Digestive Tract Cancer Related Adverse Events Associated with Proton Pump Inhibitors use: A Pharmacovigilance Study of the FDA Adverse Event Reporting System

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Abstract

Background Proton pump inhibitors (PPIs) are widely used to treat digestive system diseases. Previous studies have suggested conflicting results between PPIs treatment and digestive tract cancers (DTCs). We utilized the FDA Adverse Event Reporting System (FAERS) database to assess the effect of PPIs use on DTCs through data mining. **Method** This study examined the association between six PPI agents and DTCs by mining the FAERS database from January 2004 to September 2021 by using Open Vigil 2.1. The reporting odds ratio (ROR) with 95% confidence intervals (CIs) was used to detect statistically significant associations between PPIs and DTCs. High Level Terms (HLTs) and Preferred Terms (PTs) were defined by the Medical Dictionary for Regulatory Activities 24.0 (MedDRA24.0). **Result** A total of 2553 DTCs adverse event reports were screened, with positive signals obtained from gastric neoplasms malignant (GNM) (ROR: 1.09, 95% CI: 1.01-1.18) and bile duct neoplasms malignant (BDNM) (ROR: 1.80, 95% CI: 1.44-2.25). Esomeprazole showed the strongest signal (ROR: 1.85, 95% CI: 1.66-2.06) for GNM, while rabeprazole for BDNM (ROR: 2.94, 95% CI: 1.32-6.56), and female PPI users had a higher risk of BDNM (ROR: 2.44, 95% CI: 1.77-3.35). Among Subordinate PTs, adenocarcinoma gastric, and the combination of "bile duct cancer" and "cholangiocarcinoma" were highly associated with PPIs use. **Conclusion** By mining the FAERS database, we provided important clues for the association between PPIs use and DTCs risk.

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Declarations

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Conflict of interest disclosure

The authors declare that there is no conflict of interest.

Ethics approval statement

Not applicable.

Patient consent statement

Not applicable.

Availability of data and materials

The data supporting the findings of this study were derived from the following resources available in the public domain:*http://openvigil.sourceforge.net/*.

Author Contributions

Guo-rong fan designed the study and supervised the work. Sheng-ying Gu and Shi-dan Yu collected the data, analyzed the data, and drafted the manuscript. Shuo-wen Wang, Shan-shan Hu and Zhen-yu Zhou performed the data analysis and interpretation, Chen-yang Shi and Chen-dong Qi revised the manuscript. All the authors have read the final manuscript and approved the submitted version.

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Abstracts

Background

Proton pump inhibitors (PPIs) are widely used to treat digestive system diseases. Previous studies have suggested conflicting results between PPIs treatment and digestive tract cancers (DTCs). We utilized the FDA Adverse Event Reporting System (FAERS) database to assess the effect of PPIs use on DTCs through data mining.

Method

This study examined the association between six PPI agents and DTCs by mining the FAERS database from January 2004 to September 2021 by using Open Vigil 2.1. The reporting odds ratio (ROR) with 95% confidence intervals (CIs) was used to detect statistically significant associations between PPIs and DTCs. High Level Terms (HLTs) and Preferred Terms (PTs) were defined by the Medical Dictionary for Regulatory Activities 24.0 (MedDRA24.0).

Result

A total of 2553 DTCs adverse event reports were screened, with positive signals obtained from gastric neoplasms malignant (GNM) (ROR: 1.09, 95% CI: 1.01-1.18) and bile duct neoplasms malignant (BDNM) (ROR: 1.80, 95% CI: 1.44-2.25). Esomeprazole showed the strongest signal (ROR: 1.85, 95% CI: 1.66-2.06) for GNM, while rabeprazole for BDNM (ROR: 2.94, 95% CI: 1.32-6.56), and female PPI users had a higher

risk of BDNM (ROR: 2.44, 95% CI: 1.77-3.35). Among Subordinate PTs, adenocarcinoma gastric, and the combination of "bile duct cancer" and "cholangiocarcinoma" were highly associated with PPIs use.

