

Proton pump inhibitors and risk of periampullary cancers—A nested case–control study

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Considerable attention has been focused on long-term use of proton pump inhibitor (PPI) medications in relation to increased risk of cancer *via* stimulation of DNA-damaged cells. The aim of this study is to examine the dose-dependent effect of PPI on periampullary cancers in a national population-based cohort. A nested case–control analysis was constructed based on Taiwan’s National Health Insurance Research Database and the Taiwan Cancer Registry between the years 2000 and 2010. Cases involving patients diagnosed with periampullary cancers were selected and controls were matched to cases according to age, sex and observational period. A “PPI user” was defined as any patient receiving more than 28 cumulative defined daily doses as measured by prescription drug claims. Conditional logistic regression analysis was conducted to calculate odds ratios (ORs) and 95% confidence intervals (CIs) according to the level of PPI exposure. A total of 7,681 cases and 76,762 matched controls were included with a mean follow-up period of 6.6 years (SD: 2.0). The odds of PPI exposure in patients with periampullary cancers were higher than that of control patients with an adjusted OR of 1.35 (95% CIs: 1.16–1.57). Our results also showed that PPI exposure was slightly linked to periampullary cancers in dose-dependent manner. A similar association was observed in patients who solely took PPI but no eradication therapy for *Helicobacter pylori* infection. Long-term PPI use was associated with an increased risk of periampullary cancers in the current population-based study. Physicians must weigh potential risks of long-term maintenance against therapeutic benefit.

Key words: proton pump inhibitors, periampullary cancers, nested case–control study, *H. pylori* eradication therapy

Additional Supporting Information may be found in the online version of this article.

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The use of proton pump inhibitor (PPI) medications has rapidly increased in recent years because of its efficacy in treating gastroesophageal reflux disease (GERD) and peptic ulcer disease (PUD).¹ Because PPIs have minimal side effects and few significant drug interactions, they are generally considered safe for long-term treatment.² Since their introduction in the late 1980s, millions of individuals worldwide have been using these medications on a continuous or long-term basis. Recently, studies have explored the appropriateness and judiciousness in the use of PPI in hospital and outpatient practices.^{3,4}

Significant current concerns have focused on the long-term effect of PPIs and whether these medications can change gastric physiology,⁵ potentially leading to cell transformation, gastric adenocarcinoma, bacterial overgrowth, enteric infections or malabsorption (*e.g.*, fat, minerals and vitamins). Many retrospective observational studies found several adverse outcomes linked to PPI therapy, including hip fracture,⁶ pneumonia,⁷ acute interstitial nephritis⁸ and hypomagnesemia.⁹ Thus, the safety of the long-term use of PPI has recently been questioned.

What's new?

Proton pump inhibitor (PPI) medications are a common treatment for gastroesophageal reflux disease and peptic ulcer disease. However, some evidence indicates that long-term use of PPIs might increase cancer risk. This large Taiwanese study found that PPI exposure was indeed slightly linked to an increased risk of periampullary cancers, in a dose-dependent manner. (This was not seen in patients undergoing *H. pylori* eradication therapy, however.) These results indicate that physicians must weigh the potential risks of long-term maintenance use of PPIs against their therapeutic benefit.

Physiologically, long-term PPI use can induce acid–base imbalance in the gastrointestinal tract. Normal gastric acid has pH below 4 and has a powerful bactericidal effect. The strong acidity has the ability to kill exogenous, acid-sensitive bacteria in the stomach within a 15-min time span.¹⁰ PPIs reduce the amount of gastric acid secretion in the stomach, thereby increasing the survival of various microbes and allowing at least 50% of ingested bacterial to survive gastric trap.¹⁰ Optimal physiological processes in the gastrointestinal tract require coordination and fine balance between intracellular and extracellular pH. All cells must maintain cytoplasmic pH within a narrow range to survive.¹¹ This is particularly true in the upper gastrointestinal tract, where the pH range varies greatly. Theoretically, prolonged pH imbalance from long-term PPI use can decrease enzymatic activities in upper gastrointestinal tract and ultimately increase the possibility of DNA damage and harmful cell mutation.^{12,13}

