

Reevaluating long-term proton pump inhibitor safety: potential metabolic drug interactions and personalized prescribing

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Dear Editor,

Proton pump inhibitors (PPIs) are widely used to treat acid-related disorders and prevent aspirin/NSAID-induced ulcers and are generally considered safe and clinically beneficial. However, their use has expanded to conditions for which their benefits are not fully established, potentially exposing patients to unnecessary risks. Although several adverse effects have been reported, their clinical significance remains uncertain because much of the evidence comes from retrospective observational studies with relatively low hazard ratios. Therefore, PPIs should be prescribed when clear clinical benefits are expected, and their long-term safety should be evaluated through high-quality prospective studies.¹

Although PPIs are unlikely to act as independent carcinogens, observational studies have reported an association between their use and gastrointestinal cancer, particularly gastric cancer; however, causality remains unproven. Proposed biological mechanisms include secondary hypergastrinemia, sustained elevation of gastric pH, alterations in the gastric microbiota, and enterochromaffin-like cell hyperplasia, which may theoretically contribute to gastric mucosal changes.² Supporting these concerns, a meta-analysis of 25 cohort studies found an approximately twofold increased risk of gastrointestinal cancer among PPI users, with increased risks reported for esophageal, gastric, liver, and pancreatic cancers, but not colorectal cancer. The association was also observed among individuals using PPIs for less than one year.³ However, these findings should be interpreted cautiously because of potential confounding, particularly from *Helicobacter pylori* infection, underlying gastrointestinal disease, and treatment indications. Overall, the available observational evidence does not establish a causal relationship between PPI use and cancer development.

Omeprazole (a PPI) can cause drug–drug interactions through inhibition of CYP2C19 and CYP3A4, with its metabolites also contributing to the overall interaction magnitude. Although the parent drug alone may be sufficient to identify some interaction risks, incorporating metabolite-mediated effects may improve quantitative predictions of clinical

drug–drug interactions. Importantly, metabolite exposure and lipophilicity alone do not reliably predict inhibitory contribution.⁴ Concomitant medications that inhibit or otherwise modify CYP2C19 and CYP3A4 activity may alter omeprazole metabolism and systemic exposure, particularly in patients receiving multiple medications. However, the magnitude and clinical significance of these effects depend on the specific medication and metabolic pathway involved. The extent to which concomitant CYP-modifying medications are characterized in drug safety and epidemiological studies should be assessed on a study-by-study basis rather than generalized across the literature. Future pharmacovigilance and epidemiological studies should systematically document concomitant CYP2C19- and CYP3A4-modifying medications to better characterize potential pharmacokinetic interactions and evaluate their implications for long-term safety outcomes. Although these interactions may be clinically relevant, their implications for long-term outcomes, particularly gastric cancer risk, remain uncertain. Direct evidence establishing that these interactions modify PPI-associated gastric cancer risk is currently insufficient; therefore, this proposed relationship should be considered hypothesis-generating.

Interindividual variability in PPI metabolism and treatment response related to CYP2C19 genetic polymorphisms is well documented. The Clinical Pharmacogenetics Implementation Consortium (CPIC) has published a guideline on CYP2C19 genotype-guided PPI dosing, including recommendations relevant to drug exposure and therapeutic efficacy.⁵ However, whether CYP2C19 genotype or concomitant CYP-modifying medications influence long-term gastric cancer risk remains unresolved. Future studies integrating genotype data, detailed medication histories, PPI exposure, and relevant confounders are needed to investigate this potential relationship.

Although observational studies have reported associations between PPI use and gastric cancer, current evidence does not establish a causal relationship. CYP2C19 variability and CYP-mediated drug interactions provide a pharmacological rationale for investigating differences in PPI exposure, but a

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direct link between genotype, concomitant CYP-modifying medications, and gastric cancer risk remains unproven. This should be regarded as a hypothesis-generating research question. Future prospective studies should incorporate detailed PPI exposure and indication, concomitant medication histories, CYP2C19 genotype, and relevant confounders—including *Helicobacter pylori* infection, age, and smoking—to determine whether these factors modify gastric cancer outcomes. Personalized PPI prescribing should continue to be guided by established clinical indications and evidence-based pharmacogenetic recommendations; biological plausibility alone is insufficient to infer cancer risk.

ETHICAL DECLARATIONS

Peer Review Process

This letter was externally peer-reviewed.

Conflict of Interest

The author declares no conflicts of interest.

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Author Contributions

The author is solely responsible for the conception, data collection, analysis, and writing of this manuscript.

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