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EDITORIAL

Is *Helicobacter pylori* infection protective against esophageal cancer?

Rick Maity, Arkadeep Dhali, Jyotirmoy Biswas

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Abstract

Helicobacter pylori (*H. pylori*) infection affects a substantial proportion of the global population and causes various gastric disorders, including gastric cancer. Recent studies have found an inverse relationship between *H. pylori* infection and esophageal cancer (EC), suggesting a protective role against EC. This editorial focuses on the possible mechanisms underlying the role of *H. pylori* infection in EC and explores the role of gut microbiota in esophageal carcinogenesis and the practicality of *H. pylori* eradication. EC has two major subtypes: Esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC), which have different etiologies and risk factors. Gut microbiota can contribute to EC *via* inflammation-induced carcinogenesis, immunomodulation, lactagenesis, and genotoxin production. *H. pylori* infection is said to be inversely related to EAC, protecting against EAC by inducing atrophic gastritis, altering serum ghrelin levels, and triggering cancer cell apoptosis. Though *H. pylori* infection has no significant association with ESCC, COX-2-1195 polymorphisms and endogenous nitrosamine production can impact the risk of ESCC in *H. pylori*-infected individuals. There are concerns regarding a plausible increase in EC after *H. pylori*

eradication treatments. However, *H. pylori* eradication is not associated with an increased risk of EC, making it safe from an EC perspective.

Key Words: *Helicobacter pylori*; *Helicobacter pylori* infection; Esophageal cancer; Esophageal squamous cell carcinoma; Esophageal adenocarcinoma; Barrett's esophagus; Microbiota; Dysbiosis; Eradication

Core Tip: *Helicobacter pylori* (*H. pylori*) infection, while being a risk factor for gastric cancer, may afford protection against esophageal cancer (EC). The two major subtypes of EC, *i.e.*, esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC), have different etiologies and risk factors. Recent studies have unequivocally established the inverse association between *H. pylori* infection and EAC, however there was no significant association with ESCC. *H. pylori* infection may protect against EAC by inducing atrophic gastritis, altering serum ghrelin levels, and triggering cancer cell apoptosis. Contrary to prevailing concerns, *H. pylori* eradication does not increase the risk of EC.

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INTRODUCTION

Helicobacter pylori (*H. pylori*), a Gram-negative anaerobic bacterium that colonizes the stomach, affects nearly 43.9% of adults and 35.1% of children and adolescents globally[1]. Besides causing various gastric disorders such as peptic ulcer, dyspepsia, and gastritis, it is a well-established etiological and risk factor for gastric cancer[2,3]. Eradication of *H. pylori* infection reduces the risk of gastric cancer in infected individuals[2]. However, startling new evidence has come to light suggesting that *H. pylori* infection might have a protective role against esophageal cancer (EC)[2,4]. In a recent issue of the *World Journal of Gastroenterology*, we read with interest an article that investigated the prevalence of *H. pylori* infection in a retrospective cohort of EC patients from a tertiary-care hospital in Spain[5]. The study findings are consistent with recent systematic reviews suggesting an inverse relationship between *H. pylori* infection and the development of EC[4,5]. This editorial reviews the current demographics, etiologies, and risk factors associated with EC, as well as the available evidence and possible mechanisms underlying the role of *H. pylori* infection in EC. It also discusses the role of gut microbiota in esophageal carcinogenesis and feasibility of *H. pylori* eradication in light of the bacterium's inverse relationship with EC.

DEMOGRAPHICS, ETIOLOGIES, AND RISK FACTORS OF EC

EC is the seventh most common cancer and sixth-largest cause of cancer-related mortalities in the world[6]. It has various subtypes: Squamous cell carcinoma (SCC), adenocarcinoma (AC), sarcoma, small cell carcinoma, and rare varieties such as lymphomas and melanomas[7]. The two major subtypes, SCC and AC, make up the vast majority of EC cases; SCC accounts for around 85% of cases, whereas AC accounts for 14%[8]. EC is more common in men, with incidence and mortality rates two- to three-times greater than in women[7,8].

