Review

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The paradox of *Helicobacter pylori*: how does *H. pylori* infection protect against esophageal cancer?

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Abstract

Helicobacter pylori is a microaerophilic gram-negative bacterium infecting around half of the world's population. Despite its well-known role in gastric malignancies, its impact on esophageal cancer comes with a complex paradox. Several mechanisms have been proposed to explain its observed lack of carcinogenic activity in the esophagus, including the trigger of anti-inflammatory pathways, promoting atrophic gastritis, and esophageal microbiome modulation. However, recent studies have highlighted a significantly more complicated interplay, where *H. pylori*, typically considered a pathogen, may even deliver a protective effect against esophageal carcinogenesis. This paper aims to evaluate the prevalence of *H. pylori* infection among patients with esophageal carcinoma, discussing the underlying mechanisms of the paradoxical effects of *H. pylori* on esophageal cancer.

Keywords: dysbiosis, esophageal neoplasms, gastrointestinal neoplasms, helicobacter pylori, microbiota

Introduction

Helicobacter pylori (H. pylori), a gram-negative bacterium that predominantly colonizes the human stomach and plays a critical role in many gastroduodenal diseases like chronic gastritis, peptic ulcer disease, gastric cancer, and gastric mucosa-associated lymphoid tissue (MALT) lymphoma[1]. *H.Pylori* has been the topic of much discussion since its detection by Warren and Marshall in 1982, which challenged the assumption that stomachs were sterilized environments[2]. Generally, adults show a higher prevalence than children since most infections are picked up at an early age and consequently last into maturity[3]. The transmission route is mainly through fecal-oral and oral-oral means, with contact between individuals being common in crowded spaces[4]. Despite the common belief about the impact of *H. pylori*, recent findings raised controversial insights about the pathogenesis of *H. pylori*, even proposing potential protective roles in oncogenesis, notably esophageal adenocarcinoma[5,6]. Following the controversial current evidence and the previous understandings of *H. pylori*, this review investigates the complex association of this organism with esophageal cancer and the proposed mechanisms of its potential protective role.

HIGHLIGHTS

- As a gram-negative bacterium, *H. pylori* infects about half of the world's population.
- *H. pylori* is well-known for its role in gastric malignancies.
- The impact of *H. pylori* on esophageal malignancies is controversial, with most studies suggesting potential protective roles, particularly against esophageal adenocarcinoma.
- Atrophic gastritis and subsequent hypochlorhydria, immunomodulation, esophageal microbiome modulation, and metabolic changes are among the proposed mechanisms of the protective effect.
- Future studies should clarify the precise impact of *H. pylori* on esophageal cancer, its long-term effects, and the contributing factors, potentially redefining the eradication strategies.

Epidemiology

Esophageal cancer is the eigth most common cancer and the sixth most common cancer-related cause of mortality worldwide due to its unfavorable prognosis[7,8]. Different parts of the world show

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significant variations in the incidence of esophageal cancer, with East Asia, the Middle East, and parts of Southern Africa reporting the highest rates of esophageal cancer, potentially due to dietary habits, environmental exposures, and possible genetic predispositions[8,9].

Studies have reported a general prevalence of around 50% of the world population for *H. pylori* infection[10]. Nevertheless, the prevalence of *H. pylori* infection has been declining globally, especially in high-income countries, due to improved sanitation, better living conditions, and large-scale use of antibiotics[11,12]. A recent meta-analysis by Li *et al*.[11] showed a declining trend of *H. pylori* prevalence worldwide; the estimated global prevalence of *H. pylori* infection has decreased from 58.2% in the 1980s to 43.1% in the 2011–2022 period. However, it still remains prevalent in low-income and middle-income countries, with some studies reporting up to 70% prevalence in Africa[5,13,14]. *H. pylori* infection is usually acquired in childhood and, if left untreated, can persist till the end of life[3].

Latest studies have suggested that up to three-fourth of the noncardia and over 95% of gastric cardia malignancies are related to *H. pylori,* the role of which is evident through the decrease of gastric cancer incidence worldwide as a result of *H. pylori* eradication efforts[15,16]. Current evidence is inconclusive on the rate of coexistence for *H. pylori* infection and esophageal cancer. Meanwhile, recent population-based studies have reported an almost three-fold decrease in the risk of esophageal adenocarcinomas (HR = 0.35, 95% CI: 0.12–0.97) among the individuals infected with *H. pylori*[17].

