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Contents

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EDITORIAL

4518 Sepsis-associated liver injury: Mechanisms and potential therapeutic targets

Chen JW, Liu CY, Li S, Wu SW, Cai C, Lu MQ

ORIGINAL ARTICLE

Retrospective Study

4523 Comparing gastrointestinal dysfunction score and acute gastrointestinal injury grade for predicting short-term mortality in critically ill patients

Shen C, Wang X, Xiao YY, Zhang JY, Xia GL, Jiang RL

Prospective Study

4532 Strategic insights into the cultivation of pancreatic cancer organoids from endoscopic ultrasonography-guided biopsy tissue

Yang JL, Zhang JF, Gu JY, Gao M, Zheng MY, Guo SX, Zhang T

Basic Study

4544 Transfection of 12/15-lipoxygenase effectively alleviates inflammatory responses during experimental acute pancreatitis

Sun HW, Bai YY, Qin ZL, Li RZ, Madzikatire TB, Akuetteh PDP, Li Q, Kong HR, Jin YP

CASE REPORT

4557 Esophageal melanosis: Two case reports and review of literature

Kazacheuskaya L, Arora K

LETTER TO THE EDITOR

4566 Colon cancer screening programs prevent cancer

Flynn DJ, Feuerstein JD

4569 Does hemorrhoidal artery embolization really benefit patients with hemorrhoids?

Lei ML, Dong LL, Zhang HP, Yu YB

4576 Metabolic dysfunction-associated steatotic liver disease: The question of long-term high-normal alanine aminotransferase as a screening test

Moyana TN

4583 Endoscopic polidocanol foam sclerobanding for treatment of internal hemorrhoids: A novel outpatient procedure

Mou AN, Wang YT

4587 Evaluation of the GATIS score for predicting prognosis in rectal neuroendocrine neoplasms

Feng YN, Liu LH, Zhang HW

4591 *Helicobacter pylori*, esophageal precancerous lesions, and proton pump inhibitor overuse

Zhang F, Zhang H, Liu YM, Tang FS

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Contents

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LETTER TO THE EDITOR

Helicobacter pylori, esophageal precancerous lesions, and proton pump inhibitor overuse

Feng Zhang, Hang Zhang, Yan-Miao Liu, Fu-Shan Tang

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Abstract

This article reviews the cohort study published in the *World Journal of Gastroenterology*, which reported low rates of *Helicobacter pylori* (*H. pylori*) infection among esophageal cancer (EC) patients, coupled with proton pump inhibitor (PPI) overuse. These findings suggest a potential protective role of *H. pylori* against EC and indicate a possible association between PPI use and increased cancer risk. In light of these findings, our article examines the complex relationship between *H. pylori* and esophageal precancerous lesions, exploring the potential underlying mechanisms. We also address growing concerns regarding PPI overuse, including its potential effects on cancer therapy efficacy and the risk of drug interactions. Ultimately, this article highlights the urgent need for further research to evaluate the safety and efficacy of PPIs in cancer patients and to better understand their broader implications.

Key Words: Esophageal carcinoma; *Helicobacter pylori*; Esophageal precancerous lesions; Proton pump inhibitor; Drug abuse; Cancer

Core Tip: This article reviews a recent cohort study suggesting that *Helicobacter pylori* (*H. pylori*) infection may protect against esophageal cancer. We discuss the controversial link between *H. pylori* and esophageal precancerous lesions and address risks associated with proton pump inhibitor (PPI) overuse. The implications for cancer treatment and the need for further research on PPI safety and efficacy in cancer patients are highlighted.

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TO THE EDITOR

Esophageal cancer (EC) is the sixth leading cause of cancer-related mortality worldwide. The two predominant types are esophageal adenocarcinoma (EADC) and esophageal squamous cell carcinoma (ESCC). In the United States, United Kingdom, Australia, and Western Europe, EADC is more prevalent, whereas ESCC is more common in Africa and the Middle East. Key risk factors for EC include unhealthy lifestyle habits such as smoking, excessive alcohol consumption, obesity, as well as gastroesophageal reflux disease (GERD), Barrett's esophagus (BE), and genetic predisposition[1].

