PPIs and cancer: Is CYP2C19 a friend or foe?

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Proton pump inhibitors (PPIs) are among the most widely prescribed medications globally, offering effective relief for conditions ranging from gastroesophageal reflux disease to peptic ulcers. But their long-term safety profile, particularly regarding gastrointestinal malignancies, remains a subject of ongoing debate and epidemiological discordance. A new Mendelian randomization study, published in FASEB J, offers a deep dive into the genetic foundations of PPI-associated risks, identifying specific genetic loci that modulate disease susceptibility across diverse gastrointestinal conditions.1

KEY TAKEAWAYS

- The Pivot: Genetic variants in drug metabolism genes, particularly CYP2D6 and CYP2C19, significantly modulate the risk of various gastrointestinal cancers and benign conditions in PPI users.
- The Data: CYP2D6 variants increased hepatocellular/pancreatic cancer risk (OR 1.36-1.58, p=8.45 × 10-24 and OR 1.43-1.56, p=2.31 × 10-72, respectively) but protected against acute/chronic pancreatitis (OR 0.72-0.75, p=1.26 × 10-196 and OR 0.62-0.67, p=1.39 × 10-111).
- The Action: Clinicians should consider genetic predispositions, especially in patients requiring long-term PPI therapy, as these may influence individual risk profiles for gastrointestinal malignancies and other conditions.

The widespread use of PPIs has naturally led to extensive epidemiological research into their potential long-term adverse effects. While observational studies have frequently linked PPI use to an increased risk of various gastrointestinal disorders, including certain cancers, establishing causality has been challenging due to confounding factors inherent in such designs. This new Mendelian randomization (MR) study aimed to circumvent these limitations by leveraging genetic variants as instrumental variables, providing a more robust assessment of causal relationships.1

Researchers from the FASEB Journal team conducted a comprehensive two-sample Mendelian randomization analysis using multi-ancestry cohorts from the UK Biobank and FinnGen. They systematically investigated genes encoding both direct protein targets of PPIs and key proteins involved in PPI pharmacokinetics, assessing their impact across 24 distinct gastrointestinal diseases. The study design incorporated several validation steps, including colocalization and SMR analyses, disease and anatomical stratification, and HPA-based tissue expression profiling. Single-cell sequencing further elucidated target distribution, particularly in tumor cells.1

Unpacking the Genetic Architecture of PPI Risk

The investigation identified several genetic loci that significantly modulate gastrointestinal disease risk in the context of PPI use. CYP2D6 emerged as the most pleiotropic locus, associated with nine distinct

disease endpoints. Variants in CYP2D6 demonstrated dose-dependent carcinogenic effects, increasing the risk of hepatocellular cancer (OR 1.36-1.58; p=8.45 × 10-24) and pancreatic cancer (OR 1.43-1.56; p=2.31 × 10-72). Conversely, these same CYP2D6 variants conferred a protective effect against acute pancreatitis (OR 0.72-0.75; p=1.26 × 10-196) and chronic pancreatitis (OR 0.62-0.67; p=1.39 × 10-111). This dual role highlights the complex relationship between genetic factors in drug response and disease susceptibility.1

Other genes also played significant roles. ABCB1 and SLC22A1 exhibited pan-gastrointestinal risk modulation, suggesting broader involvement in PPI pharmacodynamics across the digestive tract. The anatomical stratification revealed context-dependent gene effects, with SLC22A1 showing specific associations in esophageal conditions, CYP2D6 in hepatic diseases, and CYP2C19 in colorectal contexts. CYP2C19 demonstrated opposing roles in carcinogenesis versus precancerous states within the colorectal region. This finding complicates the narrative around PPIs and colorectal cancer, suggesting that genetic background may dictate whether PPIs are protective or harmful at different stages of disease progression. For a deeper understanding of how genetic factors influence cancer risk, clinicians might consult resources like the Oxford Handbook of Genetics.1

The study also profiled tissue expression using the Human Protein Atlas (HPA), identifying SLC22A3 as a pan-cancer candidate due to its moderate-to-high expression in four tumor types. Single-cell sequencing data from tumor tissues further indicated that the aryl hydrocarbon receptor (AHR) was enriched in tumor cells and significantly higher than in normal cells across all five tumor tissues examined. This enrichment of AHR in tumor cells suggests a potential link to the gastrointestinal carcinogenicity of PPIs, providing a mechanistic hypothesis for further investigation.1

The Meta-Analysis Confirms a Link, But Complexities Remain

A meta-analysis conducted as part of this study confirmed a significant link between PPI use and an increased risk of gastrointestinal cancer. This overarching finding reinforces previous epidemiological observations but, the Mendelian randomization approach provides stronger evidence for a causal relationship by mitigating unmeasured confounding, which is a key benefit. The study's multi-omics integration, combining genetic, expression, and single-cell data, allowed for the identification of tissue-specific PPI pharmacodynamics and targets with dual therapeutic and carcinogenic potential. This may explain some of the epidemiological discordances observed in earlier, less granular studies.1

