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LETTER TO THE EDITOR

Role of *Helicobacter pylori* in esophageal carcinogenesis: Friend or foe?

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Abstract

In this letter, we comment on the article by López-Gómez *et al*, which explores the prevalence of *Helicobacter pylori* (*H. pylori*) infection among patients with esophageal carcinoma (EC) in a cohort of Spain population. The relationship between *H. pylori* infection and EC is very complex. Previous research results are often contradictory due to the influence of dietary habits, age, region, and other factors. López-Gómez *et al* reported a very low prevalence of previous *H. pylori* infection in their cohort of patients with EC, and most of them had previously received or concomitantly received proton pump inhibitors treatment. These results are similar to previous results, which suggest that *H. pylori* infection is related to the low incidence of EC. Therefore, this study may provide a direction for preventing EC and eradicating *H. pylori* in Spain.

Key Words: *Helicobacter pylori*; Esophageal carcinoma; Esophageal squamous cell carcinoma; Esophageal adenocarcinoma; Proton pump inhibitors

Core Tip: López-Gómez *et al* provided evidence of a very low prevalence of previous *Helicobacter pylori* infection in a Spanish cohort of patients with esophageal carcinoma, and most of those patients had previously received or concomitantly received proton pump inhibitors treatment. However, more studies (such as prospective studies or Mendelian randomization studies) are still needed to confirm the causal relationship between them in the future.

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TO THE EDITOR

Esophageal carcinoma (EC) is a malignancy that affects the esophagus and mainly consists of four types: Esophageal squamous cell carcinoma (ESCC), esophageal adenocarcinoma (EAC), undifferentiated carcinoma, and other types. According to GLOBOCAN 2020 data, EC is the eighth most common cancer worldwide, with an estimated 604100 new cases and 544076 deaths *per* year[1]. In terms of clinical manifestations, the early symptoms of EC are not obvious, but with the development of the disease, patients can experience progressive dysphagia, swallowing pain, reflux, and vomiting, which seriously affect their quality of life[2,3]. In terms of treatment methods, the main treatment methods for esophageal cancer include endoscopic therapy (endoscopic mucosal resection, endoscopic submucosal dissection, *etc.*), surgery, chemotherapy, radiotherapy, immunotherapy, targeted drug therapy, and biological therapy. Although early EC can be cured through endoscopic therapy, the treatment of advanced esophageal cancer is relatively difficult and expensive, which places a heavy economic burden on patients and their families. Therefore, exploring the risk factors and protective factors for esophageal cancer and the underlying mechanisms will contribute to the prevention and treatment of EC in the future.

Helicobacter pylori (*H. pylori*) is a gram-negative, spiral, flagellated, microaerophilic bacterium that colonizes the gastric mucosa of humans. This bacterium invades the submucosal membrane of the stomach through fecal-oral or fecal-fecal transmission, leading to gastric and duodenal diseases. In different countries, the prevalence of *H. pylori* ranges from approximately 34.7% to 50.8%[4]. It is a well-known pathogen involved in various gastric diseases, including chronic gastritis, peptic ulcers, mucosa-associated lymphoid tissue lymphoma, and gastric adenocarcinoma[5]. However, in addition to being a risk factor for stomach-related diseases, *H. pylori* may have potential protective effects on certain autoimmune diseases, such as asthma and inflammatory bowel disease[6]. Notably, the results of previous studies on the relationship between *H. pylori* and EC are contradictory, with some studies suggesting that *H. pylori* has a protective effect on EC, whereas others suggest that *H. pylori* has no protective effect[7-11].

Proton pump inhibitors (PPIs) are a class of medications that inhibit the hydrion ion potassium ion-ATPase in parietal cells, leading to a reduction in gastric acid secretion. These drugs are commonly used to treat various gastrointestinal disorders such as peptic ulcers, esophagitis, hyperacidity, *H. pylori* infection, and gastroesophageal reflux disease (GERD). However, PPIs have additional effects beyond acid suppression, which inhibits bone resorption and decreases urinary calcium excretion, potentially impacting bone health[12]. Therefore, considering the long-term use of PPIs to control GERD in clinical practice, their role in EC is also worth exploring.

Although many previous studies have investigated the relationship between *H. pylori* and EC, the conclusions drawn by different studies are inconsistent. In addition, the incidence of *H. pylori* and EC is extremely different in different regions. Here, we pay special attention to the study by López-Gómez *et al*[13] in the latest issue of the *World Journal of Gastroenterology*, analyzing the prevalence of *H. pylori* in EC patients from a tertiary hospital in Madrid, Spain, and discussing its possible mechanism.

The relationship between H. pylori infection and EC

The relationship between *H. pylori* infection and EC is very complex. Previous research results are often contradictory due to the influence of dietary habits, age, region, and other factors. Considering that the risk factors and mechanisms of EAC and ESCC are inconsistent, we discuss them separately.