Squamous cell dysplasia is recognized as a precancerous lesion for ESCC, while BE serves as a precancerous lesion for EADC. Endoscopy remains a crucial tool for screening both EC and esophageal precancerous lesions (EPL). It is estimated that 6%-15% of patients with GERD develop BE[1,2]. Proton pump inhibitors (PPIs) are first-line treatments for managing gastric acid secretion, acting as irreversible inhibitors of the H-K-adenosine triphosphatease (ATPase) in gastric wall cells.

This article is based on the article "Prevalence of *Helicobacter pylori* infection among patients with esophageal carcinoma" by López-Gómez *et al*[3], published in the *World Journal of Gastroenterology*. It explores the relationship between *Helicobacter pylori* (*H. pylori*) infection and EPL, and evaluates the benefits and risks of proton pump inhibitor (PPI) use in cancer patients. The article further addresses the issue of PPI overuse and offers recommendations for future research based on the original article.

H. PYLORI INFECTION IN PATIENTS WITH EC

The original study[3] was a retrospective cohort observational analysis consisting of 89 patients with EC. It identified *H. pylori* positive cases and collected data on patients in the cohort who had received or were currently undergoing PPI therapy. Additionally, infection rates were compared with those of patients with gastric cancer, who served as a control group. In this cohort, 4 patients (4.5%) with EC were found to be infected with *H. pylori*, and only 1 of these patients underwent treatment for *H. pylori* eradication. Notably, 86 patients (96.6%) in the cohort had been treated with PPI therapy. In contrast, the infection rate of *H. pylori* in gastric cancer patients during the same period was 66%.

The original study highlights the ongoing debate regarding the relationship between *H. pylori* infection, PPI use, and the pathogenesis of EC. The findings suggest that *H. pylori* may offer a protective effect against the development of EC, while PPI use could be linked to an increased risk of EC. These conclusions emphasize the need for further research to clarify these relationships.

However, the study's small sample size of 89 subjects may limit the generalizability of its findings. This limited sample might not accurately represent broader populations or capture the variability in *H. pylori* infection rates and PPI usage, potentially leading to biased associations. Future research should prioritize larger-scale, multi-center studies with diverse patient populations to ensure that results are more comprehensive and applicable across different groups. Increasing the sample size will help address potential confounding variables and enhance the reliability of the findings.

CONTROVERSIES AND INSIGHTS INTO THE ROLE OF *H. PYLORI* IN EPL

EC is often diagnosed at a late stage due to subtle early symptoms and delayed swallowing difficulties[4]. This underscores the need for increased vigilance in monitoring precancerous lesions to enable early diagnosis and prevention. The role of *H. pylori* in EPL remains debated.

A meta-analysis of 24 studies indicates a negative correlation between *H. pylori* infection and BE, suggesting a protective effect of *H. pylori* against EPL, as evidenced by a lower prevalence of *H. pylori* infection in BE patients [odds ratio (OR) = 0.53, 95% confidence interval [CI]: 0.45-0.64, $P < 0.001$], with significant heterogeneity ($I^2 = 79\%$; $P < 0.001$)[5]. Additionally, most studies were retrospective, which may introduce selection and recall biases[5]. Another systematic review supports the association between *H. pylori* infection and reduced BE risk (OR = 0.68, 95%CI: 0.58-0.79, $P < 0.001$), though the evidence remains relatively weak ($I^2 = 84\%$)[6]. A case-control study in rural China suggests that *H. pylori* infection may lower the risk of EPL in adult drinkers (OR = 0.32, 95%CI: 0.11-0.95), although its limited sample size affects generalizability[7].