Although postulated mechanisms of cancer related to PPI remain unclear, one theory suggests that PPIs allow the proliferation of cells with deadly mutations, in the upper gastrointestinal tract, especially in the ampulla of Vater and increase risk to developing periampullary adenocarcinomas.^{14,15} Given the widespread use of PPIs, the aim of this study is to examine the effect of PPIs on periampullary adenocarcinomas in a dose-dependent manner, based on a national population-based cohort.

Material and Methods**Data source**

The National Health Insurance Research Database (NHIRD) of Taiwan is a nationwide claims database, maintained by the National Health Insurance Administration (NHIA). It covers almost every medical reimbursement claim received by beneficiaries under the regulation of National Health Insurance (NHI) program. Since 1995, all citizens of Taiwan are required by law to enroll in the NHI. In 2012, the NHI coverage rate was 99%. The NHIRD contains claims data on beneficiary demographics, disease diagnoses, treatment procedures, prescription medications, date-of-service, reimbursement amounts and beneficiary- and provider-encrypted identifiers. To verify the accuracy of diagnoses and the rationale for treatments, the NHIA routinely audits a proportion of the NHI claims.

The Taiwan Cancer Registry (TCR) is a population-based cancer registry that standardizes medical definitions and terminology, coding and procedures of the registry's reporting system and tracking of patients with a cancer diagnosis.

Following the enactment of the Cancer Control Act in 2003, all hospitals are mandated to submit cancer data to TCR. Additionally, TCR data are subject to periodic quality-control audits and is processed according to the standard guidelines of the International Agency for Research on Cancer, resulting in 2-year time lag between collection and publication of data.

Cohort selection

Of the 23 million beneficiaries enrolled in NHI from 2000 to 2010, the eligible cohort in this study included patients who were 40 years or older and met the following criteria: (i) continuously enrolled in NHI since 2000; (ii) absence of any periampullary cancer diagnosis before 2002 and (iii) had no PPI prescription claims between 2000 and 2001 to create a new-user cohort without PPI exposure before entering the cohort.

A new-user design can eliminate two major biases by restricting the analysis to persons under observation at the start of the current course of treatment. The first bias was the healthy user effect that patients who decided to use PPI have a more favorable risk factors profile than do nonusers that is common in many observational studies. The second bias was due to the covariates for drug users at study entry often are plausibly affected by the drug itself. Investigators often do not adjust for these factors on the causal pathway, which may introduce confounding.^{16,17}

Patients diagnosed with periampullary cancers within a year of follow-up were excluded. This cohort was screened for any occurrence of periampullary cancers and if so, death up to December 2012. All deaths were confirmed by using the National Death Registry (NDR). The completeness and accuracy of death records of Taiwan is high as it is mandatory to register all death with the NDR.

Case identification and control selection

According to the International Classification of Disease of Oncology (ICD-O), periampullary cancer is classified as extrahepatic cholangiocarcinoma (ICD-O-3: C24.0), ampullary (ICD-O-3: C24.1), duodenum (ICD-O-3: C17.0), jejunum (ICD-O-3: C17.1) or pancreatic (ICD-O-3: C25.0). By definition, periampullary cancers arise within 2 cm of the major papilla in the duodenum and encompass four different types of cancers according to location: ampullary (ampulla of Vater), biliary (intrapancreatic distal bile duct), pancreatic (head–uncinate process) and duodenal (mainly from the second portion). Although these tumors have different origins, the complex

regional anatomy and their proximity to other organs generally dictate the operative approach.¹⁸ Therefore, this study considered a broader definition of periampullary cancers.

