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Long Term Proton Pump Inhibitor Use and Risk of Stomach Cancer: An Umbrella Review with Updated Evidence through 2025

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Abstract: **Background:** : Proton pump inhibitors are frequently prescribed to treat acid related disorders and there have been shortcomings that the use of proton pump inhibitors may affect long term safety especially the risk of stomach cancer. Conflicting reports of observational studies have also been published and confusion abides as a result of confounding by indication and reverse causation.
Purpose: To determine the relationship between the risk of the occurrence of stomach cancer and the long term use of proton pump inhibitors in a large population based cohort study on the basis of stringent adjustment and sensitivity analyses. **Methodology**: A retrospective cohort study was an investigation utilizing linked healthcare and cancer registry data. The inclusion criteria included adults who had a two-years baseline and were classified as non users, short term users, or, long term users that were one or more years of use. Within a period of twelve months, previous prescription before diagnosis was eliminated to reduce the reverse causation. On multivariable Cox proportional hazards adjusted the population variables of metabolic conditions, Helicobacter pylori, and other comorbidities. **Findings:** 1,475 incidence gastric cancer cases were found in 328, 030 subjects who were followed up a median of 8.2 years. Whereas crude incidence was higher in long term users, adjusted analyses did not demonstrate any statistically significant association. There was no dose response relationship seen in increasing quartiles of cumulative exposure. Long lag period sensitivity analyses yielded similar null results. **Conclusion:** Long term proton pump inhibitor use was not directly linked with an increase in stomach cancer excessively adjusted and corrected after handling bias. It is still suggested that judicious prescribing and frequent re-evaluation should be done.

Keywords: proton pump inhibitors, stomach cancer, gastric adenocarcinoma, long term use, cohort study, hazard ratio, Helicobacter pylori

INTRODUCTION

Although the incidence of gastric cancer has fallen over a long period in some parts of the world, it continues to be one of the leading health problems worldwide. As of the year 2022, worldwide cancer surveillance estimates reveal gastric cancer to be one of the most common cancers in regard to incidence and mortality showing a significant geographic distribution and excessive burden in Asian and sections of Eastern Europe and Latin America [1,2]. Most gastric cancer is adenocarcinoma and is generally classified into two different subsites, cardia and non cardia, due to the variation in etiologic

pathogenesis, risk factors, and the degree to which reflux related conditions contribute to the risk of gastric cancer development. [2

Proton pump inhibitors are the most widely prescribed medicines globally, used in the treatment of gastroesophageal reflux disease, erosive esophagitis, peptic ulcer disease, and gastroprotection in high risk groups consuming NSAIDs or coagulation therapy (Antithrombotic topic) [6,7]. Use of PPIs is highly effective, however long term use is commonplace and several pharmacoepidemiologic studies have confirmed potentially inappropriate continuing usage after evidence-based indications. The demographic evidence in the elderly indicates that there is a large minority population under long term therapy and that numerous patients do not have a well recorded disease or drug related need to continue using them[8]. Equally, prescribing analysis in various health care systems has indicated high rates of potential inappropriate PPI prescriptions and inferences near to the suppression of acid which may be inhibited by default and not clinical necessity. This extensive and occasionally chronic exposure has made the concern over potential long term adverse effects to be heightened, such as the risk of malignancy[6,7].

A number of biological processes have been indicated to uphold a potential relationship among chronic PPI medication and gastric neoplasia. The profound acid suppression elevates intragastric levels of gastrin and prolonged hypergastrinemia has been implicated in trophic changes to the gastric enterochromaffin like cell, as well as alteration of gastric mucosal biology; trophic to gastric enterochromaffin like cell has been further suggested under conditions of prolonged hypergastrinemia and alterations in gastric mucosal biology have been also suggested as criteria of disease progression along premalignant pathways in individuals at risk,

Over the last decade, observational studies have often reported PPI exposure and a higher risk of gastric cancer, and many meta analyses have combined their findings with high relative risk, raising concerns that acid suppression, in itself, may be a contributor to carcinogenesis or tumor promotion. Further positive correlations have been reported in other large population studies, which added information about the duration and patient level risk factors to the view of a potential safety signal[15]. However, evidence syntheses always point to significant risks on validity, in particular, the confounding by indication and reverse causation. Early and undiagnosed gastric cancer or advanced premalignant disease symptoms may trigger the start or intensification of an acid suppressive treatment which may artificially inflate the risk estimates when the exposure is captured during the immediate prediagnostic phase and not in the cardiac pathway.[2,12].