We propose that the observed negative correlation may result from the role of *H. pylori* infection in suppressing gastric acid secretion. This suppression could potentially lower the risk of acid reflux, thereby offering protective effects against EC and its precursors. Potential mechanisms include: (1) *H. pylori*-induced gastritis, affecting the gastric mucosa and reducing gastric acid secretion[6]; (2) Activation of the extracellular signal-regulated protein kinases 1 and 2 signaling pathway, which subsequently activates the NF-κB p50 subunit that inhibits the expression of the H,K-ATPase α subunit (*HKα*) gene and decreases gastric acid secretion through binding as a dimer to the promoter region of the *HKα* gene[8]; (3) Modulation of *HKα* gene expression by virulence factors such as cytotoxin-associated gene (Cag) A and CagL[9,10]; (4) Inhibition of gastric acid secretion by the vacuolating cytotoxin, or induction of interleukin (IL)-8 secretion by host epithelial cells, attracting neutrophils and monocytes that secrete cytokines IL-1β and tumour necrosis factor-α to inhibit gastric acid production[11]; (5) Reduction of gastric ghrelin levels due to *H. pylori* infection, potentially leading to decreased gastric acid secretion[12,13]; and (6) Secretion of fatty acids such as cis-9,10-methylene octadecanoic acid and tetradecenoic acid by *H. pylori*, which may act as acid inhibitory factors[14].

In contrast, a large cohort study found no increased risk of BE post-*H. pylori* eradication, reporting a standardized incidence ratio of 4.32 (95%CI: 3.53–5.23) at 1–2 years, decreasing to 3.09 (95%CI: 1.98–4.59 years) at 5–7.5 years[15]. We emphasize the need for large-scale cohort studies to resolve the ongoing controversy surrounding the relationship between *H. pylori* infection and EPL. Future research should focus on elucidating the mechanisms by which *H. pylori* influences EC risk and assessing how it interacts with other contributing factors.

H. pylori may have a protective role, indicating the need to reevaluate screening and prevention strategies for EC and its precursors. This could require adjustments in *H. pylori* eradication therapy and overall management approaches.

PPI OVERUSE, ESPECIALLY IN CANCER PATIENTS

PPIs irreversibly inhibit gastric acid secretion by acting on gastric parietal cells, making them essential for treating a variety of conditions. They are commonly used to manage GERD, treat erosive esophagitis, eradicate *H. pylori* infection, and address precancerous conditions such as BE. Additionally, PPIs serve as first-line therapy for eosinophilic esophagitis, manage dyspepsia caused by nonsteroidal anti-inflammatory drugs (NSAIDs) and cyclooxygenase-2 inhibitors, and prevent gastrointestinal complications associated with NSAID use[16]. They are also utilized in the management of Zollinger-Ellison syndrome, the prevention of stress ulcers in critically ill patients, and the treatment of functional dyspepsia[16]. Moreover, PPIs are frequently prescribed to manage gastric injury resulting from radiotherapy, chemotherapy, and steroid therapy in cancer patients[17]. Statistics show that approximately 20%-30% of cancer patients receive acid suppression therapy, with rates being higher among gastrointestinal cancer patients, reaching up to 35%-50%, the majority of whom are prescribed PPIs[17].

PPIs are considered potential chemotherapeutic sensitizers due to their targeting of V-ATPase[18], and cell experiments support their anti-tumor effects in EC chemotherapy[19,20]. A multicenter prospective study showed no significant difference in reflux-like symptoms or ulcer healing between ESCC patients on PPIs and those not using them (30% *vs* 34% and 84% *vs* 85%, respectively), suggesting that PPIs did not enhance treatment outcomes[21]. Additionally, combining palbociclib with PPIs was linked to shorter progression-free and overall survival in breast cancer patients, indicating potential adverse effects of PPIs in this context[22]. Moreover, cohort studies involving over 1.62 million individuals have shown that PPI use is associated with a higher cancer-specific mortality rate. The crude rate ratio for cancer-specific mortality in PPI users compared to non-users was 2.39 (16.5 deaths per 100 patient-years *vs* 6.9 deaths per 100 patient-years)[23]. These findings indicate that, despite the potential anti-tumor effects of PPIs in certain cancer treatments, their clinical use should be carefully considered, especially in the context of individual patient circumstances and specific treatment regimens.

Moreover, PPI use has been linked to an increased risk of gastric cancer and EC[24-26], and may also be associated with the development of primary liver cancer[27]. A cohort study of over 730000 long-term PPI users found that discontinuation of PPIs was associated with a reduced risk of gastric cancer [incidence rate ratio (IRR) of 0.81, 95%CI: 0.67-0.98] and EADC (IRR of 0.80, 95%CI: 0.68-0.96), underscoring the potential implications of PPI use on cancer risk[28].

