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Long-term use of proton-pump inhibitors and risk of gastric cancer: a review of the current evidence

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Abstract: Gastric cancer remains one of the leading cancers in the world with a high mortality, particularly in East Asia. *Helicobacter pylori* infection accounts for the majority of the noncardia gastric cancers by triggering gastric inflammation and subsequent neoplastic progression. Eradication of *H. pylori* can reduce, but not totally eliminate, subsequent risk of developing gastric cancer. Proton-pump inhibitors (PPIs) are one of the most widely prescribed medications worldwide. With their profound gastric-acid suppression, there are concerns about a possible carcinogenic role in gastric cancer, due to induced hypergastrinemia, gastric atrophy and bacterial overgrowth in the stomach. While randomized clinical trials to establish causality between long-term PPI use and gastric cancer are lacking, current evidence based on observational studies suggests PPIs are associated with an increased gastric cancer risk. However, opinions on causality remain divergent due to unmeasured and possible residual confounding in various studies. Our recent study has showed that even after *H. pylori* eradication, long-term PPI use is still associated with an increased risk of gastric cancer by more than twofold. Hence, long-term PPIs should be used judiciously after considering individual's risk–benefit profile, particularly among those with history of *H. pylori* infection. Further well-designed prospective studies are warranted to confirm the potential role of PPIs in gastric cancer according to baseline gastric histology and its interaction with other chemopreventive agents like aspirin, statins and metformin.

Keywords: aspirin, enterochromaffin-like cells, gastrin, gastric adenocarcinoma, *Helicobacter pylori*, *H. pylori*, PPIs, stomach cancer

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Introduction

Gastric cancer is the fifth commonest cancer and the third leading cause of cancer-related mortality worldwide.[1] In 2015, an estimated 1.3 million incident gastric cancer cases were diagnosed and there were 819,000 gastric-cancer-related deaths. *Helicobacter pylori* infection was classified by the World Health Organization (WHO) as a type I carcinogen in 1994.[2] Chronic *H. pylori* infection confers a more than threefold increase in risk of gastric cancer,[3] which accounts for 78% of all gastric cancer cases and 89% of noncardia cancers.[4] *H. pylori*-associated gastric carcinogenesis is generally believed to start from chronic gastritis, progressing to atrophic gastritis, intestinal metaplasia, dysplasia, and ultimately cancer.[5] Atrophic gastritis, intestinal metaplasia and dysplasia are therefore regarded as precancerous gastric lesions. In a prospective study, patients with corpus-predominant gastritis [relative risk (RR) 34.5; 95% confidence interval (CI) 7.1–166.7 *versus* antral-predominant gastritis], severe gastric atrophy (RR 4.9; 95% CI 2.8–19.2 *versus* absent/mild atrophy) and intestinal metaplasia (RR 6.4; 95% CI 2.6–16.1 *versus* absence of intestinal metaplasia) were all at higher risk of gastric cancer development.[6] The magnitude of risk was confirmed in another cohort study [atrophic gastritis: hazard ratio (HR) 4.5; 95% CI

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3.5–5.8; intestinal metaplasia: HR 6.5; 95% CI 4.7–8.2; dysplasia: HR 10.9; 95% CI 7.7–15.4].[7] In this regard, eradication of *H. pylori* has been shown to reduce the gastric cancer risk by 33–47%,[8–10] but a considerable proportion of *H. pylori*-eradicated individuals still progress to develop gastric cancer.

Apart from chronic *H. pylori* infection, proton-pump-inhibitor (PPI) usage is another potential risk factor for the development of gastric atrophy. With the potent acid suppression, PPIs could induce changes in the gastric environment, including hypergastrinemia and enterochromaffin cells hyperplasia.[11] There is also evidence suggesting that PPIs could contribute to bacterial overgrowth in the stomach.[12] Intuitively, PPIs worsen gastric atrophy and hence could increase the risk of gastric cancer.[10]

In this review, we will examine the latest literature to decipher the role of PPIs in gastric cancer development, particularly in relation to *H. pylori* infection.