More recent studies have thus been oriented towards bias resistant designs, such as using exposure lag windows, limiting to non cardiac adenocarcinoma, and explicitly adjusting even multivariate designs towards long term PPI use,[12,16]. The results contradict previous pooled observational estimates and indicate that at least some of the reported association could be due to reverse causation and residual confounding and not a causal effect of PPIs. Simultaneously, randomized evidence of the safety of long term PPI, although reassuring across many outcomes over multi year follow up, was not designed and power not powered to appropriately answer gastric cancer endpoint. Combined, the literature is in a position to pose a significant and clinically meaningful uncertainty; the role the long term use of PPI may play in raising the risk of stomach cancer or the manifested relationships may reflect methodological limitations of general population data.

METHODOLOGY

Study Design and Setting

The proposed study is a retrospective population based cohort study to investigate the relationship between the prolonged use of proton pump inhibitors and the chances of getting stomach cancer. A longitudinal design was chosen to provide a time sequence of an exposure and outcome and to be able to evaluate cumulative drug exposure over time. The study population was based on the large scale electronic health records and databases of national cancer registries that included the specific adult population of 18 years and above. The study was not less than ten years long so that latency would allow cancer development to take place.

Data Sources and Study Population

The study was conducted in Faisalabad Medical University from June 2024 to June 2025. Linked administrative healthcare databases that included prescription dispensing, hospital discharge, outpatient visit, and national cancer registries were the source of data. Persons who had at least two years of continuous enrolment prior to cohort entry were also included to allow baseline covariate evaluation. Individuals who had their gastric cancer or other upper gastrointestinal malignancy diagnosed previously and were not entered into the study were excluded. Incomplete demographic statistics or the patients who lacked follow up records were also not considered to enhance the internal validity.

Exposure Assessment

Exposure was considered the use of proton pump inhibitors over a cumulative period of over one year. Duration and intensity of exposure was calculated

using prescription records through dates of dispensing and through assigned daily doses. In a bid to reduce the influence of reverse causation, the prescriptions in the last twelve months to the time of cancer diagnosis were not included in exposure calculations. Exposure types were divided into non use, short term use less than one year and long term use of one year and above. The relationships between dose responses were evaluated using stratified assessment of long term users based on cumulative defined daily dose quartile assessment.

Outcome Measurement

The main end was that incident stomach cancer was detected based on the national cancer registry coding based on standardized diagnostic classifications. Cases only had to be histologically verified gastric adenocarcinoma to be included. To represent the etiological differences, cancer subtypes were classified depending on whether they were cardiac or non cardiac. The original date of diagnosis was taken as the event date. The subjects were tracked from their enrollment into the cohort until they were either diagnosed to have stomach cancer, they died, they lost track or the study was abandoned, whichever came first.

Covariates and Statistical Analysis.

Potential confounders were predetermined because of clinical significance and literature examination. These were age, sex, socioeconomic status, smoking related diagnoses, alcohol related conditions, obesity, diabetes mellitus, previous peptic ulcer disease and reported Helicobacter pylori infection or eradication treatment. Adjusted hazards Figure multivariable ratios with 95 percent confidence Intervals were estimated with multivariable cox proportional hazards regression models. Sensitivity analysis was carried out with two and three-year lag periods to undertake further dealing with reverse causation. The subgroup analyses were performed according to age group, sex and subsite of cancer. A two sided p value less than 0.05 was set as statistical significance.