Up to ten control subjects with no previous or existing diagnosis of cancer were selected from the study cohort. We used the incidence density sampling approach to match controls with each case according to age (± 1 year), sex and the follow-up period of PPI exposure. This method not only reduced potential bias in the observational studies but decreased the time-window bias by differentiating exposure opportunity time windows between subjects.¹⁹ The date of cancer diagnosis was treated as the index date. All control patients were assigned a pseudo-index date (referred as the index date here after) which corresponded to the index date of their matched cases.

PPI exposure

The duration of use for PPI was determined based on prescription claims in the NHIRD. For each prescription claim, we recorded the start and withdrawal dates, drug name and dosage. The type of PPI was selected based on the Anatomical Therapeutic Chemical (ATC) system of medications of A02BC from NHIRD. The PPIs include: Rabeprazole, Pantoprazole, Lansoprazole, Esomeprazole and Omeprazole—all covered by NHI in Taiwan.

A PPI user was defined as a patient taking PPI for ≥ 28 days during follow-up periods. We considered used the patients had no PPI exposure and those exposed PPI < 28 cumulative defined daily dose (cDDD) as the nonuser group. The major idea of this study was long-term, cumulative and high-dose exposure of PPI might change the acid–base imbalance in gastrointestinal tract resulting in cell damage. Of the patients who use PPI due to *Helicobacter pylori* eradication therapy or other indications usually being prescribed in a short-term, temporal and low-dose exposure were treated as non-PPI users in this study.

The dose–response effect was calculated using the cDDD, which is the assumed maintenance dose per day for adults. Three cDDD categories were used: 28–90 cDDD, 91–180 cDDD and > 180 cDDD.

Covariates

Covariates considered in our analysis include known risk factors associated with the study cancers, such as choledochal cysts, cholangitis, cholelithiasis, cirrhosis, alcoholic liver disease, nonalcoholic liver disease (NAFLD), hepatitis B virus (HBV), hepatitis C virus (HCV), diabetes, chronic pancreatitis, inflammatory bowel disease, PUD, GERD and cardiovascular diseases.^{20,21} Each disease condition was defined by having two or more diagnostic claims within 2 years before index date. Other medications like *H. pylori* eradication therapy, histamine-2 receptor antagonists (H2RAs), aspirin, non-steroidal anti-inflammatory drug (NSAID), statin, metformin, insulin and other antidiabetic drugs were included in our analysis in patients with ≥ 28 cDDD each year. Detailed

information related to these variables and ICD-9 diagnostic codes is provided in Supporting Information Table 1.

Subgroup and sensitivity analysis

Special attention and a subgroup analysis focused on *H. pylori* eradication therapy. Standard therapy for *H. pylori* eradication involves PPI in conjunction with antibiotic combination.²² Patients with *H. pylori* eradication therapy are more likely to have a peptic ulcer disease. Furthermore, *H. pylori* is an important risk factor to the development of gastric malignancy and dyspeptic symptoms. Thus, the use of PPI to eradicate *H. pylori* infection is necessary to significantly reduce the acid in the stomach.

To increase the robustness of our analysis, we performed two sensitivity analyses to strengthen the validity of our findings. First, we employed a 3-year washout period to exclude any patients who had been exposed to PPI before entering the cohort. A washout period avoids potential carryover effect of drugs during initial observational period. Second, we used lung cancer as a negative cancer case to ensure that any association observed in the initial analysis was not random. This is also a tool to detect confounding variables in observational studies.²³ Lung cancer was selected as its demographic characteristic is very similar to periampullary cancers.

Statistical analysis

For all variables of interest, risk estimates were computed *via* (i) univariate analyses based on matching factors and (ii) multivariate analyses with additional adjustments for potential confounders. Conditional logistic regression analysis was used to estimate the odds ratios (ORs) and 95% confidence intervals (CIs) in the risk of developing periampullary cancers with long-term PPI use. In a nested case–control study, controls are selected using incidence density sampling. Because of the low incidence of periampullary cancers, the calculated estimated incidence ratio was roughly equal to the OR.²⁴ All analyses were performed using SAS/STAT 9.2 software (SAS Institute, Cary, NC). *p* Values < 0.05 were considered significant.