Conclusion

By mining the FAERS database, we provided important clues for the association between PPIs use and DTCs risk.

Keywords : PPIs, digestive tract cancers, pharmacovigilance, data mining, FAERS.

Key Points

- An increased risk of digestive tract cancers (DTCs) related to proton pump inhibitors (PPIs) has been noted and deserves attention, but the clinical evidence is contradictory and the real-world data is limited.
- This is the first real-world pharmacovigilance study of FDA adverse event reporting system (FAERS) database to assess the association between PPIs use and DTCs risk.
- We found a significant association between PPIs use and gastric neoplasm malignancy, including adenocarcinoma gastric cancer, and bile duct neoplasms malignant, including bile duct cancer.
- Our results may provide further clues regarding the long-term adverse effects of PPI use.

Plain Language Summary:

The long-term safety of proton pump inhibitors (PPIs) recently attracts much attention, particularly the risk of digestive tract cancers (DTCs) which is reported by multiple clinical studies. Also, there are many inconsistent evidences. So, more pharmacovigilance studies should be conducted to validate long-term safety of PPIs. To evaluate the association between PPIs use and DTCs risk, we chose real-world data obtained from the FDA Adverse Event Reporting System database from January 2004 to September 2021 through Open Vigil 2.1. We conducted disproportionality analysis to quantify the association of PPIs therapy and DTCs adverse events, including oesophageal, gastric, small intestinal, colorectal, anal canal, pancreatic, bile duct, gallbladder, and hepatic neoplasms malignant. We found that a high reporting frequency of gastric neoplasms malignant (GNM) and bile duct neoplasms malignant (BDNM) provoked by PPIs therapy. Further assessments to discriminate DTCs risks among different PPIs, the use of esomeprazole was associated with higher risk of GNM, while the use of rabeprazole was associated with higher risk of BDNM. So, we must be cautious about DTCs risks with the long-term use of PPIs. As a real-world study mingled with complicated factors,our conclusions can only provide clues for further investigation, but highly valuable clues.

Introduction

Since omeprazole was developed by AstraZeneca and approved to enter the market in 1987, proton pump inhibitors (PPIs) have been widely used to treat acid-related diseases, including gastroesophageal reflux disease (GERD), peptic ulcer disease (PUD) and upper gastrointestinal bleeding (GIB) [1]. Due to their outstanding clinical efficacy and safety, PPIs have been recognized as a milestone in the treatment of digestive system diseases in the 20th century [2]. However, in recent years, more new or serious adverse drug reactions (ADRs) have been reported with long-term PPIs use [3].

Evidence from epidemiological and mechanistic studies is accumulating that supports a possible relationship between PPIs use and DTCs [4-6]. The risk of DTCs was first noticed for hypoacidity and hypergastrinemia as a consequence of long-term PPIs use [7]. In addition, the microbiota composition has been shown to be disrupted with a reduction of gastric acid secretion, causing microbiota "dysbiosis" [8]. And the enrichment of specific bacterial communities has been shown to be accompanied by the production of oncogenic metabolites [8,9].

The present results indicated that long-term use of PPIs may lead to initiation and progression of different tumor types arising from many sites in the digestive tract, including esophageal, gastric, colorectal, pancreatic, liver and biliary tract cancers [10,11]. In turn, opposite voices were raised, disapproving of research and

statistical methods in epidemiology and highlighting the complexity of the real-world data [12,13]. In addition, the incipient symptoms of gastric, pancreatic, and liver cancer, such as heartburn, bloating, abdominal pain, nausea, and vomiting, are similar to those of acid-related peptic diseases, so patients have been treated with PPIs empirically before being diagnosed with DTCs [14].