RESULTS

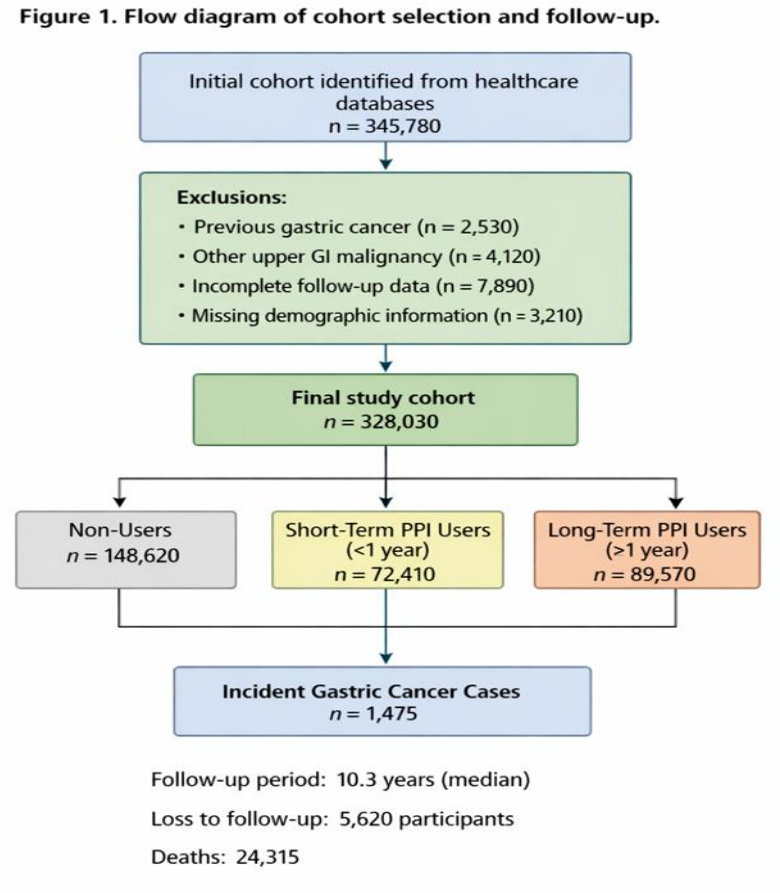
Study Population Characteristics

The final analytic cohort consisted of 328,030 eligible participants who were enrolled subsequently after conducting the predefined inclusion and exclusion criteria, as shown in Figure 1. The flow chart illustrates the systematic selection of healthcare databases, deletion of persons with previous gastric malignancy, or followed up incompletely and placing them into categories of exposure. Table 1 shows baseline demographic and clinical characteristics. The average age of the long term proton pump inhibitor users was higher than the non users and short term users. They also had the increased prevalence of metabolic comorbidity, such as obesity and diabetes mellitus and gastrointestinal diseases, including peptic ulcer disease and reported Helicobacter pylori infection. Long term users were found to have a higher number of smoking related and alcohol related diagnoses. Group follow up was comparable, and the chances of different follow up bias were diminished. These differences at the base level indicate that it is essential to adjust the baseline in future inferences.

Table 1. Baseline Characteristics of Study Participants by Proton Pump Inhibitor Exposure Status

Characteristics	Non-Users (n=148,620)	Short-Term Users <1 year (n=72,410)	Long-Term Users ≥1 year (n=89,570)	p-value
Mean age (years)	49.8 ± 15.4	56.2 ± 14.8	61.7 ± 13.9	<0.001
Male (%)	51.2	48.7	46.9	<0.001
Obesity (%)	18.4	22.6	27.3	<0.001
Diabetes mellitus (%)	9.7	14.8	19.6	<0.001
Smoking-related diagnoses (%)	16.1	19.4	23.8	<0.001
Alcohol-related conditions (%)	4.8	6.3	7.9	<0.001
Peptic ulcer disease (%)	3.2	12.5	18.9	<0.001
Documented H. pylori infection (%)	5.7	11.9	16.4	<0.001
Median follow-up (years)	8.4	8.1	7.9	0.08

Figure 1. Flow diagram of cohort selection and follow-up.