Ethics statement

This study was approved by the Taipei Medical University Joint Institutional Review Board (approval no. 201503054). Confidentiality was ensured by abiding to data regulations of the Health and Welfare Data Science Center (HWDC), Ministry of Health and Welfare, Executive Yuan, Taiwan. The HWDC encrypts individual identifiers to protect privacy before releasing information to investigators for research purposes. The informed consents of the participants were exempted under the full review process of the Joint Institutional Review Board of Taipei Medical University.

Results

Sample size

More than 8,000,000 NHI beneficiaries were eligible for the study and the final cohort for our analysis comprised of

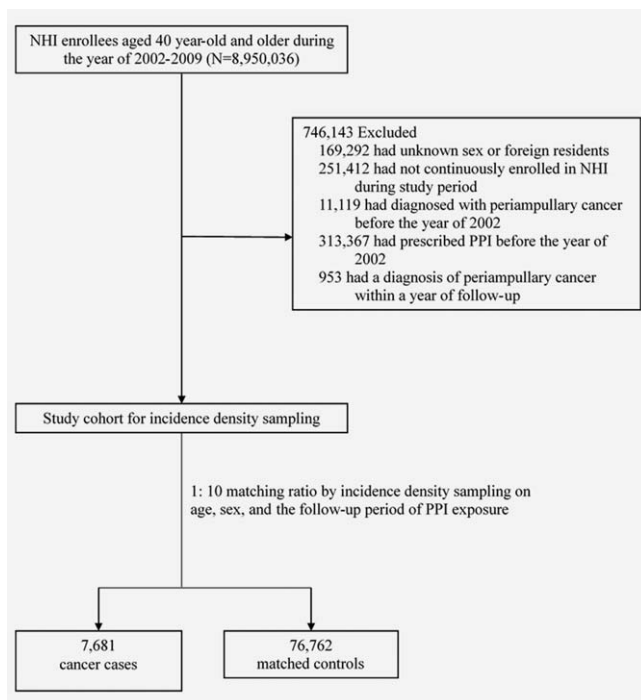


Figure 1. Study flow diagram.

7,681 cases with periampullary cancers and 76,762 matched controls (Fig. 1).

Basic characteristics

Table 1 presents the basic characteristics of cases and their matched controls. Among cases with periampullary cancers, 17.8% were diagnosed with extrahepatic cholangiocarcinoma, 21.7% with ampullary cancer, 10.1% with duodenal cancer and 50.4% with pancreatic head cancer. The mean age of the cohort was 69.5 years (SD: 11.6); 58.1% of the patients were male. Periampullary cancer patients in our study were more likely to have a disease related to bile and liver, such as cholangitis, cholelithiasis, cholecystitis, alcoholic liver disease and HBV but not NAFLD and HCV. In addition, case patients were more likely than controls to have diabetes, chronic pancreatitis, inflammatory bowel disease and PUD. The results also showed that case patients were more likely to receive *H. pylori* eradication therapy, H2RAs and antidiabetic drugs than controls.

PPI exposure and the risk of periampullary cancer

Table 2 indicates the odds of PPI exposure in periampullary cancers. Among this study cohort, 537 of 7,681 (7.0%) cancer patients and 4,449 of 76,762 (5.8%) controls have exposed to PPI ≥ 28 cDDD. The odds of PPI use with periampullary cancer cases were higher than matched control patients, with an adjusted OR of 1.35 (95% CIs: 1.16–1.57, $p < 0.001$). In considering the use of PPI according to cDDD subgroups, the highest dose–response effect was found in patients with PPI exposure of 91–180 cDDD but not in patients exposed to PPI > 180 cDDD.

Figure 2 displays the dose–response curves for risk of periampullary cancers as a function of PPI use measured by cDDD during follow-up period. The highest risk of periampullary cancer occurs in patients with PPI exposure over cDDD 180 days; the risk slightly decreased as cDDD increases past 180 days. The wider 95% CIs were due to the smaller sample size as cDDD increased.