The researchers also highlighted the need for further research into PPIs and benign gastrointestinal diseases. While the focus often falls on cancer risk, the pleiotropic effects of genes like CYP2D6 suggest that PPIs may have complex and sometimes contradictory impacts on non-malignant conditions. Understanding these complexities is critical for comprehensive patient management, especially for those on long-term PPI regimens. The study's findings on colorectal cancer risk, particularly the role of CYP2C19, align with the broader recognition of genetic influences on cancer susceptibility, as seen in research on vitamin D3 supplementation and colorectal cancer survival.1

Methodological Strengths and Lingering Questions

The use of Mendelian randomization is a significant strength of this study, as it leverages the random assortment of genetic variants at conception to mimic a randomized controlled trial, thereby reducing confounding. The large multi-ancestry cohorts (UK Biobank and FinnGen) enhance the generalizability of the findings across different populations. The multi-omics approach, integrating various data types from genetic to single-cell, provides a

comprehensive view of PPI pharmacodynamics and potential mechanisms of action. This level of detail moves beyond simple association to explore biological plausibility.1

But, like all studies, this one has its limitations. Mendelian randomization relies on several key assumptions, including that the genetic variants are valid instrumental variables, meaning they are strongly associated with PPI use, are not associated with confounders, and influence the outcome only through PPI use. While the authors employed various validation methods (colocalization, SMR analyses) to strengthen these assumptions, residual confounding or pleiotropy cannot be entirely ruled out. The study also focused on genetic predispositions rather than actual PPI use patterns, which can vary widely among individuals. The dose-dependent effects observed for CYP2D6, for example, are inferred from genetic proxies for exposure, not direct measurement of drug intake.1

The anatomical stratification, while insightful, still presents a simplified view of complex biological systems. The opposing roles of CYP2C19 in colorectal carcinogenesis versus precancerous states require further mechanistic elucidation. It is not immediately clear what specific molecular pathways are activated or inhibited at different stages of disease development. While the meta-analysis confirmed a significant link between PPI use and increased gastrointestinal cancer risk, the specific magnitude of this risk and its clinical relevance for individual patients with different genetic profiles warrant more granular investigation. The study also did not differentiate between specific PPI drugs, which may have different pharmacokinetic and pharmacodynamic profiles.1

The identification of AHR enrichment in tumor cells is a compelling hypothesis for PPI carcinogenicity, but this remains an associational finding within the study. Direct experimental evidence demonstrating how PPIs modulate AHR activity to promote carcinogenesis is still needed. The study also called for more research into benign gastrointestinal diseases, acknowledging that the current focus on cancer might overshadow other important clinical implications of PPI use. Understanding the full spectrum of PPI effects, both beneficial and adverse, is essential for informed prescribing. This comprehensive approach to understanding disease mechanisms is also critical for conditions like inflammatory bowel disease, where IBD overlap changes colorectal cancer screening for rare subtypes.1

The study's findings highlight the importance of precision medicine in gastroenterology. Genetic testing for variants in CYP2D6, CYP2C19, ABCB1, and SLC22A1 could potentially identify patients at higher or lower risk for specific PPI-related adverse events or benefits. This could guide prescribing decisions, particularly for long-term PPI users, moving towards a more individualized approach to therapy. But, the clinical utility and cost-effectiveness of such widespread genetic screening would need to be rigorously evaluated in prospective studies. The complex relationship of genetics and drug response is a recurring theme in oncology, as seen in genetic tests identifying breast cancer patients who may avoid chemotherapy.1

"Our multi-omics integration reveals tissue-specific PPI pharmacodynamics, identifying targets with dual therapeutic/carcinogenic potential that may explain epidemiological discordances."Zhu W, Fan C, Wang H. FASEB J 2025The study provides a robust genetic framework for understanding the complex relationship between PPIs and gastrointestinal health. It moves beyond simple epidemiological associations to identify specific genetic pathways that modulate risk, offering a foundation for future research into personalized PPI therapy. The next step involves translating these genetic insights into actionable clinical strategies, including the development of predictive biomarkers and targeted interventions.1

CLINICAL IMPLICATIONS

The notion that a commonly prescribed drug like a PPI could have such varied and genetically determined effects on cancer risk is a stark reminder that one-size-fits-all prescribing is increasingly untenable. Clinicians should recognize that a patient's genetic background, particularly in genes like CYP2D6 and CYP2C19, may predispose them to either increased cancer risk or protection against other gastrointestinal conditions when on PPIs. This demands a more tailored approach to long-term PPI use, moving beyond simply treating symptoms. For the pharmaceutical industry, these findings highlight the need for more targeted drug development and potentially, companion diagnostics. Understanding the genetic variants that influence drug metabolism and target engagement could lead to the design of PPIs with improved safety profiles for specific patient populations. It also highlights the importance of multi-ancestry studies to ensure that drug effects are understood across diverse genetic backgrounds, rather than being limited to predominantly European cohorts. Patients on long-term PPI therapy, particularly those with a family history of gastrointestinal cancers, may benefit from discussions with their GPs about these genetic risks. While routine genetic testing for PPI prescribing is not yet standard, this research lays the groundwork for future personalized risk assessments. It reinforces the need for regular review of PPI indications and consideration of deprescribing when appropriate, especially given the confirmed link between PPI use and increased gastrointestinal cancer risk.

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REFERENCES

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