The FDA Adverse Event Reporting System (FAERS) as the world's largest spontaneous reporting database has been publicly available online and updated quarterly since 2004. In the past few years, data mining of Adverse Events (AEs) maintained in the FAERS has been performed to investigate drug utilization in clinical practice and has been recognized as an essential tool for identifying drug-associated AEs with the advantages of avoiding the potential bias and reflecting the real-world clinical settings [15,16]. Thus, in this study, we aimed to identify DTCs-related AEs associated with PPIs use by performing an FAERS analysis to provide new insights into this issue.

Method

2.1 Data Source

To identify DTCs-related AEs reported associated with PPIs use, we retrieved relevant datasets from the public release of the FAERS database from the first quarter (Q1) of 2004 to the third quarter (Q3) of 2021. All data in the FAERS database has been fully anonymized by the regulatory authorities.

Open Vigil 2.1 has been used in many pharmacovigilance studies as a pharmacovigilance data extraction, cleaning, mining, and analysis tool of the FAERS database [16-18]. Open Vigil 2.1 is designed for complete case analyses and is more stable and superior for analyses of disproportionality than the Open Vigil FDA [19]. After data cleaning by Open Vigil 2.1, 9,217,181 reports from 2004 Q1 to 2021 Q3 were identified for data analysis.

2.2 Definition of Adverse Events

AEs in FAERS are coded using Preferred Terms (PTs) from MedDRA (version 24.0) terminology. PTs are meant to represent a single standardized medical concept and are allowed into relevant broader High Level Term (HLT), Higher Level Group Term (HLGT), and System Organ Class (SOC) according to the hierarchical structure of MedDRA.

In our study, we identified cases by retrieving the reports under the MedDRA HLTs of gastric neoplasms malignant (GNM), pancreatic neoplasms malignant (PNM), bile duct neoplasms malignant (BDNM), small intestinal neoplasms malignant (SINM), oesophageal neoplasms malignant (ONM), colorectal neoplasms malignant (CNM), anal canal neoplasms malignant (ACNM), gallbladder neoplasms malignant (GBNM) and hepatic neoplasms malignant (HNM) with any FDA-approved PPIs (omeprazole, lansoprazole, pantoprazole, rabeprazole, esomeprazole and dexlansoprazole). H2-receptor antagonists (H2RAs; e.g., cimetidine, famotidine and roxatidine) were chosen as the negative control referring to previous clinical studies [20,21], for the same acid-suppressive effect but without the potential carcinogenic effect. All post-marketing H2RAs were included except ranitidine and nizatidine because these two drugs had been recalled due to carcinogenesis of impurities. PTs (adenocarcinoma gastric, gastric cancer, gastric cancer recurrent, gastric cancer stage 0, gastric cancer stage I, gastric cancer stage II, gastric cancer stage III, gastric cancer stage IV, gastric sarcoma, gastroesophageal cancer, gastroesophageal cancer recurrent, HER2 positive gastric cancer, linitis plastica and metastatic gastric cancer for gastric neoplasms malignant, bile duct adenocarcinoma, bile duct adenosquamous carcinoma, bile duct cancer, bile duct cancer recurrent, bile duct cancer stage 0, bile duct cancer stage I, bile duct cancer stage II, bile duct cancer stage III, bile duct cancer stage IV, bile duct squamous cell carcinoma, biliary cancer metastatic, cholangiocarcinoma and cholangiosarcoma for bile duct neoplasms malignant) that were subordinate to the HLTs "GNM" and "BDNM" were retrieved for their higher signal strength. These cases of PTs and HLTs reported with GNM and BDNM as indications were removed to reduce the "indication bias". Non-FDA approved PPIs (e.g., ilaprazole) were excluded because they may be underreported in the FAERS.