Subgroup analysis

Another analysis was performed by stratifying patients into two groups: (i) patients with *H. pylori* eradication therapy and (ii) patients without *H. pylori* eradication therapy. We found that patients with PPI use but not *H. pylori* eradication therapy had significantly higher odds of having periampullary cancers than their matched control group, with an adjusted OR of 1.33 (95% CIs: 1.11–1.60, $p = 0.003$) (see Table 3).

Sensitivity analysis

Sensitivity analysis was performed by selecting another matched case–control cohort with no PPI exposure for 3 years (i.e., a longer washout period) before the date of entry. Results showed a similar result to our primary analysis. In addition, we also used lung cancer as a negative cancer case and conducted another nested case–control study to confirm that use of PPI was not associated with increased risk of lung cancer when compared to the matched control patients (see Table 4).

Discussion

This population-based nested case–control study found an association between PPI use and increased risk of periampullary cancers. Subgroup analysis showed similar trends when focusing on patients without *H. pylori* eradication therapy. Two sensitivity analyses were performed using: (i) longer washout period to reduce a carryover effect of drugs and (ii) lung cancer as a negative cancer case to rule out unobserved confounding bias additionally confirmed the initial findings. Periampullary cancers are relatively rare compared with the other gastrointestinal cancers; however, over 60% of the patients died within a year, once diagnosed in this cohort. Thus, identifying the potential risk of the cancers is significantly important.

Long-term PPI use and carcinoma has remained questionable for years. The first published report involved endochromaffin cell-derived (ECL cell-derived) neuroendocrine carcinoma. The authors postulated whether carcinoma was secondary to hypergastrinemia due to PPI use over a 15-year course.²⁵ As found in this study, long-term use of PPI was associated with the risk of periampullary cancers. There are two possible mechanisms that contribute or explain our finding. First, pronounced acid suppression has been shown to cause elevated serum gastrin levels in individuals. Prolonged and increased gastrin can stimulate an increase in intermediates known to have trophic effects on normal gastrointestinal mucosa and can stimulate carcinogenesis. Numerous *in vitro* and *in vivo* studies have explored trophic effects of gastrin on numerous cancers including pancreatic,²⁶ liver,²⁷ esophageal²⁸

Table 1. Basic characteristics of periampullary cancer cases and matched controls

	Cancer cases	Matched controls	Unadjusted OR (95% CIs)
	N (%)	N (%)	
No.	7,681	76,762	
Male	4,463(58.1)	44,607(58.1)	–
Age, mean (SD)	69.47(11.6)	69.53(11.6)	–
Cancer site			
Extrahepatic cholangiocarcinoma	1,370(17.8)		
Ampullary cancer	1,665(21.7)		
Duodenal cancer	775(10.1)		
Pancreatic head cancer	3,871(50.4)		
Previous or coexisting medical condition			
Choledochal cysts	3(<1)	31(<1)	0.97(0.30–3.17)
Cholangitis	200(2.6)	126(<1)	16.8(13.4–21.1)*
Cholelithiasis	553(7.2)	1,284(1.7)	4.71(4.25–5.23)*
Cholecystitis	58(<1)	57(<1)	10.3(7.13–14.9)*
Hemochromatosis	4(<1)	39(<1)	1.03(0.37–2.87)
Cirrhosis	108(1.4)	1,033(1.3)	1.05(0.86–1.28)
Alcoholic liver disease	49(<1)	272(<1)	1.82(1.34–2.47)*
NAFLD	7(<1)	269(<1)	1.38(0.98–1.94)
HBV	127(1.7)	812(1.1)	1.58(1.31–1.91)*
HCV	98(1.3)	860(1.1)	1.14(0.93–1.41)
Diabetes	1,923(25.0)	13,900(18.1)	1.53(1.45–1.62)*
Chronic pancreatitis	84(1.1)	61(<1)	14.6(10.4–20.5)*
Inflammatory bowel disease	52(<1)	286(<1)	1.83(1.36–2.46)*
PUD	2,968(38.6)	26,360(34.3)	1.43(1.35–1.53)*
GERD	213(2.8)	1,855(2.4)	1.16(1.00–1.35)
Cardiovascular disease	1,663(21.7)	16,110(21.0)	1.04(0.98–1.11)
Medication			
<i>H. pylori</i> eradication therapy	1,826(23.8)	16,656(21.7)	1.27(1.13–1.44)*
H2RAs	322(4.2)	2,568(3.3)	1.00(0.94–1.06)
Aspirin	1,496(19.5)	14,987(19.5)	1.09(1.03–1.15)
NSAIDs	1,733(22.6)	16,282(21.2)	1.03(0.94–1.13)
Statins	532(6.9)	5,194(6.8)	1.44(1.33–1.55)*
Metformin	906(11.8)	6,579(8.6)	1.61(1.37–1.89)*
Insulins	178(2.3)	1,118(1.5)	1.38(1.29–1.47)
Other antidiabetic drug	1,197(15.6)	9,116(11.9)	1.46(1.36–1.57)*