The etiologies and risk factors of EC slightly vary across the two main subtypes, although the mechanisms underlying this variation have not yet been fully determined[4]. Smoking is an established risk factor for both esophageal SCC (ESCC) and AC, whereas alcohol consumption is associated only with ESCC[4,9,10]. Obesity, particularly central obesity, can lead to gastroesophageal reflux disease, which causes esophageal AC (EAC) either directly or *via* a pre-cancerous lesion known as Barrett's esophagus[9,10]. A low intake of fruits and vegetables is associated with an increased susceptibility to EC, possibly due to the deficiency of vitamins and minerals[4,9]. Table 1 summarizes the risk factors for ESCC and EAC.

ROLE OF GUT MICROBIOTA IN ESOPHAGEAL CARCINOGENESIS

In addition to the above-mentioned risk factors, gut microbiota has been discovered to play a key role in esophageal carcinogenesis[4,11,12]. The term "gut microbiota" primarily refers to the microorganisms (mostly bacteria) that live in the human digestive system, mostly encompassing the esophageal, oral, and intestinal microbiota[12]. The esophageal microbiome can be classified into two subtypes: Type I microbiota (comprising mainly Gram-positive bacteria like *Streptococcus*) and Type II microbiota (mainly Gram-negative bacteria prevalent in dysbiotic states). The healthy

Table 1 Risk factors of esophageal squamous cell carcinoma and adenocarcinoma

Squamous cell carcinoma	Adenocarcinoma
Male gender	Male gender
Alcohol	Tobacco smoking
Tobacco smoking	Obesity (BMI > 25 kg/m^2)
HPV infection	Barrett's esophagus
Low intake of fruits and vegetables	GERD
Consumption of hot beverages, pickled vegetables, processed and red meat	Low intake of fruits and vegetables
	Consumption of processed and red meat
Low socioeconomic status	High socioeconomic status
Genetic factors: Howel-Evans syndrome, Fanconi anemia, Bloom syndrome	Genetic factors: Familial Barrett's esophagus

BMI: Body mass index; GERD: Gastroesophageal reflux disease; HPV: Human papillomavirus.

esophageal microbiome is primarily constituted by microorganisms belonging to six phyla (Proteobacteria, Firmicutes, Bacteroidetes, Actinobacteria, Fusobacteria, and TM7), with *Streptococcus* as the dominant genus[13]. These microbiota achieve symbiosis with the immune system and carry out various physiological functions such as metabolism and immune maturation[12]. Any alterations in the gut microbiota can lead to the development of esophageal diseases, including EC.