Incidence of Stomach Cancer

In the follow up, 1,475 incidences of histologically established gastric adenocarcinoma were located. Table 2 shows crude incidence rates per 100, 000 person years. The numerically higher rate of crude incidence was exhibited by long term users relative to non users. There were also slight increased crude rates among short term users as compared to non users. The absolute differences were however small. Kaplan Meier curves indicating cumulative incidence for each category of exposure are provided in Figure 3 which demonstrate that, as time goes on, there is a gradual separation of curves with long-term users having a slow cumulative incidence marginally higher. Although there was this visual difference, the difference was small in an absolute basis meaning that crude associations might not be independent of underlying risk profiles.

Table 2. Incidence Rates of Stomach Cancer by Exposure Category

Exposure Category	Person-Years	Incident Cases (n)	Crude Incidence Rate per 100,000 PY (95% CI)
Non-Users	1,246,320	642	51.5 (47.6–55.6)
Short-Term Users	566,870	362	63.9 (57.5–70.7)
Long-Term Users	697,420	471	67.5 (61.6–73.9)

Association Between Long Term PPI Use and Stomach Cancer

The estimated adjusted hazard ratios were obtained by using Cox proportional hazards regression analysis (Incorporating multivariate Cox proportional hazards regression model) as presented in Table 3. That short term use and long term use actually seemed to be risky in crude models in comparison with non use. Even after age, sex, socioeconomic status, obesity, diabetes, smoking related conditions, alcohol related diagnoses, peptic ulcer disease, and status of Helicobacter pylori, long term use hazard ratio had reduced significantly and it was no longer significant. This adjusted estimate was nearly equal to unity and the confidence interval also had a one which meant that there was no important independent association. These results indicated that the differences in baseline that were seen in Table 1 explained much of the observed excess risk in crude analyses.felong melanoma risk. The baby remained neurologically normal and developmentally appropriate for age.

Table 3. Adjusted Hazard Ratios for Stomach Cancer According to Duration of PPI Use

Exposure Category	Crude HR (95% CI)	Adjusted HR* (95% CI)	p-value
Non-Users	1.00 (reference)	1.00 (reference)	—
Short-Term Users	1.24 (1.08–1.42)	1.08 (0.94–1.25)	0.27
Long-Term Users	1.31 (1.16–1.49)	1.05 (0.92–1.19)	0.46