Impact of *H. pylori* on gastrointestinal malignancies

Gastric cancer

H. pylori infection is a leading cause of gastric cancer, particularly noncardia gastric adenocarcinoma[18]. It acts as a chronic inflammation promoter, leading to a cascade of pathological changes, including chronic gastritis, intestinal metaplasia, dysplasia, and, ultimately, neoplasia[19]. Recent research employing advanced methods, such as cell lineage tracing and single-cell RNA sequencing, has improved the understanding of the molecular identity and behavior of gastric stem cells under normal and infected conditions. The *H. pylori* virulence factors, such as cytotoxin-associated gene A (CagA) and vacuolating cytotoxin gene A (VacA), play critical roles in its pathogenicity[20]. CagA-positive strains are associated with a higher risk of gastritis and gastric cancer due to their potency in disrupting cellular signaling pathways and the inflammation-promoting and epithelial-mesenchymal transition (EMT)-inducing characteristics[21,22]. Recent studies have suggested the role of oncogenic signaling pathways, such as Wnt/β-catenin and PI3K/AKT/mTOR, in *H. pylori*-related gastric cancer[23,24]. Studies have also estimated that *H. pylori* is present in over half of the global population, although significant variations have been observed through its prevalence and the risk of gastric cancer in each region, with the highest incidences observed in East Asia and South America[15]. Eradication of *H. pylori* has been significantly linked to decreased risk of gastric cancer in long-term studies[25]. A Cochrane meta-analysis by Ford and colleagues has reported with moderate certainty evidence that eradicating *H. pylori* reduces the incidence of gastric cancer and gastric cancer-related mortality in healthy, asymptomatic infected Asian individuals[26].

Colorectal cancer

The link between *H. pylori* and colorectal cancer remains controversial. Studies have suggested a potential association, possibly through systemic inflammatory responses and alterations in gut microbiota[27]. However, conflicting studies have found no significant correlation[28]. Meta-analyses and cohort studies have yielded mixed results, with some indicating a modest increased risk of colorectal cancer in *H. pylori*-infected individuals and others showing no significant correlation[29,30].

Esophageal cancer

The majority of previous studies have reported an inverse association between *H. pylori* infection and esophageal cancer, mostly with low degrees of certainty. *H. pylori*'s role in inducing atrophic gastritis and reducing gastric acid secretion may lower the incidence of gastroesophageal reflux disease (GERD), a major risk factor for esophageal adenocarcinoma, therefore suggesting a potential protective effect on esophageal adenocarcinoma[31]. Nevertheless, the relationship between *H. pylori* and esophageal squamous cell carcinoma is even less clear, with several key studies suggesting increased rates subsequent to *H. pylori* infections in some populations[32]. Some studies suggest a protective effect similar to esophageal adenocarcinoma, while others find no significant association or potentially increased risk. Most importantly, the mechanisms of the potential protective role are yet undefined and mostly unclear[33]. Table 1 summarizes the key studies evaluating the impact of *H. pylori* infection on the incidence of esophageal cancer and its subtypes.

Mechanisms of *H. pylori* protective role in esophageal cancer

The proposed mechanisms for this protective effect include:

Atrophic gastritis and hypochlorhydria

One of the primary proposed mechanisms of *H. pylori's* protective effect against esophageal cancer is by inducing atrophic gastritis[17]. *H. pylori* infection leads to chronic gastritis, which in some individuals progresses to atrophic gastritis, characterized by the loss of gastric glandular cells and a subsequent reduction in acid secretion. This acid reduction decreases GERD and Barrett's esophagus, and, eventually, esophageal adenocarcinoma.

Esophageal microbiome modulation

H. pylori infection affects the composition of the upper gastrointestinal tract microbiome, including the esophagus, which is reported to have the possibility of a protective or carcinogenic role[45,46]. Esophageal microbiomes can be categorized into two main classes: type I and type II microbiomes[47,48]. Typical type I microbiome, primarily consisting of gram-positive *Streptococcus* bacteria, is observed within normal populations, whereas the type II microbiota consists of a majority of gram-negative bacteria and is associated with esophagitis and Barrett's esophagus. *H. pylori* is generally expected to shift the environment towards the gram-negative bacteria; however, the abundance of *H. pylori* bacteria potentially inhibits the proliferation and function of other gram-negative bacteria. Nevertheless, the precise mechanisms and effects of *H. pylori* esophageal microbiome-modulation are unknown.