Esophageal carcinogenesis can be induced by the gut microbiota *via* the following mechanisms: (1) Inflammation-induced carcinogenesis: Studies have shown that diet-induced alterations in the gut microbiota lead to increased levels of pro-inflammatory cytokines and immune cells[14]. Dysbalance between the gut microflora and immune system can disrupt the local microenvironment homeostasis and eventually lead to chronic inflammation. Persistent release of pro-inflammatory cytokines can activate toll-like receptors (TLR) and nucleotide-binding oligomeric domain-like receptors, triggering tumorigenesis[12]; (2) Immunomodulation: A taxonomic shift towards Type II microbiota has been observed in patients with gastroesophageal reflux disease (GERD) and BE. Lipopolysaccharide-producing Gram-negative bacteria can cause inducible nitric oxide synthase to be overexpressed, which impairs lower esophageal sphincter relaxation and increases intra-gastric pressure, thus predisposing to GERD, a risk factor for EC. Additionally, lipopolysaccharides can bind to TLR 4, leading to nuclear factor-kappa B activation and expression of cyclooxygenase-2 (COX-2), which blocks apoptosis and induces tumor cell proliferation and angiogenesis[14]. *Fusobacterium nucleatum* causes aberrant activation of the Wnt/β-catenin pathway, causing an increased production of chemokines that contribute to carcinogenesis and therapeutic resistance in EC[12,14]; (3) Lactagenesis: Studies have found that lactate-producing bacteria, such as *Staphylococcus* and *Lactobacillus*, are abundant in patients of GERD, BE, and EAC[14]. According to the Warburg effect, cancer cells are characterized by accelerated glycolysis and excessive lactate formation even under aerobic conditions. Lactate is thought to play a crucial role in all steps of carcinogenesis, *i.e.*, angiogenesis, immune escape, cell migration, metastasis, and self-sufficiency of cancer cells; therefore, the goal of the Warburg effect is now believed to be the augmented production of lactate (also known as lactagenesis)[15]. By converting glucose into lactate, the lactate-producing bacteria support the survival and proliferation of cancer cells[4]. Given that lactate-producing bacteria are significantly increased in EAC, the microbial contribution to lactagenesis and its effect on esophageal cells need to be explored[14]; and (4) Genotoxin production: Certain pathogens are capable of producing compounds called genotoxins, which damage the host DNA, causing cell death, oncogene activation, or downregulation of tumor suppressor genes[16]. A variety of Gram-negative bacteria (such as *Escherichia coli*, *Campylobacter*, and *H. pylori*) can produce cytolethal distending toxin, which damages structural DNA and stimulates carcinogenesis[17]. Colibactin (produced by certain members of Enterobacteriaceae) and nitrosamines are genotoxins that cause DNA damage by alkylation[17,18]. *H. pylori* produces a toxin named cytotoxin-associated gene A (cagA) that promotes production of reactive oxygen species and causes oxidative DNA damage. While cagA-positive strains of *H. pylori* have been implicated in gastric cancer, their role in EC remains unknown[17].

H. PYLORI: FRIEND OR FOE IN EC?

Till date, six meta-analyses have investigated the association between *H. pylori* infection and EC, and they have all indicated a negative correlation. While the meta-analyses have emphatically confirmed the inverse association of *H. pylori* infection with EAC, no significant association could be found with ESCC[19-24]. But significant regional variances have been observed, with certain regions (such as Asia and the Middle East) showing an inverse association and others displaying a positive association with *H. pylori* infection, especially with cagA-positive strains; these regional variances may be attributed to dietary cultures and lifestyles that differ from one region to another[19-21]. Thus, *H. pylori*'s association with ESCC is not clear and needs to be explored by further population-based studies. While analyzing the

Table 2 Summary of meta-analyses regarding the association between *Helicobacter pylori* infection and esophageal cancer

Authors	Year of publication	Number of studies	Association of *H. pylori* infection with ESCC	Association of *H. pylori* infection with EAC
Gao *et al*[19]	2019	35	No significant association in the general population: OR 0.84 (95%CI: 0.64-1.09)/OR 0.74 (95%CI: 0.54-0.97); Inverse relationship in the Middle Eastern population: OR: 0.34 (95%CI: 0.22-0.52 or 0.26-0.44); Positive association with the North American population: OR: 1.83 (95%CI: 1.17-2.87)	Inverse relationship: OR 0.55 (95%CI: 0.43-0.70)/OR 0.23 (95%CI: 0.15-0.36)
Nie *et al*[20]	2014	28	No significant association with the general population: OR 1.16 (95%CI: 0.83-1.60); Inverse association with Asian population: OR 0.74 (95%CI: 0.57–0.97); Positive association with non-Asian population: OR 1.41 (95%CI: 1.02–1.94)	Inverse relationship: OR 0.57 (95%CI: 0.44-0.73)
Xie *et al*[21]	2013	27	No significant association in the general population: OR 0.83 (95%CI: 0.63-1.03); Inverse relationship with the East Asian population: OR 0.66 (95%CI: 0.43-0.89)	Inverse relationship: OR 0.59 (95%CI: 0.51-0.68)
Islami and Kamangar [22]	2008	19	No significant association: OR 1.10 (95%CI: 0.78-1.55)	Inverse relationship: OR 0.56 (95%CI: 0.46-0.68)
Zhuo *et al*[23]	2008	195	No significant association: OR 0.80 (95%CI: 0.45-1.43), $Z = 0.75$, $P > 0.05$	Inverse relationship: OR 0.58 (95%CI: 0.48-0.70), $Z = 5.79$, $P < 0.01$
Rokkas *et al* [24]	2007	72	No significant association: OR 0.85 (95%CI: 0.55-1.33), $P = 0.48$	Inverse relationship: OR 0.52 (95%CI: 0.37-0.73), $P < 0.001$