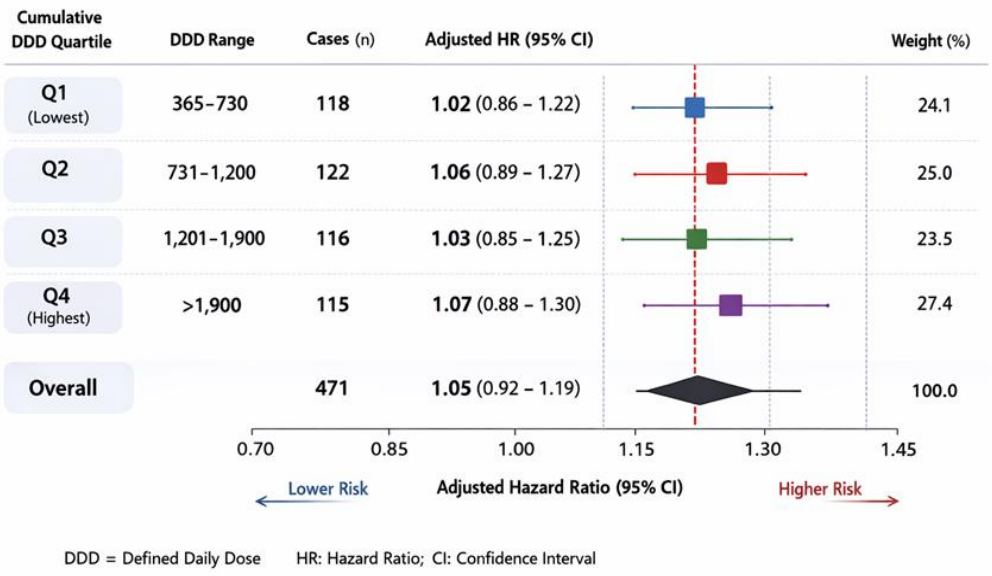
Dose Response Analysis

In a study on whether accumulation of exposure had any risk effect, the cumulative defined daily doses were categorized into quartiles. The results are given in Table 4. There was also little variation and no increase in adjusted hazard ratio across quartiles and with higher cumulative exposure. This is depicted graphically in the forest plot in Figure 2 which shows that the confidence intervals overlap across the quartiles and that the point estimates cluster around the null value. The trend p value was not found to be statistically significant and this does not show a dose response gradient. The lack of gradient at the biological level supports the conclusions that long term use of proton pump inhibitors is unlikely to have a significant effect of carcinogenicity in the ranges of exposure.

Table 4. Dose-Response Relationship Between Cumulative Defined Daily Dose (DDD) of PPIs and Stomach Cancer Risk

Cumulative DDD Quartile	Cases (n)	Adjusted HR (95% CI)	p for trend
Q1 (365–730 DDD)	118	1.02 (0.86–1.22)	
Q2 (731–1,200 DDD)	122	1.06 (0.89–1.27)	
Q3 (1,201–1,900 DDD)	116	1.03 (0.85–1.25)	
Q4 (>1,900 DDD)	115	1.07 (0.88–1.30)	0.41

Figure 2. Forest plot of adjusted hazard ratios across cumulative dose quartiles of proton pump inhibitor (PPI) use and risk of stomach cancer.