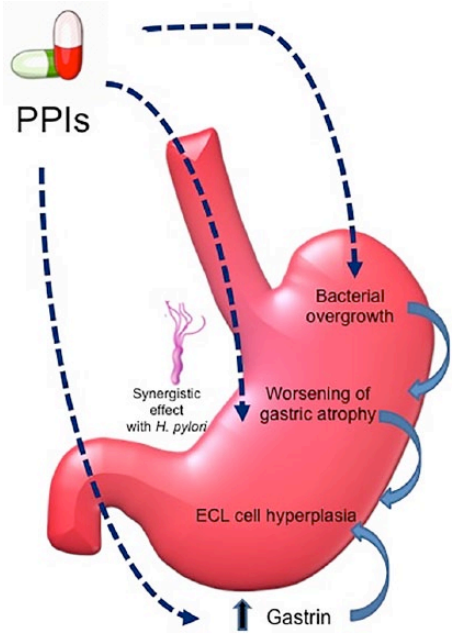

Figure 1. Postulated mechanisms underlying the carcinogenic effects of proton-pump inhibitors on gastric cancer development.
ECL, enterochromaffin like; *H. pylori, Helicobacter pylori*; PPIs, proton-pump inhibitors.

Potential carcinogenic mechanisms of proton-pump inhibitors

Proton-pump inhibitors (PPIs) have become one of the most commonly prescribed medications worldwide since their introduction in 1980s,[13] and have been the cornerstone of the management of upper gastrointestinal diseases including peptic ulcer disease (PUD), *H. pylori* infection, dyspepsia, and gastroesophageal reflux disease (GERD). However, emerging data have shown that long-term PPIs are associated with a number of side effects, including bone fracture,[14] *Clostridium difficile* infection,[15] pneumonia,[16] myocardial infarction and stroke,[17] although a causality has not yet been confirmed.

Potent acid suppression has long been suspected a risk factor of gastric cancer by worsening gastric atrophy with ensuing hypergastrinemia and bacterial overgrowth in the stomach. Animal studies have shown that acid suppression by omeprazole[18] and the insurmountable histamine-2 receptor antagonist (H2RA) loxtidine[19] induce gastric mucosa neoplasia in rodents. However, evidence on human subjects remains controversial. Herein, we summarize the postulated mechanisms underlying the carcinogenic effects of PPIs on gastric cancer development (Figure 1).

Interaction with Helicobacter pylori infection

H. pylori typically colonizes the gastric antrum, and cause an antrum-predominant gastritis in most infected subjects.[20] Antral mucosal inflammation in turn stimulates gastric secretion, maintaining a normal- or high-acidic environment. However, when the acid production is suppressed by PPIs, the pattern of gastritis shifts to a corpus-predominant gastritis with resultant impairment of parietal cell function; a phenomenon that does not occur in *H. pylori*-negative patients.[21] As such, the acid-suppressive effect of PPIs is further enhanced by *H. pylori*-induced corpus gastritis.[22,23] In a cohort study of 177 patients, atrophic gastritis only developed in *H. pylori*-infected but not *H. pylori*-negative patients with long-term PPI use during a mean follow up of 5 years.[24] A systematic review also showed that the risk of corpus atrophy was more pronounced in *H. pylori*-infected than *H. pylori*-negative PPI users [odds ratio (OR) 11.45; 95% CI: 6.25–20.99].[11]

Hypergastrinemia

In response to suppression of gastric-acid production by PPIs, there is a compensatory increase in gastrin production as a negative feedback.[25] A

recent systematic review by Lundell and colleagues[11] including 16 studies with 1920 patients showed that during long-term (>3 years) PPI use, the mean gastrin levels rose to one to three times the upper limit of normal. The progrowth effect of gastrin is suspected to play a role in gastric cancer development.[26–28] Hypergastrinemia drives the hyperplasia of enterochromaffin-like (ECL) cells in the oxyntic mucosa, which occurs in 10–20% of patients with long-term PPI use.[29] It has been reported that the risk of ECL-cell hyperplasia is higher in *H. pylori*-infected than *H. pylori*-negative patients (OR 2.45; 95% CI 1.47–4.10).[11] Similar results were reported in two randomized clinical trials on acid reflux control by either antireflux surgery or long-term PPI therapy.[30] Analysis of the insulin–gastric (INS-GAS) transgenic mice raised the possibility that hypergastrinemia may promote gastric cancer through the gastrin receptor, cholecystokinin receptor-2 (CCK2R).[31] With the overexpression of amidated gastrin through the insulin promoter upstream of the human gastrin coding sequences,[32] these mice developed gastric intestinal metaplasia and dysplasia, and some even developed gastric corpus cancer,[33] which was accelerated by infection by *Helicobacter felis* or *H. pylori*. In another study, PPIs (omeprazole) led to a faster progression to dysplasia in *H. felis*-infected INS-GAS mice.[34]