H. pylori: Helicobacter pylori; ESCC: Esophageal squamous cell carcinoma; EAC: Esophageal adenocarcinoma; OR: Odds ratio.

association between *H. pylori* infection and the subtypes of EC, it would be prudent to consider the limitations of the meta-analyses, which include heterogeneity among study populations, confounding bias, and varying diagnostic criteria. The relevant information from all the meta-analyses has been summarized in Table 2.

The apparent protective role played by *H. pylori* in EAC can be explained by the following mechanisms: (1) Development of atrophic gastritis: *H. pylori* infection can cause atrophic gastritis; this lowers gastric acid secretion, reduces gastroesophageal reflux, and is postulated to protect against GERD, a risk factor for EAC[2,4]. Successful eradication of *H. pylori* is associated with a higher risk of GERD, especially in Asians[25]; (2) Alteration of plasma ghrelin: *H. pylori* may influence serum ghrelin levels, which is a key regulator of obesity and is known to stimulate cancer development and progression. *H. pylori* eradication is postulated to increase serum ghrelin levels, which stimulates adipogenesis and inhibits lipolysis, resulting in obesity[20,26]. By impacting the functioning of the lower esophageal sphincter, obesity predisposes to GERD, which is a risk factor for both BE and EAC[20]; and (3) Induction of cancer cell apoptosis: *In vitro*, *H. pylori* has been shown to preferentially trigger apoptosis in Barrett's-derived EAC cells over normal esophageal cells. By increasing Fas protein expression in tumor cells, *H. pylori* activates the *Fas*-caspase pathway, which leads to apoptosis by causing fragmentation of cellular DNA[27]. Table 3 summarizes the above-mentioned protective mechanisms.

In ESCC, the role of *H. pylori* infection is not entirely clear. The overexpression of COX-2 can influence the inverse association between *H. pylori* infection and ESCC. COX-2-1195G/A, a single nucleotide polymorphism, can not only modify the transcription of COX-2 but also the risk of developing ESCC. The inverse association between *H. pylori* infection and ESCC (especially in the lower third of the esophagus) is enhanced in patients carrying the COX-2-1195AA homozygous genotype[28]. On the other hand, *H. pylori*-induced atrophic gastritis and the ensuing decrease in gastric acidity may favor the proliferation of bacteria that produce nitrosamines, a known genotoxin. Gastric nitrosamines can come in contact with the esophageal mucosa and get converted into carcinogenic compounds by cytochrome P450. Thus, endogenous nitrosamines produced as a secondary effect of *H. pylori* infection may be implicated in ESCC[18]. Further studies are required to establish the roles of COX-2-1195 polymorphisms, atrophic gastritis, and endogenous nitrosamines in the pathogenesis of ESCC. The mechanisms underlying the protective role of *H. pylori* infection against EAC have been summarized in Table 3.

FEASIBILITY OF *H. PYLORI* ERADICATION

Since the dawn of humanity, *H. pylori* has coexisted with us and was previously commonly prevalent in human stomachs. With the advent of antibiotics and improved sanitation, this bacterium is fast disappearing from human populations, especially in Western nations[22].

H. pylori infection can lead to peptic ulcers, which is the main indication for eradication treatment[29]. Eradication of *H. pylori*, besides healing chronic active gastritis and peptic ulcer disease, is an effective strategy for preventing gastric cancer[2]. It comprises a regimen of antibiotics and proton pump inhibitors and has been shown to reduce the risk of developing gastric cancer by nearly 50%[2,30].