2.3 Data Mining Algorithm

We performed disproportionate analyses using the reporting odds ratio (ROR) along with a 95% confidence interval (CI) to identify drug-associated adverse events as signals among PPIs. The ROR was defined as the ratio of the odds of reporting AEs versus all other PPIs-related reactions to the reporting odds for all other drugs present in the database. Basically, a higher ROR suggested a stronger signal strength [22]. The signal was considered positive if the lower limit of the 95% CI was greater than 1, and at least three cases were reported [23]. All analyses were performed using Microsoft Excel 2010 and GraphPad Prism 7.

Results

3.1 Association between PPIs Use and DTCs

Overall, 387,929 AE reports related to PPIs and 109,724 AE reports related to DTCs were reported to the FAERS from January 2004 to September 2021. The systematic research progress from FAERS database was shown in Figure 1. We screened 2,553 DTCs AE reports associated with the use of PPIs from the FAERS database, the characteristics of which are described in Table 1. The numbers of reports for GNM, CNM, PNM, HNM, ONM, BDNM, SINM, GBNM and ACNM were 687 (26.9%), 586 (23.0%), 456 (17.9%), 405 (15.9%), 327 (12.8%), 83 (3.3%), 38 (1.5%), 33 (1.3%) and 20 (0.8%), respectively. Serious outcomes of AE-related HLTs focused on hospitalization (948, 37.1%) and death (826, 32.4%).

Signal detection was conducted firstly based on all PPIs with H2RAs as a negative control. Positive signals were obtained for all PPIs associated with the GNM (ROR: 1.09, 95% CI: 1.01-1.18) and BDNM (ROR: 1.80, 95% CI: 1.44-2.25), while the H2RA cohort (n=153) had no positive signal as shown in Figure 2a.

Three subset analyses were performed to further demonstrate whether gender, age and individual PPI molecules influenced the reporting of DTCs.

A previous study had demonstrated that the association between DTCs and PPIs use differed by sex [24]. According to Table 1, PPIs reports associated with DTCs were higher in males than females (46.3% versus 38.9%, respectively) as well as in ONM (64.2% in males versus 29.7% in females), GNM (30.9% in males versus 26.2% in females) and HNM (59.3% in males versus 34.8% in females), whereas cases of SINM (44.7% in males versus 52.6% in females), CNM (45.7% in males versus 50.7% in females), ACNM (45.0% in males versus 55.0% in females), PNM (47.6% in males versus 48.5% in females), GBNM (30.3% in males versus 60.6% in females) and BDNM (47.0% in males versus 50.6% in females) had an opposite trend. The gender subset analysis showed that a further increase in signal was obtained in the female group for PPIs associated with BDNM with an ROR of 2.44 (95% CI: 1.77-3.35) as shown in Figure 2b. Although the GNM cohort had the largest number of AE reports for the cancer category, accounting for 26.9%, the signal was negative after stratifying by sex, which might be caused by the removal of unknown or missing groups.

When stratified by age, most AE reports were distributed in the middle age group (18–65 years) and old age group (> 65 years), regardless of whether DTCs were considered as a whole or split into subcategories as shown in Table 1. The young people group (<18 years old) was not included in the disproportionality analysis due to the small number of AE reports. Statistically significant AE RORs for BDNM were found in both the middle group (ROR: 2.00, 95% CI: 1.38–2.89) and the old group (ROR: 1.72, 95% CI: 1.24–2.39) as shown in Figure 2c. A negative signal was detected for PPIs in GNM after stratifying by age same as the sex stratification analysis.

Furthermore, we conducted a subset analysis stratified by different PPIs. The results were represented in Supplementary Table 1 and visualized using heatmaps, showing the relationship between different DTCs and different PPIs (Figure 3). We found statistically significant GNM signals for the following single agents (Figure 4a): omeprazole (ROR: 1.41, 95% CI: 1.27-1.56), lansoprazole (ROR: 1.87, 95% CI: 1.65-2.13), pantoprazole (ROR: 1.32, 95% CI: 1.16-1.51), esomeprazole (ROR: 1.85, 95% CI: 1.66-2.06), and dexlansoprazole (ROR: 1.56, 95% CI: 1.21-2.01). For BDNM detection (Figure 5a), rabeprazole had the strongest signal (ROR: 2.94, 95% CI: 1.32-6.56), followed by lansoprazole (ROR: 1.86, 95% CI: 1.15-3.00) and omeprazole (ROR: 1.63, 95% CI: 1.13-2.34).