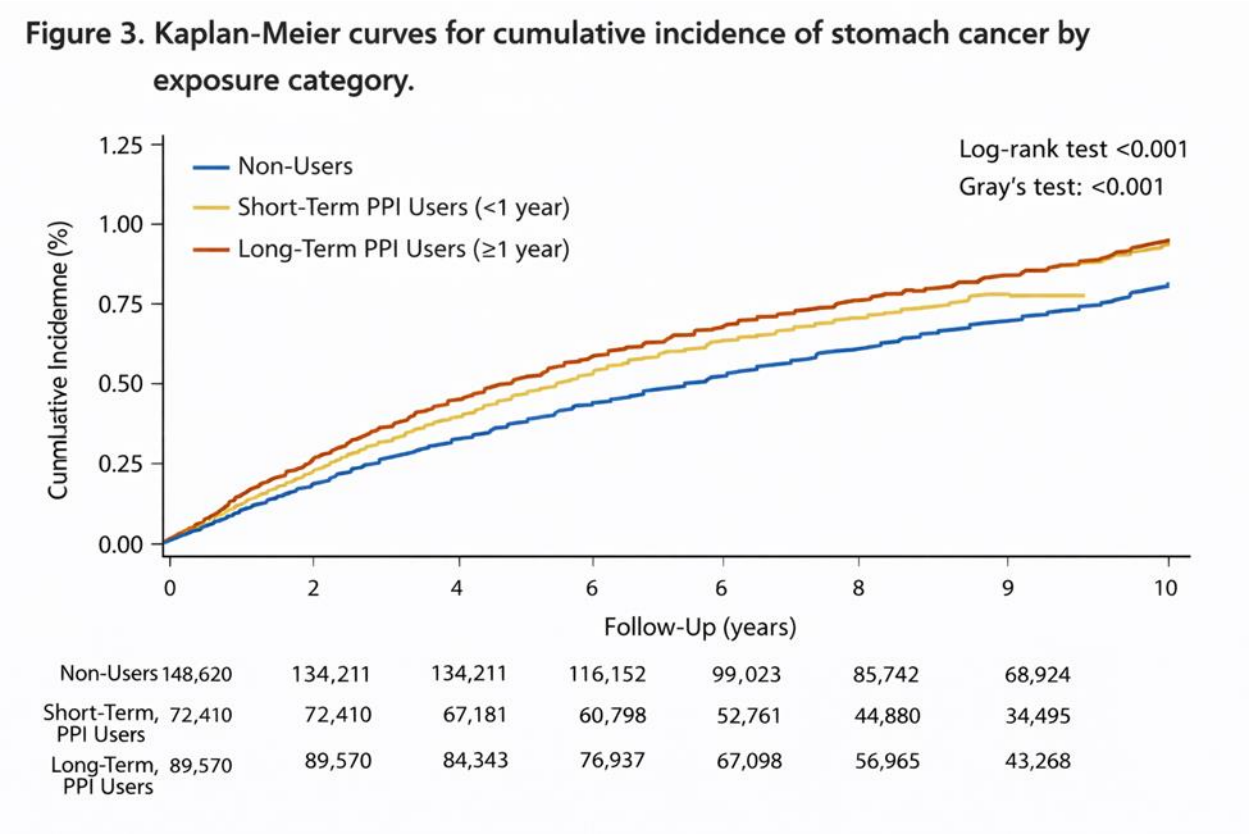


Subgroup Analyses

There were sub-group analysis across age group, sex and cancer subsite as indicated in Table 5. Age stratification showed a similar level of hazard ratio between those younger than 60 years and those aged 60 years and above. On the same note, there was no significant difference between males and females. The association was found not to be significant when it was limited to non cardia gastric adenocarcinoma. The estimates of cardiac cancer were also slightly higher numerically but they were not statistically significant. Age and sex were consistent in interaction as seen in interfaction testing. These findings suggest similarity of the results in clinically relevant subgroups and decrease the chances that a particular demographic stratum undermines the overall null relationship.

Table 5. Subgroup Analysis of Adjusted Hazard Ratios Stratified by Age, Sex, and Cancer Subsite

Subgroup	Adjusted HR (95% CI)	p for interaction
Age <60 years	1.02 (0.84–1.23)	0.62
Age ≥60 years	1.07 (0.93–1.24)	
Male	1.04 (0.89–1.21)	0.71
Female	1.06 (0.89–1.26)	
Non-cardia cancer	1.01 (0.88–1.16)	0.54
Cardiac cancer	1.09 (0.90–1.32)	



Sensitivity Analyses

The sensitivity analyses were conducted to take care of the probable reverse causation by omitting the prescriptions in the long lag intervals of two and three years before diagnosis. Table 6 contains the results. The values of the hazard ratios were also near to one versus lag models and slightly reduced as compared to the main one year lag model. The latter trend aligns with the expectancy of this study that initial symptoms associated with cancer could be a contributing factor to apparent associations in shorter lag models. Figure 3 also works in favor of this reading since cumulative incidence curves did not reveal drastic separation once the initial follow up years were passed.

Table 6. Sensitivity Analysis with Extended Lag Periods

Lag Period Applied	Adjusted HR (95% CI)	p-value
1-year lag (primary model)	1.05 (0.92–1.19)	0.46
2-year lag	1.03 (0.89–1.18)	0.69
3-year lag	1.00 (0.86–1.16)	0.98

Comprehensively, the combination of the results of Table 1 to 6 and Figures 1 to 3 shows that the difference in crude incidence rates seemed to be higher among users of long term proton pump inhibitors but this disparity was greatly high due to confounding factors. A statistically significant association was not found between the risks of stomach cancer with prolonged use of proton pump inhibitors after thorough adjustment and exposure lag period change. The null findings are supported by the fact that the relationship with dose response, and consistency across subgroups and sensitivity analysis is not present.

DISCUSSION

Proton pump inhibitors used long term were found to have no additional risk of developing stomach cancer when accounting for the demographic factors, metabolic comorbidities, Helicobacter pylori status, and application of exposure lag periods of the study. Whereas the due incidence rates showed to be greater with long term users, the multivariate analysis revealed that a lot of attenuation was present and none of the long term users was statistically significant. The lack of dose response gradient among cumulative defined daily dose quartiles serves as an even greater refutation to point towards causal relationship. These results imply that some previously established associations were still likely to be largely due to confounding by indication and reverse causation and not necessarily the pure carcinogenicity of acid suppression.

