

## Use of Proton Pump Inhibitors and risk of gastric cancer

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Cheung KS, Chan EW, Wong AYS, Chen L, Wong ICK, Leung WK. Long-term proton pump inhibitors and risk of gastric cancer development after treatment for *Helicobacter pylori*: a population-based study. *Gut* 2018; 67: 28-35.

*Helicobacter pylori* infection is associated with atrophic gastritis, which can progress to gastric cancer in some patients. Proton pump inhibitor (PPI) use has also been reported as a risk factor for atrophic gastritis. The risk is particularly high among individuals infected with *H. pylori* who are susceptible to the development of corpus atrophy.

Cheung et al. (1) retrospectively studied a cohort in which PPIs were used. They showed a positive association between regular PPI use and gastric cancer in their study in Hong Kong.

Although PPIs are generally considered safe, recent data have demonstrated various adverse effects associated with the long-term use of PPIs including bone fracture, (2) *Clostridium difficile* infection (3), pneumonia (4), myocardial infarction, and even stroke (5). Apart from systemic adverse effects, there are concerns on the long-term safety profile of PPIs in the stomach. The use of PPIs is associated with profound acid suppression, which can worsen atrophic gastritis (6). The risk is considerably high among individuals infected with *H. pylori* who are susceptible to the development of corpus atrophy (7). Moreover, PPIs stimulate the production of gastrin, which is a potent growth factor, and hypergastrinemia has been shown to induce hyperplasia of enterochromaffin-like cells (7).

In the current study, investigators evaluated the association between PPI use and gastric cancer in 63,397 patients treated with clarithromycin-based triple therapy for *H. pylori* infection. Approximately 5% of patients were prescribed PPIs after *H. pylori* eradication therapy (medi-

an duration of PPI use, 3 years). They found the following results:

- Gastric cancer incidence was 0.2% during the median follow-up of 8 years.
- Compared with non-PPI users, a higher percentage of patients on chronic PPI therapy (weekly use or more) developed gastric cancer (adjusted HR, 2.4).
- Increasing dose and duration of therapy were associated with greater risks of gastric cancer (adjusted HR, 4.6 for daily use and 8.3 for daily use for  $\geq 3$  years).
- Histamine-2 receptor antagonist use was not associated with gastric cancer.

To the best of our knowledge, this is the first study to demonstrate that long-term PPIs use, even after *H. pylori* eradication therapy, is still associated with an increased risk of gastric cancer. One of the strengths of this study is the use of data from a large population-based database with complete information on subsequent diagnoses and drug prescriptions, thus minimizing recall biases. Another strength of the study was the use of strict exclusion criteria as well as propensity score adjustment to control for potential confounders in determining the causal relationship between PPI use and gastric cancer development. The authors also limited the inclusion criteria for 6 months for diagnosing gastric cancer diagnosis. They used 6 months as the a priori cut-off because a previous study that specifically addressed the issue of protopathic bias showed that this was the most appropriate lag time to be used for assessing the association between PPI and gastric cancer risk (8).

There are also some limitations of the study. First, the information of some risk factors (e.g., diet, family history, and socioeconomic status) was not present in the electronic database. Moreover, the identification of certain

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parameters (smoking, alcohol use, and obesity) via coding may underestimate their true prevalence. Second, although patients who failed triple therapy were identified by the repeated prescription of clarithromycin-based triple therapy or the prescription of second- or third-line therapies, it is likely that a small proportion of patients who failed *H. pylori* eradication therapy might be missed.

The authors reported data from China (which has a relatively higher gastric cancer prevalence), and caution should be exercised in extrapolating results from China to other parts of the world. Urgent and larger population-based prospective studies on the safety issue of PPIs are needed. Until then, PPI use should be limited in these patients.

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