Long-term use of PPIs may increase the risk of several adverse events, including pneumonia, chronic renal failure, cancer, vitamin B12 deficiency, and hypomagnesemia (95%OR: 1.17-2.74, $P < 0.001$), and elevate the likelihood of rehospitalization and two-year mortality risk[29]. Additionally, PPI use is associated with a higher risk of cardiovascular diseases and heart failure[30,31], as well as potential risks for fractures, liver disease, and cognitive disturbances[32,33]. Psychological effects, such as suicidal ideation and depression, have also been observed[34]. A recent nationwide study conducted in Denmark found that PPI use is linked to an increased incidence of dementia, with an IRR of 1.36 (95%CI: 1.29-1.43)[35].

Despite these findings, recent studies suggest that changes in physician awareness and prescribing patterns regarding these potential adverse effects remain limited[36]. PPIs are frequently prescribed without comprehensive gastrointestinal evaluation and follow-up[37]. The prevalence of long-term PPI therapy is high, often due to insufficient monitoring and reassessment[24]. Although the American Gastroenterological Association offers guidance on the timing for discontinuing PPI therapy[38], and its best practice guidelines, reviewed by experts, primarily address the risks of long-term PPI use and offer constructive recommendations[39], they appear to lack specific considerations for the cancer patient population.

The potential adverse effects and risks associated with PPI raise significant concerns regarding their widespread use. In general wards and primary care settings, inappropriate PPI use has been identified in over 50% of cases[16], resulting in nearly 20 billion pounds in unnecessary economic costs annually[40]. The primary causes of PPI overuse include ulcer

prevention in low-risk patients, stress ulcer prophylaxis outside of intensive care units, overtreatment of functional dyspepsia, and the lack of regular reassessment for patients undergoing chronic PPI therapy[16,40].

In cancer patients, PPIs are frequently utilized, with their use during chemotherapy potentially offering benefits such as mucosal protection and symptom relief. However, the use of PPIs without concurrent use of NSAIDs during radiotherapy can be inappropriate due to the risk of interactions and increased complication rates[17]. Additionally, the combination of PPIs with oral anticancer drugs may adversely affect treatment outcomes. For example, using PPIs alongside certain tyrosine kinase inhibitors can significantly influence clinical results[41]. This effect is largely attributable to the ability of PPIs to alter gastric pH, which can interfere with the absorption of specific oral anticancer medications[41,42].

Given these negative outcomes and potential risks, further research is necessary to evaluate the safety and efficacy of combined PPI therapy with chemotherapy and radiotherapy, as well as to understand the impact of PPIs on the effectiveness and interactions of anticancer drugs. Large-scale, multi-center randomized controlled trials involving diverse patient populations should be conducted to evaluate the impact of PPIs on outcomes for patients undergoing chemotherapy and radiotherapy. These studies should assess safety profiles, adverse events, and quality of life for cancer patients using PPIs. Additionally, it will be important to investigate how PPIs may affect the efficacy of anticancer treatments, including potential interactions that influence drug absorption and metabolism. Understanding the mechanisms by which PPIs alter treatment effects or exacerbate side effects will be essential for optimizing patient care.

The widespread and potentially inappropriate use of PPIs raises significant concerns and imposes substantial economic burdens. While PPIs are crucial for managing EPL, their overuse may be linked to an increased risk of EC. This calls for a reassessment of PPI prescribing practices and the development of improved management strategies, including cautious prescribing of long-term PPI therapy, regular follow-up, and a multidisciplinary approach to personalized treatment plans. This perspective is essential for optimizing care in cancer patients as well.

CONCLUSION

The role of *H. pylori* infection in EC development and its effect on EPL remain contentious. Further research is needed to clarify its impact on precancerous lesions for effective early detection and prevention. While PPIs are generally safe, their overuse poses risks and economic concerns. Improved management practices and rigorous monitoring are crucial. The frequent, and sometimes inappropriate, use of PPIs among cancer patients underscores the need for more research into their safety, efficacy, and potential interactions of PPI use in this population.

FOOTNOTES

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