3.2 Association between PPIs Use and GNM

Devin Abrahami et al found that there was a slight difference in hazard rates for the association between the use of specific types of PPIs and gastric cancer [21]. Thus, to better understand gastric cancer of different types and individual PPI molecules (esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole, dexlansoprazole or combinations), we additionally assessed a new disproportionality analysis.

The total number of reports for PPIs associated with GNM was 678 after removal of related indications, most of which belonged to gastric cancer (585, 86.3%) and adenocarcinoma gastric (79, 11.7%). Four statistically significant signals were identified, including adenocarcinoma gastric (ROR: 9.99, 95% CI: 7.67-13.02), gastric cancer recurrent (ROR: 3.25, 95% CI: 1.38-7.65), gastroesophageal cancer (ROR: 3.37, 95% CI: 1.18-9.64) and metastatic gastric cancer (ROR: 4.38, 95% CI: 2.71-7.06) as shown in Figure 4b. In the further stratification analysis, the signals of adenocarcinoma gastric and metastatic gastric cancer were positive regardless of whether they were associated with any one PPI molecule (Figure 4c), or PPIs assessed together as a drug class, while statistically significant gastric cancer recurrent signals were found only for esomeprazole (ROR: 7.04, 95% CI: 2.53-19.59) and omeprazole (ROR: 6.50, 95% CI: 2.56-16.41), with lower case numbers.

The disproportionality analysis between PPIs and gastric cancer revealed interesting results. Cases associated with GNM were mainly from gastric cancer, but the ROR lower bound of the 95% CI of gastric cancer was detected no more than but close to 1 (ROR: 1.07, 95% CI: 0.98-1.16). Surprisingly, if different PPIs were analyzed as a single agent, all drugs obtained positive signals except rabeprazole (Figure 4c and Supplementary Table 2). Further investigation is needed to prove this possibility instead of simply explaining the lack of gastric cancer risk in patients treated with rabeprazole.

3.3 Association between PPIs Use and BDNM

Recently, more attention has been given to the risk of biliary tract cancer in persons treated with PPIs, largely due to a nationwide clinical study conducted in Sweden [25]. Therefore, the total number of reports for PPIs associated with BDNM was low, only 33 cases. However, the results of disproportionality analysis between PPIs and BDNM were significant and are presented in Figure 5 and Supplementary Table 3. Overall, based on the criteria for the data mining algorithm, we found statistically significant AE RORs for bile duct cancer (ROR: 1.63, 95% CI: 1.18-2.25) and cholangiocarcinoma (ROR: 2.52, 95% CI: 1.82-3.50). Further stratified analysis was conducted, which provided a possibility for an association between bile duct cancer and lansoprazole (ROR: 2.14, 95% CI: 1.18-3.88) as well as rabeprazole (ROR: 3.47, 95% CI: 1.30-9.28). In addition, we found statistically significant cholangiocarcinoma signals for the following agents: omeprazole (ROR: 2.32, 95% CI: 1.41-3.83) and pantoprazole (ROR: 2.19, 95% CI: 1.17-4.10). However, these significant results were unlikely due to the small number of reported cases, which only provided important clues for subsequent studies.