Table 1

Key studies evaluating the impact of H. pylori infection on esophageal cancer.

Authors	Year	Country	Study design	Study population	Outcomes
Vieth *et al.*[34]	2000	Germany	Retrospective observational study	Patients with reflux disease or non-ulcer dyspepsia ($n=2201$)	A total of 1054 and 138 cases of Barrett and Barrett's neoplasia were recorded, respectively. *H. pylori* infection was not associated with Barrett and Barrett's neoplasia
Anandasabapathy *et al.*[35]	2007	United States	Retrospective observational study	A total of 109 patients with Barrett's metaplasia, dysplasia, or esophageal adenocarcinoma	Data regarding the presence of *H. pylori* was available for 78 patients. High-grade dysplasia/Esophageal adenocarcinoma was observed in 21/62 *H. pylori*-negative and 4/16 *H. pylori*-positive patients (OR: 2.73, 95% CI: (0.94–7.98)
Khoshbaten *et al.*[36]	2011	Iran	Case–control study	Adults with and without esophageal squamous cell carcinoma ($n=100$ in each group)	*H. pylori* presence showed a significant association with a lower risk of cancer development (58 *H. pylori*-positive in the case group vs 83 in the control group – OR = 0.28, 95% CI: 0.15–0.54)
Sonnenberg *et al.*[37]	2017	United States	Case–control study	Patients referred for esophagogastroduodenoscopy ($n=596\,479$)	Barrett's metaplasia was observed in 76 475 individuals, and 37 601 had *H. pylori* gastritis. A significant reverse association was observed between gastric *H. pylori* and dysplasia/adenocarcinoma (OR = 0.3, 95% CI: 0.26–0.37)
Poyrazoglu *et al.*[38]	2017	Turkey	Retrospective observational study	Esophageal squamous cell carcinoma patients ($n=95$) and control group of dyspeptic individuals ($n=151$)	*H. pylori* was reported in 84/95 (case) and 128/151 (control) patients. A significantly lower rate of *H. pylori* was observed in patients with esophageal squamous cell carcinoma compared with the control group
Vohlonen *et al.*[39]	2018	Finland	Cohort study	*H. pylori* antibody positive ($n=6625$) and negative ($n=5391$) middle-aged men	A total of 10 cases of esophageal cancer were reported in the antibody-positive group, in contrast with 29 cases in the antibody-negative (control group) (RR = 0.28, 95% CI: 0.13–0.6). Most cases of esophageal cancer were squamous type
Gao *et al.*[40]	2022	China	Case–control study	Adenocarcinoma of the esophagogastric junction ($n=349$) and control ($n=1859$) patients	*H. pylori*-positive patients had a significantly higher risk of elevated risk for adenocarcinoma of the esophagogastric junction (OR = 1.95, 95% CI: 1.47–2.63)
Poosari *et al.*[41]	2023	Thailand	Case–control study	Newly-diagnosed esophageal cancer patients ($n=105$) and healthy controls ($n=108$)	*H. pylori*-positive patients had a significantly higher risk of esophageal squamous cell carcinoma (adjusted OR = 2.76, 95% CI: 2.55–12.19) but a nonsignificantly lower risk of esophageal adenocarcinoma (adjusted OR = 0.67, 95% CI: 0.25–1.76)
Yan *et al.*[42]	2024	China	Cohort study	Middle-aged (40–69) participants regardless of the status of *H. pylori* infection ($n=27\,085$)	A total of 104 cases of esophageal cancer were observed. Unlike gastric cancer, no significant increase was observed in the risk of esophageal cancer (HR = 1.07, 95% CI: 0.73–1.57)
Wiklund *et al.*[43]	2024	Denmark, Finland, Iceland, Norway, and Sweden	Cohort study	Adult individuals within *H. pylori* eradication ($n=661\,987$)	A total of 550 cases of esophageal adenocarcinoma were observed. Following *H. pylori* eradication, the incidence of esophageal adenocarcinoma (standardized incidence ratio = 0.89, 95% CI: 0.82–0.97) and squamous cell carcinoma (standardized incidence ratio = 0.99, 95% CI: 0.89–1.11) did not increase
Lopez-Gomez *et al.*[44]	2024	Spain	Retrospective observational study	Adults with esophageal or gastroesophageal junction cancer ($n=89$)	Four patients were positive for *H. pylori* presence, three of which had esophageal adenocarcinoma)

HR, hazard ratio; OR, odds ratio; RR, relative risk.

