Proton pump inhibitors and risk for gastric cancer: Is it real?

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Cite this article as: *Akriviadis E, Liava C. Proton pump inhibitors and risk for gastric cancer: Is it real?. Turk J Gastroenterol 2019 30(3); 309-10.*

We read, with interest, the study by Cheung et al. (1) who found that the long-term use of proton pump inhibitors (PPIs) in Chinese patients with prior eradication of *Helicobacter pylori* was associated with an increased risk of development of gastric cancer.

However, although interesting, these results need further clarification. Patients in this study were recruited from a territory-wide health database of Hong Kong. The successful eradication of *H. pylori* was defined as no need for subsequent prescriptions of either repeated courses of clarithromycin-based triple therapy or a second- or third-line regimen. The authors suggested that the success rate of the regimen used for the eradication of *H. pylori* infection was actually effective in 90% of cases in the community. However, recent evidence suggests that clarithromycin resistance rates have reached approximately 30% in Italy and Japan, approximately 40% in Turkey, and approximately 50% in China (2). Furthermore, because serology and stool antigen tests were unavailable, no specific information was provided on the methods used to confirm the successful eradication of *H. pylori* infection (whether upper endoscopy or urea breath test (UBT) was used?) Additionally, it is unclear whether the time for confirming the successful eradication of *H. pylori* was at least 4 weeks after treatment completion, according to the guidelines (2).

This information is important because many of the subjects who are considered having successfully eradicated *H. pylori* infection may actually have not. Treatment with PPIs before endoscopy reduces the sensitivity of antral and corpus biopsies for the detection of *H. pylori*, both by urease testing and histological examination, and leads to false-negative results on UBT (2). As a result, it remains possible that some *H. pylori*-positive patients were included in the study. This could be a factor of "contamination" of data in view of the well-documented increased risk for gastric cancer in patients with refractory *H. pylori* infection, a risk that could even be intensified in such patients kept on maintenance PPIs therapy (2).

Additionally, the study by Cheung et al. (1) fails to address other risk factors that were not balanced between the two groups of patients. PPIs users were older by approximately 10 years and had more comorbidities, such as gastroesophageal reflux disease (GERD) (18.1% vs. 4.5%), diabetes mellitus (23.6% vs. 11%), hypertension (40.8% vs. 19.5%), and ischemic heart disease (27.7% vs. 8.0%), and were more frequently (41.3% vs. 19.7%) treated with statins than non-users. The incidence of gastric cancer progressively rises with age (2). Patients in the study of Cheung et al. (1) were mainly Chinese; therefore, the results may not be applicable in all ethnic groups because Asians are at a higher risk of gastric cancer than the Western populations (2).

Importantly, a previous study in Japan conducted by Take et al. (3) reported that even after the eradication of *H. pylori* infection and extinction of gastric inflammation, the annual rate of gastric cancer was 0.30% and cancer could develop even with the complete resolution of gastric inflammation. These results suggest that the risk of cancer development persists in approximately 1 of 300 Asian patients despite the prior eradication of *H. pylori* and need to be compared with results of Cheung et al. (1) who found a composite risk of 0.24% in the entire patient population after a median follow-up of 7.6 years. In the study by Cheung et al. (1), the total risk of gastric cancer in PPIs users over the entire follow-up period was not numerically specified; however, in the online supplementary data, the authors quote an annual incidence ranging between 0.00% and 0.18% over a 12-year follow-up period; although the authors mentioned an increased (2.4-fold) risk of gastric cancer in PPIs users, it appears that the actual risk is still lower than the mean annual risk of 0.30% observed in the study by Take et al. (3).

A final issue is that the increased risk of gastric cancer reported in the study of Cheung et al. (1) refers to a specific population that is considered having successfully eradicated *H. pylori* infection and subsequently contin-

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Received: ***September 17, 2018*** *Accepted:* ***February 15, 2019***

DOI: 10.5152/tjg.2019.18674

ues PPIs. In our practice and predictably in most Western countries, the current long-term use of PPIs is mostly prescribed for patients with GERD, frequently with no previous exposure to *H. pylori*. "Gastroprotection" with the use of low-dose maintenance PPIs is also commonly advised for patients on chronic aspirin regimens, many of whom are elderly and/or have a history (even remote) of peptic ulcer disease.

Admittedly, some other studies (4,5) have suggested that the long-term use of PPIs is a risk factor for gastric cancer. Importantly, in the study by Brusselaers et al. (4), the highest risk of gastric cancer was observed in patients infected by *H. pylori* (SIR = 9.76; 95% CI: 8.87-10.71) and in those with peptic ulcer disease (SIR = 8.75; 95% CI: 8.12-9.41), which is also related to *H. pylori* infection in the majority of cases. Moreover, the same study (4) reported that the risk of gastric cancer was the highest among individuals receiving PPIs for periods shorter than 1 year'. In the latter group, the authors found, in marked contrast with patients who received long-term therapy with PPIs, a decreasing risk of gastric cancer when the use of PPIs was continued for over 5 years, an observation that does not support a possible carcinogenic effect of chronic PPIs use. Furthermore, we read the fine print of the article by Waldum et al. (5). These data exclusively refer to the risk of enterochromaffin-like (ECL) cell-derived tumors and appear mainly valid in animals exposed to high doses of PPIs and will have to be confirmed on robust evidence in clinical studies in humans.

We propose that the intriguing results of the study of Cheung et al. (1) should not change the practice of prescribing PPIs. We strongly advocate the judicious use of PPIs at the lowest effective dose for patients on maintenance treatment regimens. However, an abrupt change of clinicians' attitude on the management of such patients is recommended, and a possible withdrawal of PPIs from their maintenance regimens may lead to a significant impairment of the quality of life of patients with GERD and to serious complications in all groups of patients requiring long-term therapy with PPIs.

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