Many previous meta-analyses have shown that *H. pylori* is associated with a reduction in the risk of EAC[7-9]. Barrett's esophagus (BE), which can develop from GERD, can develop into EAC. A meta-analysis investigated the relationships between *H. pylori* and BE or GERD, and the results revealed that *H. pylori* was associated with a low risk of both BE and GERD[14]. These findings suggest that *H. pylori* may play a role in multiple stages of tumorigenesis. The underlying mechanisms may include the following aspects[15]: (1) *H. pylori* infection may promote gastric emptying by inhibiting ghrelin levels, thereby reducing the risk of BE and EAC; (2) Excessive secretion of gastric acid promotes the pathogenesis of GERD and BE. Atrophy of the gastric mucosa after *H. pylori* infection can reduce gastric acid secretion and reflux, thereby reducing the risk of EAC; (3) *H. pylori* can promote the apoptosis of EAC cells; (4) Eradication of *H. pylori* may promote the occurrence of EAC by affecting the distribution of esophageal microorganisms; and (5) *H. pylori* may increase the pressure on the lower esophageal sphincter by promoting gastrin secretion, thereby reducing the occurrence of GERD.

In contrast, the relationship between *H. pylori* and ESCC is inconclusive. Some retrospective studies have shown that *H. pylori* has a protective effect on ESCC[10,11]. The meta-analysis suggested that *H. pylori* did not have a protective effect on ESCC in the overall population [odds ratio (OR) = 0.84; 95% confidence interval (CI): 0.64-1.09], whereas the subgroup analysis suggested that *H. pylori* had a protective effect in the Middle East (OR = 0.34; 95%CI: 0.22-0.52) or East Asia population (OR = 0.66; 95%CI: 0.43-0.89)[7,8]. These results may be related to the inconsistent dietary habits, drinking habits and genetic factors across different regions. To date, ESCC still accounts for the vast majority of ECs. Therefore, it is necessary to study the different roles played by *H. pylori* in the ESCC of different regions.

The potential effect of H. pylori infection on EC in Spain

López-Gómez *et al*[13] conducted a retrospective study that included 89 patients with EC in a Spanish hospital from February 2008 to December 2023. Among these patients, 47 (52.8%) had EAC and 37 (41.6%) had ESCC. The results revealed that there were a total of 4 cases of *H. pylori* infection in EC, including 3 cases in EAC (accounting for 6.3% of all EAC cases), and 1 case in ESCC (accounting for 2.7% of all ESCC cases). It is obvious that the infection rate of *H. pylori* in this cohort was much lower than that in the general population, whether it was EAC or ESCC. In summary, these results suggest that *H. pylori* may have a protective effect on EAC and ESCC in Madrid, Spain.

The role of PPIs in EC

There are many kinds of PPIs commonly used, including lansoprazole, pantoprazole, rabeprazole, omeprazole, esomeprazole and so on. In recent years, PPIs have become one of the most commonly used drugs because of their good effects. Although short-term use is often considered safe, long-term use is associated with risks such as cancer and osteoporosis[12,16,17]. Previous studies have shown that long-term use of PPIs can increase the risk of gastric cancer and colorectal cancer while reducing the risk of cervical cancer, breast cancer, and ovarian cancer[17-19]. However, whether the use of PPIs affects the occurrence of EC remains unclear. Considering that PPI drugs can inhibit the growth of *H. pylori* and that *H. pylori* is associated with a low risk of EAC, the use of PPIs may be associated with the risk of EAC. In the study of López-Gómez *et al*[13], 86 (96.6%) of 89 patients with EC had used or were using PPIs, suggesting a possible correlation between PPIs and EC.

Clinical significance and future research directions

The study of López-Gómez *et al*[13] provided new evidence for the relationship between *H. pylori* infection and esophageal cancer in Spain. The abuse of PPIs may be one of the factors leading to EC. Therefore, long-term clinical use of PPIs should be treated with caution. Although many previous studies and meta-analyses have concluded that *H. pylori* can reduce the risk of EAC, there are no relatively reliable prospective studies. In addition, international consensus recommendations advocate for PPI therapy in patients with BE because high-quality evidence derived from randomized controlled trials indicates that PPIs play a chemo-preventative role in developing Barrett's associated neoplasia. Considering that PPIs are commonly used drugs for BE, it is still unclear whether PPIs are the cause or result of EC. Therefore, in the future, we can use Mendelian randomization analysis or perform prospective studies to obtain more reliable conclusions. In addition, we can explore the mechanism by which *H. pylori* affects EC through additional animal and cell tests. Moreover, we can identify relevant targets through multi-omics analysis, providing new ideas to prevent EC in the future.

CONCLUSION

The study of López-Gómez *et al*[13] suggested that *H. pylori* infection was associated with a low risk of EC in Spain. Further study revealed that most patients with EC had used or were using PPIs, suggesting that PPIs may be associated with the occurrence of EC in this region. These results may provide new insights into the prevention and treatment of EC in Spain.

FOOTNOTES

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