Table 3 Mechanisms underlying the protective role of *Helicobacter pylori* infection against esophageal adenocarcinoma

Mechanism	Description	Implications
Development of atrophic gastritis	The inflammatory processes in chronic *H. pylori* infection can cause gastric atrophy by loss of gastric glands and partial replacement by intestinal epithelium. This reduces the number of parietal cells which secrete hydrochloric acid, the main constituent of gastric acid	Lower gastric acidity reduces the risk of GERD and BE, risk factors for EAC
Alteration of plasma ghrelin levels	*H. pylori*-induced gastric atrophy leads to reduced gastric ghrelin production, subsequently decreasing plasma ghrelin levels. Contrastingly, eradication of *H. pylori* increases ghrelin levels, thus leading to obesity. Thus, *H. pylori* infection is inversely related to obesity	Ghrelin is a key regulator of obesity and has been implicated in the pathogenesis and differentiation of esophageal cancers. Obesity can predispose individuals to GERD, which is a risk factor for both BE and EAC
Induction of cancer cell apoptosis	*In vitro*, *H. pylori* induces apoptosis in Barrett's-derived EAC cells at a higher rate than in healthy esophageal cells. *H. pylori* activates the *Fas*-caspase cascade by increasing Fas protein expression in EAC cells, which leads to apoptosis through the fragmentation of cellular DNA	*H. pylori* infection can induce apoptosis and thus reduce the rate of esophageal cancer progression

H. pylori: *Helicobacter pylori*; GERD: Gastroesophageal reflux disease; BE: Barrett's esophagus; EAC: Esophageal adenocarcinoma.

Keeping in mind the inverse association of *H. pylori* infection with EAC, eradication treatments should have been associated with an increased incidence of EC following successful eradication. However, recent cohort studies have debunked this hypothesis, proving that *H. pylori* eradication does not increase the risk of EC[29,31]. A possible explanation is that eradication treatment cannot reverse the chronic gastric atrophy caused by *H. pylori* infection, which protects against both BE and EAC by causing diminished gastric acid secretion and gastroesophageal reflux[29,31]. The adoption of healthier lifestyles and dietary habits may be another factor contributing to the reduced incidence of EAC post-*H. pylori* eradication[29]. Thus, *H. pylori* eradication treatment is safe from an EC perspective, and there is no reason to withhold *H. pylori* eradication in cases where it is indicated[29,31]. Nevertheless, large multicentric studies with long follow-up periods are required to thoroughly evaluate this topic.

CONCLUSION

H. pylori, a Gram-negative bacterium that causes various gastric disorders, shows an inverse relationship with EC. EC has two major subtypes, *i.e.*, EAC and ESCC, which have slightly different etiologies and risk factors. Additionally, gut microbiota can contribute to carcinogenesis in four ways: Inflammation-induced carcinogenesis, immunomodulation, lactagenesis, and genotoxin production. The inverse association of *H. pylori* infection with EAC has been unequivocally confirmed, but no significant association has been observed with ESCC. *H. pylori* infection protects against EAC by inducing atrophic gastritis, influencing serum ghrelin levels, and triggering cancer cell apoptosis. While COX-2-1195 polymorphisms can modify the inverse association between *H. pylori* infection and ESCC, endogenous nitrosamines produced as a secondary impact of *H. pylori*-induced atrophic gastritis may increase the risk of ESCC. There are concerns regarding a plausible increase in EC after *H. pylori* eradication treatments. Fortunately, *H. pylori* eradication is not associated with an increased risk of EC as determined by recent cohort studies, possibly because *H. pylori*-induced atrophic gastritis cannot be reversed by eradication treatment. Thus, *H. pylori* infection affords a degree of protection against the development of EC (especially EAC), and *H. pylori* eradication treatment is safe from an EC perspective.

FOOTNOTES

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