Immunomodulation and inflammatory effects

H. pylori infection provokes complex immune responses through chronic inflammation pathways and regulatory mechanisms, such as regulatory T-cell stimulation[49,50]. This immune modulation and interfering with cellular signaling pathways promotes a balanced immune environment—despite Barrett's esophagus-promoting changes (such as E-cadherin methylation) induced by *H. pylori*[51–53]. In *H. pylori*-infected individuals, increased interleukin (IL)-1β expression has been associated with greater gastric atrophy and hypochlorhydria[54,55]. Lower acid secretion levels are directly linked to a lower risk of neoplastic lesion formation.

Impact on apoptosis and cell proliferation

Some studies have recorded pro-apoptotic effects of *H. pylori*[56]. Promoting apoptosis in potentially precancerous esophagus cells reduces the likelihood of malignant transformations. Furthermore, contrasting reports are available on the impact of *H. pylori* on cell proliferation and repair mechanisms, which are determinant in the context of carcinogenesis[57–59].

Competition with other pathogenic microorganisms

H. pylori might outcompete other potentially harmful bacteria in the upper gastrointestinal tract. By establishing itself within the gastric niche, *H. pylori* can suppress the colonization and overgrowth of other pathogens that might otherwise contribute to carcinogenic processes in the esophagus, such as *Porphyromonas gingivalis* and Epstein–Barr virus (EBV)[60,61]. This competitive exclusion can help maintain a microbial environment less prone to promoting esophageal cancer.

Nitrosative and oxidative stress modulation

H. pylori affects the levels of nitrosative and oxidative stress in the gastric and esophageal mucosa[62]. Chronic infection has been associated with increased nitric oxide (NO) production, which in turn can lead to the formation of reactive nitrogen species (RNS). These species can induce DNA damage and mutagenesis. In order to avoid being killed by the reactive oxygen species (ROS) and RNS, *H. pylori* modifies the functioning of infiltrating immune cells[63]. The controlled production of ROS and RNS under the influence of *H. pylori* might also play a role in modulating cellular processes that prevent uncontrolled cell proliferation and carcinogenesis. However, the evidence in this regard is still inconclusive.

Hormonal and metabolic changes

Various gastrointestinal hormones, such as gastrin, are affected by *H. pylori* infection[64]. Changes in gastrin levels can affect gastric acid secretion and motility, indirectly affecting the esophageal environment[65]. *H. pylori* infection-related changes in gastric metabolic activity may potentially create an environment less favorable for esophageal cancer development.

Future direction

While *H. pylori* eradication remains crucial for preventing gastric cancer and peptic ulcers, its potential protective role against esophageal cancer suggests a more delicate approach to maximize health benefits. Future studies are required with larger, more diverse populations to confirm the role of *H. pylori* against esophageal cancer and to understand the long-term impacts of proton pump inhibitors (PPIs). The impact of population differences and potential genetic predisposing factors should be acknowledged through future studies, since certain populations with a high incidence of esophageal cancer are exposed to environmental factors such as smoking, alcohol consumption, and dietary habits, which may interact with *H. pylori* infection in complex ways. The molecular and microbiological mechanisms by which *H. pylori* influences esophageal carcinogenesis should be further studied to provide a clearer insight into its dual role in gastrointestinal malignancies. Developing personalized treatment strategies considering individual patient risk factors, including *H. pylori* status and PPI use, could improve clinical outcomes and cancer prevention efforts.

Conclusions

The interplay between *H. pylori* infection and gastrointestinal malignancies is complex. Recent studies are suggestive of a protective role for *H. pylori* against esophageal cancer; however, further studies are required to improve our insight into these complicated associations and to advance evidence-based clinical practices aimed at optimizing patient care and cancer prevention.

Ethical approval

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Consent

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Author contribution

E.B. and E.N.: data curation and writing – original draft; S.P.L. and M.A.A.: data curation and writing – review and editing; S.H.: conceptualization and writing – review and editing; M.S.H.: conceptualization, data curation, project administration, and writing – original draft.

Conflicts of interest disclosure

The authors declare no conflicts of interest.