Furthermore, another study also suggested that promotion of growth of gastric carcinomas of 'intestinal type' might be due to the indirect effect of hypergastrinemia, *via* stimulation of the release of signal substances (e.g. histamine, regenerating-gene protein) from the ECL cells.[35] In line with these animal studies, clinical evidence from a case-control study nested within the all-male Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study of 29,133 Finnish male smokers with more than 24 years of follow up, reported that a higher gastrin level (fourth quartile *versus* first quartile) was associated with an increased risk of noncardia gastric cancer (OR 1.92; 95% CI 1.21–3.05).[36]

Although ECL cells are generally believed to play little role in human gastric carcinoma development, ECL-cell neuroendocrine tumors (NETs)[37] and adenocarcinomas[38] were observed in cases of pernicious anemia (autoimmune gastritis with corpus atrophy and thus low gastric-acid output). Early studies showed that the distinction between gastric NETs and adenocarcinomas may be difficult in both animals[39] and humans,[40,41] as ECL cells may lose many of their neuroendocrine characteristics during neoplastic transformation. However, some studies later suggested that a proportion of the gastric adenocarcinomas, in particular, the signet ring subgroup of gastric carcinomas of 'diffuse type,' indeed develop from the ECL cells.[42–44] With improved sensitivity of immunohistochemical methods for detecting neuroendocrine/ECL-cell makers, it was shown in one study that virtually all gastric adenocarcinomas in patients with severe hypergastrinemia were malignant NETs.[45]

Non-Helicobacter pylori bacterial overgrowth

Acid suppression of PPIs can lead to both luminal and mucosal non-*H. pylori* bacterial overgrowth in the stomach that may exacerbate chronic inflammation.[12] It has been shown that non-*H. pylori* bacterial overgrowth is a risk factor for atrophic gastritis (antrum: RR 5.07; 95% CI 1.05–24.40; corpus: RR 6.38; 95% CI 0.78–53.89).[46] The simultaneous infection with *H. pylori* and non-*H. pylori* bacteria has a synergistic effect on inducing a higher level of serum cytokines [interleukin (IL)-1 beta and IL-8] and increasing the risk of atrophic gastritis. Moreover, there is an increase in the number of bacteria including nongastric microorganisms (mainly from oral flora) that possess nitrate reductase to produce N-nitroso compounds from food nitrates, known gastric carcinogens.[47,48] Interestingly, it has been shown that gastric microbiota alteration is distinct in atrophic gastritis.[49] PPI users showed similarly high gastric microbial diversity as healthy subjects. A relatively high gastric microbial diversity, dominated by streptococcus, was observed in autoimmune gastritis, while a decreased microbial abundance and diversity was induced by *H. pylori* infection.

Clinical studies on the association between proton-pump inhibitors and gastric cancer

The incidence of gastric cancer indeed has been gradually declining in the past 50 years with an average estimated annual percentage decrease of 2.5% per year.[50] This observation has therefore been used as an argument against the potential carcinogenic role of PPIs, which has been available only since 1989. However, it could not be over-emphasized that reduction in the prevalence of *H. pylori* and improvement in food processing

actually contribute to this observed decline in gastric cancer incidence,[51] hence masking the possible effect of PPIs on increasing gastric cancer incidence.

As gastric cancer is a relatively rare disease which requires a long-time lag to develop, randomized clinical trials (RCTs) demonstrating the potential carcinogenic effects of PPIs are both resource and labor intensive. More importantly, there may be an ethical issue in randomizing patients to receive intervention to observe primary adverse outcome. As such, the determination of the causal relationship could, at best, be determined by well-designed observational studies controlling for known confounding factors, with minimization of biases.

