

# Proton-pump inhibitors should be strictly prescribed in clinic

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As gastric cancer is one of the most prevalent gastrointestinal malignancies, it brings about great burden all over the world. Various factors, including *Helicobacter pylori* (HP) infections, smoking, high-salt diet, and intake of nitroso compounds, have been proven to be associated with the carcinogenesis of stomach.<sup>1–4</sup> To improve the status of microenvironment of gastric mucosa, proton-pump inhibitors (PPIs) are widely used in clinic.<sup>5</sup> In recent years, however, some studies have shown that PPI overuse was associated with increased risk of gastric cancer. On the contrary, no significant relationships were found in other studies. A recent study entitled ‘Association between proton-pump inhibitors and the risk of gastric cancer: a systematic review with meta-analysis’ by Segna *et al.*<sup>6</sup> provided a relatively high-grade evidence for the controversial relationship, considering the quality of systematic reviews.<sup>7,8</sup>

As the largest study, Segna *et al.* included 1,662,881 subjects in 13 studies consisting of five retrospective cohort and eight case-control studies for meta-analysis. The research found that the risk of gastric cancer was increased twofold among PPI users in comparison with controls. To accurately analyze the effectiveness of PPI on gastric cancer, Segna *et al.* conducted various subgroup analyses. The authors first performed subgroup analysis based on tumor location. And they found that PPI use was associated with increased risk of non-cardia cancer rather than that of cardia cancer. Although the heterogeneity is substantial within both the subgroups, the relationship between PPI use and non-cardia cancer is consistent. The discrepancy within different locations may be attributed to the different mechanisms of carcinogenesis. In terms of PPI use duration, Segna also conducted subgroup analyses and showed that PPI use for less than 1 year is related to increased risk of gastric cancer rather than PPI

use for more than 1 year. When it comes to the results, the authors speculated that the difference may be associated with HP eradication. However, the conclusion should be drawn owing to the limited studies for subgroup analyses.

Just as the authors mentioned in the articles, the study indeed has some limitations. Even though many confounding factors were included in this meta-analysis, the largest study still provided a relative reliable evidence on PPI use and gastric cancer. As we all know, the carcinogenesis of gastric cancer is a multistep and long-time process, of which the superficial gastritis, atrophic gastritis, dysplasia, and cancer are the classical processes. Therefore, all the factors that could affect the stomach mucosa status may influence the relationship between PPI use and the risk of gastric cancer. Furthermore, the difference in PPI indications could also lead to the variations of the risk of gastric cancer. For example, PPI use for HP eradication or atrophic gastritis makes it difficult to accurately evaluate the PPI used and the risk of gastric cancer, considering the close relationship of these factors with gastric cancer. All the included studies do not have enough and detailed information; therefore, the meta-analysis of these factors is not able to precisely identify the relationships between PPI use and gastric cancer. However, the conclusions they get could still provide some foundation for doctors.

## Declarations

*Ethics approval and consent to participate*

Not applicable.

*Consent for publication*

Not applicable.

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#### Availability of data and materials

Not applicable.

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