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References

[1] Reyes VE. Helicobacter pylori and its role in gastric cancer. Microorganisms 2023;11:1312.
[2] Marshall B, Warren JR. Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. The Lancet 1984;323:1311–5.
[3] Narayanan M, Reddy KM, Marsicano E. Peptic ulcer disease and helicobacter pylori infection. Mo Med 2018;115:219–24.
[4] Kayali S, Manfredi M, Gaiani F, *et al*. Helicobacter pylori, transmission routes and recurrence of infection: state of the art. Acta bio-medica : Atenei Parmensis 2018;89(8-s):72–6.
[5] Miller AK, Williams SM. Helicobacter pylori infection causes both protective and deleterious effects in human health and disease. Genes Immun 2021;22:218–26.
[6] Ali A, AlHussaini KI. Helicobacter pylori: a contemporary perspective on pathogenesis, diagnosis and treatment strategies. Microorganisms 2024;12:222.
[7] Then EO, Lopez M, Saleem S, *et al*. Esophageal cancer: an updated surveillance epidemiology and end results database analysis. World J Oncol 2020;11:55–64.
[8] Liu CQ, Ma YL, Qin Q, *et al*. Epidemiology of esophageal cancer in 2020 and projections to 2030 and 2040. Thorac Cancer 2023;14:3–11.
[9] Zhang HZ, Jin GF, Shen HB. Epidemiologic differences in esophageal cancer between Asian and Western populations. Chin J Cancer 2012;31:281–6.
[10] Malfertheiner P, Camargo MC, El-Omar E, *et al*. Helicobacter pylori infection. Nat Rev Dis Primers 2023;9:19.
[11] Li Y, Choi H, Leung K, *et al*. Global prevalence of Helicobacter pylori infection between 1980 and 2022: a systematic review and meta-analysis. The Lancet Gastroenterol Hepatol 2023;8:553–64.
[12] Zhou XZ, Lyu NH, Zhu HY, *et al*. Large-scale, national, family-based epidemiological study on Helicobacter pylori infection in China: the time to change practice for related disease prevention. Gut 2023;72:855–69.
[13] Borka Balas R, Meliț LE, Mărginean CO. Worldwide prevalence and risk factors of helicobacter pylori infection in children. Children (Basel, Switzerland) 2022;9:1359.
[14] Hussein RA, Al-Ouqaili MTS, Majeed YH. Detection of Helicobacter Pylori infection by invasive and non-invasive techniques in patients with gastrointestinal diseases from Iraq: a validation study. PLoS One 2021;16:e0256393.
[15] Shirani M, Pakzad R, Haddadi MH, *et al*. The global prevalence of gastric cancer in Helicobacter pylori-infected individuals: a systematic review and meta-analysis. BMC Infect Dis 2023;23:543.
[16] Chen Y-C, Malfertheiner P, Yu H-T, *et al*. Global prevalence of helicobacter pylori infection and incidence of gastric cancer between 1980 and 2022. Gastroenterology 2024;166:605–19.
[17] Holleczek B, Schöttker B, Brenner H. Helicobacter pylori infection, chronic atrophic gastritis and risk of stomach and esophagus cancer: results from the prospective population-based ESTHER cohort study. Int J Cancer 2020;146:2773–83.
[18] Lu Y, Xiao F, Wang Y, *et al*. Prevalence of helicobacter pylori in non-cardia gastric cancer in China: a systematic review and meta-analysis. Front Oncol 2022;12:850389.
[19] Meliț LE, Mărginean CO, Borka Balas R. The most recent insights into the roots of gastric cancer. Life 2024;14:95.
[20] Kishk RM, Soliman NM, Anani MM, *et al*. Genotyping of helicobacter pylori virulence genes cagA and vacA: regional and national study. Int J Microbiol 2021;2021:5540560.
[21] Takahashi-Kanemitsu A, Knight CT, Hatakeyama M. Molecular anatomy and pathogenic actions of Helicobacter pylori CagA that underpin gastric carcinogenesis. Cell Mol Immunol 2020;17:50–63.
[22] Al-Ouqaili MTS, Hussein RA, Majeed YH, *et al*. Study of vacuolating cytotoxin A (vacA) genotypes of ulcerogenic and non-ulcerogenic strains of Helicobacter pylori and its association with gastric disease. Saudi J Biol Sci 2023;30:103867.