There are two meta-analyses based on RCTs assessing precancerous gastric lesions and PPIs.[52,53] Not surprisingly, no association between PPIs and gastric cancer was found as the follow up in these studies was relatively short (maximum follow up was 36 months). On the other hand, a systemic review of three observational studies by Tran-Duy and colleagues showed that PPIs were associated with an increased gastric cancer risk (pooled OR 1.43; 95% CI: 1.23–1.66).[54] Inconsistent results were, however, observed when the effect of PPIs was studied according to duration of PPI use (<1 year, ⩾1 year and >3 years). If only patients with PPI use < 1 year were compared with non-PPI users, the pooled OR was 1.76 (95% CI 1.24–2.52). However, no statistically significant association was observed for patients using PPI ⩾ 1 year (pooled OR 1.31; 95% CI 0.79–2.19), but the greatest risk was noted for those using PPI > 3 years (pooled OR 2.45; 95% CI 1.41–2.45). The authors proposed that PPIs may be prescribed for a short period as part of the *H. pylori* eradication regimen for those using PPI < 1 year; and when sufficiently long enough time is allowed, PPIs and *H. pylori* infection act synergistically to increase the gastric cancer risk in those using PPI > 3 years.

On the other hand, previous reassuring studies on the long-term safety of PPIs neither had sufficient observation period nor adequate power with small sample size.[29,55] Moreover, there are other limitations of previous studies. First, all except the study by Poulsen *et al.*[56] failed to adjust for *H. pylori* status or eradication. As such, the establishment of causal relationship between PPIs and gastric cancer is severely compromised by this most important confounding factor for gastric cancer development. Second, indication bias is possible as only the study by Garcia and colleagues[57] took the indication of PPIs (GERD, PUD and dyspepsia) into analysis. Third, protopathic bias (or reverse causality) exists, since the presence of prediagnosis cancer symptoms may warrant the prescription of PPIs. Fourth, most of the studies failed to take into account the potential role of other medications in gastric cancer development, including statins,[58] metformin,[59] aspirin,[60] nonsteroidal anti-inflammatory drugs (NSAIDs) and cyclooxygenase-2 (COX-2) inhibitors.

To address the confounding effect of *H. pylori* infection, we have recently carried out a territory-wide retrospective cohort study on *H. pylori*-eradicated patients (n = 63,397). During a median observation period of 7.6 years [interquartile range (IQR):5.1–10.3 years],[61] PPI use (defined as at least weekly use) was associated with an increased gastric cancer risk (HR 2.44; 95% CI 1.42–4.20). On the other hand, H2RAs, which served as negative control exposure, were not associated with an increased cancer risk (HR 0.72; 95% CI 0.48–1.07). With non-PPI use as the reference group, the risk of gastric cancer by PPI use increased with increasing frequency (HR 2.43 for weekly to less-than-daily use, and HR 4.55 for daily use) and duration (HR 5.04, 6.65 and 8.34 for ⩾1 year, ⩾2 years and ⩾3 years, respectively). The adjusted absolute risk difference was 4.29 more gastric cancer cases per 10,000 person-years in PPI users than non-PPI users. Furthermore, another matched cohort of PPI users who had not received *H. pylori* therapy (n = 142,460) was recruited for comparison. Of note, PPI users without prior *H. pylori* therapy had the lowest incidence rate of gastric cancer (0.8 cases per 10,000 person-years) among the three groups (non-PPI users with prior *H. pylori* therapy: 2.9 per 10,000 person-years; PPI users with prior *H. pylori* therapy: 8.1 per 10,000 person-years). Therefore, the presence of current or even prior *H. pylori* infection appears to be a more important determinant of gastric cancer risk than PPIs, and PPI-associated gastric cancers are more likely to occur in subjects with underlying *H. pylori*-associated gastric damage.

Our study is the first to demonstrate that long-term PPI use is still associated with an increased gastric cancer risk even after *H. pylori* eradication, with a dose- and time-response relationship.

