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Proton pump inhibitor therapy after *Helicobacter pylori* eradication may increase the risk of gastric cancer

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Context

Helicobacter pylori infection is the most common cause of gastric cancer. Whether *H. pylori* eradication reduces or eliminates the risk of gastric cancer depends on the risk at the time of cure. In those with mucosal damage and hypochlorhydria, *H. pylori* eradication may result in return of acid secretion. Proton pump inhibitor (PPI) therapy can profoundly reduce acid secretion after *H. pylori* therapy. However, the effect of PPIs on the risk of gastric cancer after *H. pylori* eradication is unknown.

Methods

Cheung *et al* reported a population-based study to determine whether PPI use after *H. pylori* eradication altered the risk of subsequent gastric cancer.[1] The study cohort consisted of Hong Kong residents whose *H. pylori* infection was cured using clarithromycin-containing triple therapy from 2003 to 2012. They excluded those with previous gastrectomy, gastric cancer within 1 year of *H. pylori* therapy, failed *H. pylori* eradication or incident gastric ulcer after therapy. Development of incident gastric cancer was determined using diagnosis codes. They attempted to account for selection bias inherent in observational studies by including a negative control group of histamine-2 receptor antagonist (H2RA) users with similar comorbidities as PPI users. To further reduce confounding, a second cohort of PPI users without *H. pylori* infection was matched to PPI users treated for *H. pylori.*

Findings

The cohort consisted of 63 397 individuals with a median follow-up of 7.6 years during which 153 subjects (0.24%) developed gastric cancer. Using propensity score-adjusted analysis, PPI use was associated with a 2.44-fold increase (95% CI 1.42 to 4.20) in gastric cancer risk compared with non-users. The gastric cancer association was dose dependent

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Competing interests

Patient consent Not required.

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(daily PPI use increased risk 4.55fold) and time dependent for PPI use (HR 5.04, 6.65, 8.34 for duration 1, 2, 3 years, respectively). They reported no association between H2RA use and gastric cancer risk despite more frequent H2RA usage. When PPI users with *H. pylori* eradication were matched to PPI users without *H. pylori*, PPI use was associated with an 8.1-fold higher incidence of gastric cancer than PPI use without *H. pylori* infection.

Commentary

The authors rigorously attempted to account for bias and their conclusions are believable.[1] They note that PPIs cause more profound acid suppression than H2RAs. Although different in structure and potency, all PPIs potently suppress acid such that the effect is unlikely be related to a specific PPI. Gastric cancer is an inflammation-related cancer caused by *H. pylori*-induced mucosal inflammation with progressive mucosal damage.[2] The severity of inflammation relates to *H. pylori* virulence and the host's genetic ability to mount an inflammatory response (eg, IL-1 polymorphisms).[2] The natural history is typically progressive extension of mucosal atrophy from the antrum to the corpus with loss of parietal and chief cells, reduced acid secretion[2] and development of corpus pseudopyloric metaplasia, identifiable as spasmolytic peptide expressing mucosa.[2] Islands of intestinal metaplasia appear within this pseudopyloric metaplasia. Risk stratification involves characterising the degree and extent of antral and corpus atrophy.[2]

Gastric cancer results from genetic instability caused by *H. pylori* directly and by inflammation-associated reactive oxygen and nitrogen species.[3] Progressive mucosal damage and extensive gastric atrophy produce hypochlorhydria or achlorhydria and an exponential increase in cancer risk.[2]. The hypochlorhydric environment also allows acid-intolerant bacteria to colonise the stomach and produce carcinogens from ingested food and nitrates.[34]

Gastric cancer risk after *H. pylori* cure relates to risk at the time of cure. Cure interrupts the inflammation–atrophy–metaplasia–cancer cascade but does not reverse the genetic instability caused by *H. pylori*.[2] Without the presence of *H. pylori*, inflammation-inhibited parietal cells regain function, new parietal cells may appear and regulation of normal acid secretion returns, which together increase gastric acidity. In those without complete atrophy, cure of *H. pylori* and return of gastric acid production make the intragastric environment inhospitable to carcinogen-producing bacteria.[34] PPI use in patients with hypochlorhydria or achlorhydria may attenuate or prevent the beneficial effects of increased gastric acidity and promote perpetration of a carcinogen-producing microbiome, thus partially abrogating the benefits of *H. pylori* eradication.[34] This scenario is more likely in older patients. We suggest that continued PPI use after *H. pylori* eradication might indirectly increase gastric cancer risk in a subgroup of high-risk subjects by permitting maintenance of a carcinogen-producing, acid-intolerant microbiome.

Implications for practice

This study suggests that use of PPIs after *H. pylori* eradication should be based on actual need for acid suppression. Whenever possible, antisecretory therapy with H2RA would be preferred for those with residual atrophic changes.

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