[23] Morgos DT, Stefani C, Miricescu D, *et al*. Targeting PI3K/AKT/mTOR and MAPK Signaling Pathways in Gastric Cancer. Int J Mol Sci 2024;25:1848.
[24] Zuo W, Yang H, Li N, *et al*. Helicobacter pylori infection activates Wnt/β-catenin pathway to promote the occurrence of gastritis by upregulating ASCL1 and AQP5. Cell Death Discov 2022;8:257.
[25] Chiang T-H, Chang W-J, Chen SL-S, *et al*. Mass eradication of Helicobacter pylori to reduce gastric cancer incidence and mortality: a long-term cohort study on Matsu Islands. Gut 2021;70:243–50.
[26] Ford AC, Yuan Y, Forman D, *et al*. Helicobacter pylori eradication for the prevention of gastric neoplasia. Cochrane Database Syst Rev 2020;7:Cd005583.
[27] Ralser A, Dietl A, Jarosch S, *et al*. Helicobacter pylori promotes colorectal carcinogenesis by deregulating intestinal immunity and inducing a mucus-degrading microbiota signature. Gut 2023;72:1258–70.
[28] Luo F, Zhou P, Ran X, *et al*. No evident causal association between Helicobacter pylori infection and colorectal cancer: a bidirectional Mendelian randomization study. Sci Rep 2023;13:18544.
[29] Zuo Y, Jing Z, Bie M, *et al*. Association between Helicobacter pylori infection and the risk of colorectal cancer: a systematic review and meta-analysis. Medicine 2020;99:e21832.
[30] Choi DS, Seo SI, Shin WG, *et al*. Risk for colorectal neoplasia in patients with helicobacter pylori infection: a systematic review and meta-analysis. Clin Transl Gastroenterol 2020;11:e00127.
[31] Xie FJ, Zhang YP, Zheng QQ, *et al*. Helicobacter pylori infection and esophageal cancer risk: an updated meta-analysis. World J Gastroenterol 2013;19:6098–107.
[32] Gao H, Li L, Zhang C, *et al*. Systematic review with meta-analysis: association of helicobacter pylori infection with esophageal cancer. Gastroenterol Res Pract 2019;2019:1953497.
[33] Zhang C, Chen Y, Long Y, *et al*. Helicobacter pylori and gastrointestinal cancers: recent advances and controversies. Clin Med Insights Oncol 2024;18:11795549241234637.
[34] Vieth M, Masoud B, Meining A, *et al*. Helicobacter pylori infection: protection against Barrett's mucosa and neoplasia? Digestion 2000;62:225–31.
[35] Anandasabapathy S, Jhamb J, Davila M, *et al*. Clinical and endoscopic factors predict higher pathologic grades of Barrett dysplasia. Cancer 2007;109:668–74.
[36] Khoshbaten M, Zadimani A, Bonyadi MR, *et al*. Helicobacter pylori infection reduces the risk of esophageal squamous cell carcinoma: a case-control study in Iran. Asian Pac J Cancer Prev 2011;12:149–51.
[37] Sonnenberg A, Turner KO, Spechler SJ, *et al*. The influence of Helicobacter pylori on the ethnic distribution of Barrett's metaplasia. Aliment Pharmacol Ther 2017;45:283–90.
[38] Poyrazoglu OB, Dulger AC, Gultepe BS. Helicobacter Pylory infection in patients with esophageal squamous cell carcinoma. Clinics 2017;72:150–3.
[39] Vohlonen IJ, Hakama M, Härkönen M, *et al*. Oesophageal cancer incidence in 20-year follow-up in a population-based sample of 12 000 middle-age men with or without Helicobacter pylori infection in Finland. Gut 2018;67:1201–2.
[40] Gao P, Cai N, Yang X, *et al*. Association of and gastric atrophy with adenocarcinoma of the esophagogastric junction in Taixing, China. Int J Cancer 2022;150:243–52.
[41] Poosari A, Nutravong T, Namwat W, *et al*. Relationship between Helicobacter Pylori infection and the risk of esophageal cancer in Thailand. Asian Pac J Cancer Prev 2023;24:1073–80.
[42] Yan X, Zeng H, Li H, *et al*. The current infection with and association with upper gastrointestinal lesions and risk of upper gastrointestinal