Several efforts of our study in minimizing the bias to determine a possible causal relationship should be noted. First, the large sample size and long observation time allows for an accurate estimation of the gastric cancer incidence among PPI users. Second, protopathic bias was avoided by excluding PPI prescriptions in the 6 months preceding gastric cancer diagnosis. Third, indication bias was unlikely a significant issue as a similar increase in gastric cancer risk was not observed for H2RAs, which are less potent than PPIs in terms of acid suppression. In addition, the lowest gastric cancer risk among PPI users without prior *H. pylori* therapy argues against a significant indication bias. Fourth, comorbid conditions and medications, which had not been adequately addressed in previous studies were included in the propensity score adjustment. Nevertheless, several limitations exist, including failure to capture some of the risk factors like lifestyle factors, family history and histology information from the electronic healthcare database system.[62]

Four recent studies by other groups, published after our study, had findings consistent with ours. Among the four studies, one is a nationwide population-based study from Sweden, a country with a relatively low gastric cancer incidence.[63] It examined the gastric cancer risk in PPI users and H2RA users as compared with the Swedish background population of the same age, sex and calendar period (7.1–7.6 million adults). The standardized incidence ratio (SIR) of gastric cancer with PPI use was 3.38 (95% CI 3.25–3.53). Despite a sensitivity analysis to address protopathic bias (all gastric cancer cases diagnosed within 1 year of the study commencement were excluded), the risk remained albeit attenuated (SIR 1.6; 95% CI 1.51–1.71). Again, H2RA use was not a significant risk factor (SIR 0.57; 95% CI: 0.29–0.99).

The remaining three studies were from Asia, including two from Taiwan and one from Japan. The two Taiwanese studies were both case-control studies (controls were age- and sex-matched with cases in a 1:1 ratio). The first one ($n = 2122$) showed that PPIs were associated with an increased gastric cancer risk by 2.48 fold (95% CI 1.92–3.20) among GERD patients.[64] A higher risk was demonstrated by an increase in defined daily dose. The second study ($n = 1298$) also showed a similar result, with longer duration of PPI use conferring a higher risk as compared with non-PPI use [$\leqslant$6 month PPIs: OR 1.59 (95% CI 1.24–2.05) *versus* >6 month PPIs: OR 2.00 (95% CI 1.36–2.95)].[65] The Japanese study was a retrospective cohort study of 571 *H. pylori*-eradicated patients, which addressed one important limitation of previous studies by adjusting for gastric precancerous lesions (corpus atrophy and intestinal metaplasia).[66] During a mean follow up of 6.9 years, PPI use was associated with an increased gastric cancer risk (HR 3.61; 95% CI 1.49–8.77). Such an association was only observed among patients with intestinal metaplasia, indicating PPIs potentially increase gastric cancer risk in patients with pre-existing gastric precancerous lesions. Notably, the risk of PPIs was higher among patients with mild intestinal metaplasia than those with severe changes [HR 16.0 (95% CI 1.90–134) *versus* HR 3.06 (95% CI 0.62–15.0)], which may be related to the small sample size from the subgroup analysis. Table 1 summarizes the characteristics and results of various observational studies.

However, it is noteworthy that some important risk factors (e.g. diet, smoking, alcohol, family history of gastric cancer) were not taken into consideration in some of these observational studies. In addition, residual confounding is inherent in all observational studies. Therefore, a causal relationship between PPIs and gastric cancer still cannot be firmly established. Nevertheless, fulfillment of the Bradford Hill criteria may help to strengthen the possible causal relationship.[67]

Effect of proton-pump inhibitors on gastric cancer in different subgroups

In a meta-analysis of seven studies,[68] Wan and colleagues found that the risk of PPIs was more prominent among Asians than Whites [OR 2.44 (95% CI 1.89–3.00) *versus* OR: 1.86 (95% CI 0.54–3.18)]. The effect of PPIs on gastric cancer is also site specific, with higher risk for noncardia than cardia gastric cancer [OR 2.45 (95% CI 1.44–3.45) *versus* OR 1.64 (95 % CI 0.23–3.51)].

In the nationwide Swedish study,[63] the risk of PPIs appears to be similar between males (SIR 3.65; 95% CI 3.45–3.85) and females (SIR 3.07; 95% CI 2.87–3.28). Importantly, the risk was most pronounced in younger age groups. The highest risk was observed among PPI users < 40 years when compared with non-PPI users (SIR 22.76; 95% CI 15.94–31.52), while the lowest

Table 1. Summary of observational studies on the association between proton-pump inhibitors and gastric cancer development.