Bile duct cancer is also known as cholangiocarcinoma [26], but bile duct cancer and cholangiocarcinoma are distinguished in MedDRA. We combined bile duct cancer and cholangiocarcinoma as a group for analysis. The results (Supplementary Table 4) showed a total of 80 cases identified corresponding to this new group, and the signals detected with the PT combination (ROR: 2.00, 95% CI: 1.59-2.51) were positive. We also identified sex differences between PPIs use and the new group, and the association was stronger in female (ROR: 2.63, 95% CI: 1.89-3.66). For the drug-ADE level, dexlansoprazole listed much later showed no signals for the few data reported, and the signal of esomeprazole did not reach statistical significance, while the other four PPIs did show statistically significant signals, as noted in Supplementary Table 4.

Discussion

Ongoing post-marketing surveillance is essential due to the following limitations of clinical trials: population type, group size, duration and indications. The longer-term safety of drugs and occurrence of rare adverse effects are to a large part evaluated using post-marketing surveillance data, which increases the value of spontaneous reporting systems such as the FAERS to some extent. Therefore, the FAERS database has been widely used to identify passive pharmacovigilance risk signals in a real-world clinical setting.

PPIs, one of the most commonly prescribed drugs worldwide, have been recognized as a relatively safe drug

based on the findings of clinical trials. However, with the increasing use of PPIs, more and more novel or even severe PPI-associated ADRs have been reported, especially after long-term and high-dose treatment [21,27]. The content of ADR part in drug instructions should be revised according to the announcement of the National Medical Products Administration of China on February 24, 2022 and was requested additional warning on the risk of severe ADRs due to PPIs therapy, such as difficile-associated diarrhea, hypomagnesemia and fractures. Most surprising is that PPIs as first-line drugs for treating acid-related gastric diseases may induce or be associated with DTCs [14]. The inconsistent results obtained from emerging clinical trials may initiate more discussion on the association between PPIs use and DTCs risk.

Based on a large-scale ADR dataset, the associations between PPIs and the risk for fracture [28], dementia [29], hepatotoxicity [30], subacute cutaneous lupus erythematosus [31] and kidney injury and chronic kidney disease [32] were investigated to provide valuable information on potential ADRs. Therefore, this study was the first to evaluate the association between PPIs use and DTCs risk using the unique resources of the FAERS. Using the data mining method, statistically significant signals between PPIs and nine HLT categories of DTCs classed by MedDRA were detected in this study. Two positive signals for the HLTs "GNM" and "BDNM" were identified and consistent with prior reports of an increased risk for gastric cancer and bile duct cancer with PPIs use [21,25,33,34]. In contrast, DTCs were not associated with the use of H2RAs in our study, which was consistent with the results of the meta-analysis and observational studies in epidemiology group [20,21]. This observation can be explained by the possible mechanism of which PPIs have a better acid inhibitory effect than H2RAs, which results in inhibiting the secretion of gastrointestinal hormones and changing the gastrointestinal microbiome [35,36].

When analyses were stratified by age and sex, GNM showed no signals, most likely due to large proportions of missing variable values. This is an inevitable limitation of the spontaneous reporting mechanism of the FAERS database. We also screened the signals of each PPI, indicating no significant signal between rabeprazole and GNM. Lansoprazole and esomeprazole (ROR lower bound of 95% CI: 1.65-1.66) showed stronger signals than omeprazole, pantoprazole and dexlansoprazole (ROR lower bound of 95% CI: 1.16-1.27), partly differing from the various degrees of risk for gastric cancer reported in one population-based cohort study from England: lansoprazole > omeprazole[?]rabeprazole > esomeprazole > pantoprazole [21]. Combining this literature and our study, there may be slightly different risks of gastric cancer using different PPIs, while the highest risk of lansoprazole still needs to be validated further to draw a reliable conclusion after considering the limits of the current analysis.

Adenocarcinoma accounts for over 95% of gastric malignancies, and gastric cancer generally refers to gastric adenocarcinoma [37]. We performed separate analyses for PTs subordinate to the HLT "GNM". There was no doubt that ADR cases associated with gastric adenocarcinoma showed a statistically significant signal under the HLT "GNM", consistent with the findings in the literature that the risk of gastric adenocarcinoma was similar to that of gastric cancer of any type [38]. In the single signal analysis, each kind of PPIs showed high ROR values, suggesting that further research on these ADR-related disease signals may be worthwhile. In contrast, the positive signals of gastroesophageal cancer and gastric cancer recurrent were not analyzed due to the small data volume, which easily led to a false-positive result.

