CONCLUSION

Several studies have revealed an association between *H. pylori* and extra-gastric tumors. Inflammation response, systemic immune responses, microbiome disorders, and hypergastrinemia caused by *H. pylori* infection may contribute to this process. Although this review highlights the relationship between *H. pylori* infection and tumorigenesis beyond the stomach, the underlying mechanism remains unclear. However, it should be noted that not all people infected with *H. pylori* develop tumors. Occurrence of tumors is relative to the heterogeneity of pathogenic substances of *H. pylori* strains and population heterogeneity, such as lifestyle habits. It is anticipated that these findings will prompt clinicians to focus on *H. pylori* infections and offer new strategies for the management of extra-gastric tumors.

ACKNOWLEDGEMENTS

We would like to give the heartfelt thanks to all the people who have ever helped in this paper. We are also grateful to all those who devoted much time to reading this thesis and gave us much advice, which will benefit us in our later study.

FOOTNOTES

Author contributions: Zhao SQ and Zheng HL contributed to drafting the manuscript and making charts; Shi YY was responsible for designing and revising this review; Zhong XT, Wang ZY, and Su Y provided suggestions and contributed to discussion; All authors have read and approved the article.

Supported by Beijing Natural Science Foundation, No. J230002.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

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S-Editor: Li L
L-Editor: A
P-Editor: Guo X

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