References	Study design	Sample size	Patient characteristics/ region	Factors considered (regression model or stratified analysis)	*Results
Garcia Rodriguez *et al*.[57]	Nested case-control study (matched with age, sex, and calendar year)	10,522	United Kingdom	1, 2, 4, 5, 13,14	OR 1.75 (95% CI 1.10–2.79)
Tamim *et al*.[80]	Nested case-control study (matched with age and sex)	8229	Canada	1,2, 17	OR 1.46 (95% CI: 1.22–1.74)
Poulsen *et al*.[56]	Population-based cohort study	280,872	Denmark	1, 3–5, 9, 10, 13, 17	IRR 2.3 (95% CI 1.2–4.3; patients with ⩾5 years of follow up)
Cheung *et al*.[61]	Population-based cohort study	63,397	*H. pylori*-eradicated patients/Hong Kong	1–12, 16, 17	HR 2.44 (95% CI 1.42–4.20)
Brusselaers *et al*.[63]	Nationwide population-based cohort study	843,003 PPI or H2RA users (*versus* general population of 7.1–7.6 million)	Sweden	1–3, 6, 10, 13, 16, 17	SIR 3.38 (95% CI 3.25–3.53)
Peng *et al*.[64]	Case-control study (matched with age, sex, and calendar year)	2122 (1:1 ratio)	GERD patients/ Taiwan	1, 2, 10, 13, 14	OR 2.48 (95% CI 1.92–3.20)
Lai *et al*.[65]	Case-control study (matched with age, sex, and calendar year)	1298 (1:1 ratio)	Taiwan	1–8, 10, 13, 17	⩽6-month PPI: OR 1.59 (95% CI 1.24– 2.05) >6-month PPI: OR 2.00 (95% CI 1.36–2.95)
Niikura *et al*.[66]	Retrospective cohort study	571	*H. pylori*-eradicated patients/Japan	3, 10, 15	HR 3.61; 95% CI 1.49–8.77

*Results are presented after adjustment for covariates.
1, age; 2, sex; 3, *Helicobacter pylori* status; 4, smoking; 5, alcohol; 6, history of PUD; 7, DM; 8, other comorbidities; 9, aspirin/NSAIDs/COX-2 inhibitors; 10, H2RAs; 11, statins; 12, metformin; 13, calendar period; 14, socioeconomic status; 15, gastric histology; 16, indication bias; 17, protopathic bias; CI, confidence interval; COX-2, cyclooxygenase-2; DM, diabetes mellitus; IRR, incidence rate ratio; GERD, gastroesophageal reflux disease; HR, hazard ratio; H2RAs, histamine-2 receptor antagonists; OR, odds ratio; PPIs, proton-pump inhibitors; PUD, peptic ulcer disease; NSAIDs, nonsteroidal anti-inflammatory drugs; SIR, standardized incidence ratio.

risk was found among PPI users aged ⩾ 70 years (SIR 2.76; 95% CI 2.61–2.92). The authors provide several explanations, which included an increased prevalence of atrophic gastritis in relation to obesity[69] as well as acceleration of gastric carcinogenesis in younger age groups (with a higher likelihood of a positive family history[70]), hence increasing the vulnerability to the potential carcinogenic effect of PPIs.

Stratified analysis according to PPI indications was also performed in this study.[63] The risk was much

larger among *H. pylori*-infected (SIR 9.76; 95% CI 8.87–10.71) than *H. pylori*-negative patients (SIR 2.91; 95% CI 2.78–3.05). Among the common indications for PPIs, the risk was highest in patients with PUD (SIR 8.75; 95 CI 8.12–9.41), while the risk was similar among those with gastroduodenitis (SIR 3.68; 95% CI 3.31–4.09), dyspepsia (SIR 3.07; 95% CI 2.58–3.63) and GERD (SIR 3.04; 95% CI 2.80–3.31).