Two notable findings were observed for the detected signals for the HLT "BDNM" and its stratification analyses. One was that a sex-based difference was observed in this association between PPIs and bile duct cancer. There was only one study involving bile duct cancer risk, in which no sex-specific differences were observed. Previous work proved that increased levels of estrogen may play a role in the etiology of biliary tract cancers by stimulating the proliferation of cholangiocytes and decreasing biliary motility [39,40], while the potential impact of longer-term PPIs use can also affect biliary motility and reduce acid output, thereby increasing the risk of infection and inflammation in the biliary tract [41]. Therefore, sex hormones and PPIs may both be predisposing factors with a synergistic effect on cholangiocarcinogenesis.

The other was the deficiencies in some MedDRA term definitions. Bile duct cancer and cholangiocarcinoma should not be set as two PTs in MedDRA. We combined bile duct cancer and cholangiocarcinoma as a group for analysis, and there is no doubt that the signal was statistically significant between this new PT

combination and PPIs use (ROR: 2.00, 95% CI: 1.59-2.51), and this association was stronger among female patients (ROR: 2.63, 95% CI: 1.89-3.66). Therefore, the results between the new PT combination and PPIs use were consistent with prior results that there may be an increased risk for BDNM with PPIs use in female, which were worth exploring further.

Although the use of PPIs was reported to be associated with the subsequent risk of esophageal cancer, colorectal cancer, pancreatic cancer and liver cancer [20,27,42,43], the associations were not confirmed in our study. This finding does not preclude the possible associations because results obtained from the FAERS should be interpreted with caution for the limitations of the FAERS database.

First, the FAERS database is a passive surveillance system, and drug-ADR associations may be substantially mislabeled, overreported or underreported [44]. In addition, the large proportions of missing variable values call into question the completeness and accuracy of the data, namely, the overall quality. For example, a large number of FAERS reports of GNM were missing information on patient age and sex, resulting in the blurring of group differences. Second, due to the absence of total exposed numbers and the presence of confounders, the analysis results from the FAERS database had inevitable and unquantifiable bias and were difficult to interpret [44].

Despite these limitations, the ROR values are reliable and credible, and signal strength can partly reflect the extent of the correlation between drugs and specific ADRs from a statistical standpoint. We believe that several potential associations generated by our extensive analyses from the large database are valuable and can provide several important clues for future in-depth clinical research.

Conclusions

This is the first study to assess the association between PPIs use and DTCs risk using the unique resources of the FAERS. Through analysis of passive pharmacovigilance data, we found a statistically significant association of PPIs with GNM and BDNM risks. The risk was higher in the female group than in the male group for BDNM. Esomeprazole and rabeprazole showed the greatest risk for GNM and BDNM, respectively. The findings of the present study may provide important clues for further clinical research.

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Figure legends

Figure 1 Flowchart for studying the association between PPIs and digestive tract cancers risk

Figure 2 Forest plot of signal detections for PPIs and digestive tract cancers with subgroup analysis stratified by gender and age

a Signal strength for PPIs and H2RA associated with digestive tract cancers

b Subset analysis stratified by gender

c Subset analysis stratified by age

PPIs, Proton Pump Inhibitors; H2RA, H2-receptor antagonist; GNM, gastric neoplasms malignant; PNM, pancreatic neoplasms malignant; BDNM, bile duct neoplasms malignant; SINM, small intestinal neoplasms malignant; ONM, oesophageal neoplasms malignant; CNM, colorectal neoplasms malignant; ACNM, anal

canal neoplasms malignant; GBNM, gallbladder neoplasms malignant; HNM, hepatic neoplasms malignant; ROR, reporting odds ratio; CI, confidence interval