cancer: insights from multicenter population-based cohort study. Int J Cancer 2024;155:1203–11.
[43] Wiklund AK, Santoni G, Yan J, *et al*. Risk of esophageal adenocarcinoma after helicobacter pylori eradication treatment in a population-based multinational cohort study. Gastroenterology 2024;167:485–492.e3.
[44] López-Gómez MMM, Fuerte R, Muñoz M, *et al*. Prevalence of Helicobacter pylori infection among patients with esophageal carcinoma. World J Gastroenterol 2024;30:3479–87.
[45] Chen CC, Liou JM, Lee YC, *et al*. The interplay between Helicobacter pylori and gastrointestinal microbiota. Gut Microbes 2021;13:1–22.
[46] Elghannam MT, Hassanien MH, Ameen YA, *et al*. Helicobacter pylori and oral–gut microbiome: clinical implications. Infection 2024;52:289–300.
[47] Yang L, Lu X, Nossa CW, *et al*. Inflammation and intestinal metaplasia of the distal esophagus are associated with alterations in the microbiome. Gastroenterology 2009;137:588–97.
[48] Park CH, Lee SK. Exploring esophageal microbiomes in esophageal diseases: a systematic review. J Neurogastroenterol Motil 2020;26:171–9.
[49] Fan J, Zhu J, Xu H. Strategies of Helicobacter pylori in evading host innate and adaptive immunity: insights and prospects for therapeutic targeting. Review. Front Cell Infect Microbiol 2024;14:1342913.
[50] Marzhoseyni Z, Mousavi MJ, Ghotloo S. Helicobacter pylori antigens as immunomodulators of immune system. Helicobacter 2024;29:e13058.
[51] Shah SC, Tepler A, Peek RM Jr, *et al*. Association between helicobacter pylori exposure and decreased odds of eosinophilic esophagitis-a systematic review and meta-analysis. Clin Gastroenterol Hepatol 2019;17:2185–198.e3.
[52] Neuper T, Frauenlob T, Posselt G, *et al*. Beyond the gastric epithelium — the paradox of Helicobacter pylori-induced immune responses. Curr Opin Immunol 2022;76:102208.
[53] Maleki Kakelar H, Barzegari A, Dehghani J, *et al*. Pathogenicity of Helicobacter pylori in cancer development and impacts of vaccination. Gastric Cancer 2019;22:23–36.
[54] Hong JB, Zuo W, Wang AJ, *et al*. Helicobacter pylori infection synergistic with IL-1β gene polymorphisms potentially contributes to the carcinogenesis of gastric cancer. Int J Med Sci 2016;13:298–303.
[55] Wroblewski LE, Peek RM Jr, Wilson KT. Helicobacter pylori and gastric cancer: factors that modulate disease risk. Clin Microbiol Rev 2010;23:713–39.
[56] Parra-Cid T, Calvino-Fernández M, Benito-Martínez S, *et al*. Role of reactive oxygen species and apoptosis in helicobacter pylori infection. Laher I, ed. Systems Biology of Free Radicals and Antioxidants. Springer Berlin Heidelberg; 2014:1849–70.
[57] Lin L-L, Huang H-C, Ogihara S, *et al*. Membrane repair against H. pylori promotes cancer cell proliferation. Nature Prec 2010;4:1–24.
[58] Lin L-L, Huang H-C, Ogihara S, *et al*. Helicobacter pylori disrupts host cell membranes, initiating a repair response and cell proliferation. Int J Mol Sci 2012;13:10176–92.
[59] Deng R, Zheng H, Cai H, *et al*. Effects of helicobacter pylori on tumor microenvironment and immunotherapy responses. Review. Front Immunol 2022;13:923477.
[60] Kong J, Liu Y, Qian M, *et al*. The relationship between porphyromonas gingivalis and oesophageal squamous cell carcinoma: a literature review. Epidemiol Infect 2023;151:e69.
[61] Palrasu M, Zaika E, El-Rifai W, *et al*. Role of bacterial and viral pathogens in gastric carcinogenesis. Cancers 2021;13:1878.
[62] Han L, Shu X, Wang J. Helicobacter pylori-mediated oxidative stress and gastric diseases: a review. Front Microbiol 2022;13:811258.
[63] Kumar S, Dhiman M. Helicobacter pylori secretary proteins-induced oxidative stress and its role in NLRP3 inflammasome activation. Cell Immunol 2024;399-400:104811.
[64] Meng W-P, Wang Z-Q, Deng J-Q, *et al*. The role of H. pylori CagA in regulating hormones of functional dyspepsia patients. Gastroenterol Res Pract 2016;2016:7150959.
[65] Wang JS, Varro A, Lightdale CJ, *et al*. Elevated serum gastrin is associated with a history of advanced neoplasia in Barrett's esophagus. Am J Gastroenterol 2010;105:1039–45.