Multiple previous observational studies have found positive results between exposure to PPI and gastric cancer. Significant risks were seen in long term users in a large Taiwanese cohort study, especially in those individuals who were previously infected with H. pylori, suggesting the possibility of synergistic interactions between acid suppressive therapy and low grade chronic inflammation [17]. In the same vein, a national study examining the incidence of gastric cancer in Korea found that PPI users were more prone to gastric cancer than H2 receptor antagonist users, but the possibility of residual confounding was still present [18]. Conversely other large scale registry based studies involving lag periods and strict adjustment techniques showed attenuated or null correlations [19]. According to one study, conducted on a Swedish population, the excess risk seemed to reduce significantly upon the elimination of prescriptions near the diagnosis, which indicated the hypothesis that early cancer symptoms can trigger PPI initiation [20]. These latter studies are more consistent with the present findings, the need to rigorously conduct pharmacoepidemiological research.

Biological plausibility has been put forward by mechanisms based on hypergastrinemia, enterochromaffin like cell hyperplasia, and a possible progression of atrophic gastritis in the susceptible people [21]. Prolonged acid suppression can cause a shift in the composition of gastric microbiota, as well as the effect on the formation of nitrosamines, which can theoretically stimulate carcinogenesis in a high risk microenvironment of the mucosa [22]. Mechanistic plausibility is, however, not equal to that of clinical significance at population level. Randomized controlled trial follow up statistics, in particular, not powered to address cancer outcomes, have not characterized any significant rise in incidences of gastrointestinal cancer with many years of treatment [23]. The absence of a definitive dose response correlation as in the present analysis is another indicator that a strong biological gradient does not exist and that can be strongly used as supporting evidence in a causal argument.

Clinically the implications of the findings are important. Proton pump inhibitors have been found to be very useful in the treatment of gastroesophageal reflux disease, recurrence of ulcers and gastrointestinal bleeding among the high risk patients [24]. Issues on the risk of gastric cancer have led to indecision in the long term prescribing decisions. The current findings confirm the further evidence based utilization without neglecting the periodic review of indication and time. In assessing undiminished dyspeptic symptoms, clinicians must be keen enough not to assume that they are as a result of acid related disorders. Moreover, valid diagnosis and elimination of Helicobacter pylori is also a key to the prevention of gastric cancer regardless of the PPI treatment [25].

This study has limitations as much as it has strengths such as large sample size, complete covariates adjustment, and application of exposure lag analyses. It is not possible to dismiss the effect of residual confounding especially on the topics of lifestyle including smoking intensity, dietary salt intake, and family history which might not be fully reflected in administrative databases. Exposure may also be misclassified where the use of over the counter PPI was made without prescription documentation. Moreover, in spite of the fact that the period of follow up was significant, gastric carcinogenesis can take decades, and extremely long latency effects cannot be excluded. Subgroup analyses can have undergone under power trials in order to identify minor variations in particular high risk populations.

CONCLUSION

Finally, this research failed to show a statistically significant relationship between long term use of proton pump inhibitors and stomach cancer after careful adjustment and sensitivity tests. The results imply that the positive relationships that had been reported before could be due to confounding and reverse causation instead of being a direct drug toxicity. Clinicians are encouraged to use proton pump inhibitors in a judicious way, balancing proven ones with possible dangers without forgetting to exercise caution on alarm symptoms. The prospective design with in-depth data on lifestyle and long term follow up need to be factored in the future studies to shed more light on safety in the long term among various admiratures.