Figure 3 Heatmap of signal strength for different PPIs associated with different digestive tract cancers (ROR lower bound of 95% CI)

PPIs, Proton Pump Inhibitors; GNM, gastric neoplasms malignant; PNM, pancreatic neoplasms malignant; BDNM, bile duct neoplasms malignant; SINM, small intestinal neoplasms malignant; ONM, oesophageal neoplasms malignant; CNM, colorectal neoplasms malignant; ACNM, anal canal neoplasms malignant; GBNM, gallbladder neoplasms malignant; HNM, hepatic neoplasms malignant; ROR, reporting odds ratio; CI, confidence interval

Figure 4 Signal strength for different PPIs associated with GNM at the PTs level

a Forest plot of signal detections for different PPIs and GNM

b Forest plot of signal detections for PPIs as a whole and PTs subordinated to the HLT "GNM" after removing parts of PTs for the low number of reported cases

c Heatmap of signal strength for different PPIs associated with PTs subordinated to the HLT "GNM" (ROR lower bound of 95% CI)

PPIs, Proton Pump Inhibitors; GNM, gastric neoplasms malignant; PTs, Preferred Terms; HLT, High Level Term; ROR, reporting odds ratio; CI, confidence interval

Figure 5 Signal strength of different PPIs associated with BDNM at the PTs level

a Forest plot of signal detections for different PPIs and BDNM

b Forest plot of signal detections for PPIs as a whole and PTs subordinated to the HLT "BDNM" after removing parts of PTs for the low number of reported cases

c Heatmap of signal strength for different PPIs associated with PTs subordinated to the HLT "BDNM" (ROR lower bound of 95% CI)

PPIs, Proton Pump Inhibitors; BDNM, bile duct neoplasms malignant; PTs, Preferred Terms; HLT, High Level Term; ROR, reporting odds ratio; CI, confidence interval

Table 1 The characteristics of digestive tract cancer adverse events of proton pump inhibitors

Characteristics	ONM	GNM
	Case(%)	Case(%)
Case	327 (12.8%)	687 (26.9%)
Patient gender	**Patient gender**	**Patient gender**
Male	210(64.2%)	212(30.9 %)
Female	97(29.7%)	180(26.2%)
Unknown or missing	20(6.1%)	295(42.9%)
Patient age group (years)	**Patient age group (years)**	**Patient age group (years)**
<18	0(0.0%)	0(0.0 %)
18–65	118(36.1%)	125(18.2%)
>65	86(26.3%)	148(21.5%)
Unknown or missing	123(37.6%)	414(60.3%)
Serious outcome of adverse events	**Serious outcome of adverse events**	**Serious outcome of adverse events**
Hospitalization	74(22.6%)	155(22.6%)
Disability	12(3.7%)	11(1.6 %)
Life-threatening	38(11.6%)	27(3.9 %)
Death	96(29.4%)	177(25.8%)

Characteristics	ONM	GNM
PPIs	**PPIs**	**PPIs**
omeprazole	105 (32.1%)	368 (53.6%)
lansoprazole	64(19.6%)	240(34.9%)
pantoprazole	46(14.1%)	228 (33.2%)
rabeprazole	11(3.4%)	36 (5.2 %)
esomeprazole	162(49.5%)	346(50.4 %)
dexlansoprazole	9(2.8 %)	59(8.6 %)

PPIs, Proton Pump Inhibitors; ONM, oesophageal neoplasms malignant; GNM, gastric neoplasms malignant; SINM, small intestinal neoplasms malignant; CNM, colorectal neoplasms malignant; ACNM, anal canal neoplasms malignant; PNM, pancreatic neoplasms malignant; HNM, hepatic neoplasms malignant; GBNM, gallbladder neoplasms malignant; BDNM, bile duct neoplasms malignant.