Effect of different proton-pump inhibitors on gastric cancer risk

Animal studies showed that longer-acting PPIs could produce a higher risk of gastric tumors due to greater systemic exposure from a higher concentration time (area under the curve), leading to more gastrin stimulation.[26,27,71] However, a meta-analysis concludes that different PPIs can be used interchangeably based on potency as reflected by the percentage time pH $>$ 4 over a 24 h period (omeprazole 30 mg is equivalent to lansoprazole 30 mg, esomeprazole 20 mg and rabeprazole 20 mg).[72] In a US Food and Drug Administration (FDA)-mandated long-term follow-up study of 61,864 PPI users, the risk of gastric cancer was comparable between the use of pantoprazole (a longer-acting PPI) and other shorter-acting PPIs (any combination of omeprazole, esomeprazole, lansoprazole or rabeprazole; HR 0.68; 95% CI 0.24–1.93) after adjusting for age, sex, *H. pylori* treatment, cumulative PPI dose and total years of PPI treatment. Although twice-daily PPI dosage suppresses gastric-acid production for a longer duration than once-daily dosage,[72] current data on risk of gastric cancer are lacking and further studies are required.

Potential chemopreventive agents to reduce proton-pump-inhibitor-associated gastric cancer risk

Meta-analyses have shown that aspirin reduces gastric cancer risk without stratification according to *H. pylori* status.[73,74] To address this issue, we conducted another study on the effect of aspirin specifically on *H. pylori*-eradicated subjects. Aspirin was shown to be associated with a lower gastric cancer risk among *H. pylori*-eradicated subjects (HR 0.30; 95% CI 0.15–0.61), with a frequency–, duration–, and dose–response relationship being observed.[60] A subsequent *post hoc* analysis[75] showed that the harmful effect of PPIs was higher (HR 3.73; 95% CI 2.11– 6.60) among nonaspirin users, while PPIs were not associated with an increased risk of gastric cancer among aspirin users (HR 0.35; 95% CI 0.04–2.74). The potential detrimental effect of PPIs on gastric cancer appears to be negated by aspirin use, although this observation necessitates validation by studies from other centers. Nevertheless, our study finding prompts the investigation of the role of other potential chemopreventive agents, such as metformin[76] and statins,[58] in reducing gastric cancer risk among PPI users should be further explored.

Recommendations on proton-pump inhibitor use in clinical practice

Despite the potential harmful effects of PPIs, they are so far the most effective therapy for PUD, GERD and in preventing aspirin-/NSAID-related upper gastrointestinal bleeding (UGIB). Indeed, the rational use of PPIs should be promoted to minimize any potential side effects associated with long-term use, rather than irrational avoidance. Physicians should consider the lowest effective dose of PPIs with a finite treatment period, particularly for nonerosive GERD and nonulcer dyspepsia. A stepdown approach to less potent acid-suppressive agents such as H2RAs should also be considered in appropriate settings.

However, certain clinical conditions may mandate long-term PPI use. For instance, individuals who are at high risk of aspirin-/NSAID-related UGIB should be given long-term PPIs.[77] Barrett's esophagus is another condition in which long-term use of PPIs is recommended.[78] If long-term PPI use is necessary, it is advisable to have *H. pylori* tested and eradicated if present so as to prevent the development of corpus atrophy, hence reducing gastric cancer risk.[79] It has also been proposed that nonfasting chromogranin A be used as a serological marker in long-term PPI users to monitor the degree of ECL-cell hyperplasia.[51] The effectiveness of this approach, however, has not yet been studied by prospective clinical studies and cost-effectiveness studies according to local gastric cancer incidence and different subgroups.

Conclusion

Emerging evidence from multiple observational studies suggests long-term use of PPIs is associated with a higher risk of gastric cancer development. However, the risk is likely limited to individuals with current or past history of *H.*

pylori infection, particularly those with underlying precancerous gastric lesions. Physicians should prescribe PPIs according to individual's risk–benefit profile rather than withholding PPIs from those with genuine indications, such as Barrett's esophagus or high risk of UGIB. This is particularly important for aspirin users at high risk of UGIB, as aspirin may negate the potential harmful effects of PPIs on gastric cancer development. Further well-designed prospective studies are warranted to confirm the potential role of PPIs in gastric cancer according to baseline gastric histology and its interaction with other chemopreventive agents like aspirin, statins, and metformin.

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