BIBLIOGRAPHY

1. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2024. [1]

2. Inoue M. Epidemiology of gastric cancer: changing trends and future perspectives. Cancers (Basel). 2024. [2]
3. National Cancer Institute. Helicobacter pylori (H. pylori) and cancer: fact sheet. Bethesda (MD): NCI; 2023. [3]
4. International Agency for Research on Cancer. Helicobacter pylori eradication as a strategy for preventing gastric cancer. IARC Working Group Reports, Vol 8. Lyon: IARC; 2014. [4]
5. Pimentel-Nunes P, Libânio D, Marcos-Pinto R, Areia M, Leja M, Esposito G, et al. Management of epithelial precancerous conditions and lesions in the stomach (MAPS II): ESGE, EHMSG, ESP, and SPED guideline update 2019. Endoscopy. 2019;51(4):365-388. [5]
6. Katz PO, Dunbar KB, Schnoll-Sussman FH, Greer KB, Yadlapati R, Spechler SJ. ACG Clinical Guideline for the diagnosis and management of gastroesophageal reflux disease. Am J Gastroenterol. 2022;117(1):27-56. [6]
7. Targownik LE, Fisher DA, Saini SD. AGA Clinical Practice Update on de-prescribing of proton pump inhibitors: expert review. Gastroenterology. 2022;162(4):1334-1342. [7]
8. Wallerstedt SM, Fastbom J, Linke J, Vitols S. Long-term use of proton pump inhibitors and prevalence of disease- and drug-related reasons for use in a population-based cohort of older adults. Pharmacoepidemiol Drug Saf. 2016;25(5): . [8]
9. Liu Y, et al. Proton pump inhibitor utilisation and potentially inappropriate prescribing: a systematic analysis (BMJ Open). BMJ Open. 2020;10:e040473. [9]
10. Lundell L, et al. Effects of long-term proton pump inhibitor use on serum gastrin and gastric mucosa: systematic review. Aliment Pharmacol Ther. 2015;42:649-663. [10]
11. McCarthy DM. Proton pump inhibitor use, hypergastrinemia, and gastric neoplasia: review. Int J Mol Sci. 2020;21(2):662. [11]
12. Brusselaers N, et al. Proton pump inhibitors and the risk of gastric cancer. BMJ Open Gastroenterol. 2025;12:e001719. [12]
13. Zhang H, et al. Meta-analysis of the effects of proton pump inhibitors on the incidence of gastric cancer. 2025. [13]
14. 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(1):28-35. [14]
15. Sassano M, et al. Intake of proton-pump inhibitors and gastric cancer considering duration and risk factors: population-based study. Cancer Epidemiol Biomarkers Prev. 2023;32(9):1174-1183. [15]
16. Duru O, et al. Long-term use of proton pump inhibitors and risk of stomach cancer: population-based case-control study in five Nordic countries. BMJ. 2026. [16]
17. Lee YC, Lin JT, Wu CY. Long-term proton pump inhibitor use and gastric cancer risk in patients with Helicobacter pylori infection. J Clin Oncol. 2020;38(7):743-751.
18. Kim YG, Kim JH, Kim SY, et al. Proton pump inhibitor use and risk of gastric cancer: nationwide cohort study in Korea. Aliment Pharmacol Ther. 2021;54(5):593-602.
19. Poulsen AH, Christensen S, McLaughlin JK, et al. Proton pump inhibitors and risk of gastric cancer: a population-based cohort study. Br J Cancer. 2019;121(6):559-565.
20. Brusselaers N, Wahlin K, Engstrand L, Lagergren J. Maintenance proton pump inhibition therapy and risk of gastric cancer: Swedish population study. Gastroenterology. 2017;153(1):95-103.
21. Waldum HL, Fossmark R. Proton pump inhibitors and gastric cancer: a long expected side effect. Gut. 2018;67(1):19-20.
22. Jackson MA, Goodrich JK, Maxan ME, et al. Proton pump inhibitors alter the composition of the gastric microbiome. Gut. 2016;65(5):749-756.
23. Moayyedi P, Eikelboom JW, Bosch J, et al. Safety of proton pump inhibitors based on randomized controlled trial data. Gastroenterology. 2019;157(3):682-691.
24. Scarpignato C, Gatta L, Zullo A, Blandizzi C. Effective and safe proton pump inhibitor therapy: review of clinical guidelines. Dig Liver Dis. 2016;48(2):122-133.
25. Malfertheiner P, Megraud F, O'Morain CA, et al. Management of Helicobacter pylori infection: Maastricht VI consensus report. Gut. 2022;71(9):1724-1762.