* $p < 0.001$.

Abbreviations: H2RAs: histamine-2 receptor antagonists; HBV: hepatitis B virus; HCV: hepatitis C virus; GERD: gastroesophageal reflux disease; NAFLD: nonalcoholic fatty liver disease; NSAID: nonsteroidal anti-inflammatory drug; OR: odds ratio; PUD: peptic ulcer disease.

and colon.²⁹ It is therefore conceivable that the trophic effects of gastrin allow sporadic mutations to ultimately proliferate and progress to neoplastic precursors.

Second, it is hypothesized that chronic use of PPI might induce a metaplasia-dysplasia-carcinoma sequence. If a PPI fails to suppress gastric acid, then unconjugated bile salts may diffuse into the epithelial cells and cause mucosal meta-

plasia. Pharmacologically, hypochlorhydria induced by daily PPI use produces periods during the day in which pH of the gastric juice is at or near a neutral pH levels.³⁰ A study by Shindo *et al.* showed that hypochlorhydria can induce major changes in the gastric flora and affect the pH of small bowel fluid to allow bacterial overgrowth.³⁰ Moreover, the Shindo *et al.*'s study revealed that PPI treatment in patients with

Table 2. The odds of PPI exposure of periampullary cancer cases and matched controls

	Cancer cases	Matched controls	Unadjusted OR (95% CIs)	p Values	Adjusted OR (95% CIs) ¹	p Values
	N (%)	N (%)				
Sample size	7,681(100)	76,762(100)				
PPI exposure						
Non-PPI user	7,144(93.0)	72,313(94.2)	1.00(Ref.)		1.00(Ref.)	
PPI user	537(7.0)	4,449(5.8)	1.56(1.35–1.81)	<0.001	1.35(1.16–1.57)	<0.001
cDDD						
0–27	7,144(93.0)	72,313(94.2)	1.00(Ref.)	<0.001 ²	1.00(Ref.)	0.001 ²
28–90	96(1.2)	936(1.2)	1.34(1.04–1.74)		1.33(1.01–1.73)	
91–180	221(2.9)	1,784(2.3)	1.61(1.34–1.94)		1.48(1.22–1.79)	
>180	220(2.9)	1,729(2.3)	1.60(1.34–1.91)		1.26(1.04–1.52)	

¹Adjusted for choledochal cysts, cholangitis, cholelithiasis, cholecystitis, cirrhosis, alcoholic liver disease, NAFLD, HBV, HCV, diabetes, chronic pancreatitis, inflammatory bowel disease, PUD, GERD, cardiovascular disease, H2RAs, aspirin, NSAIDs, statins, metformin, insulins, other antidiabetic drugs and *H. pylori* eradication therapy.

²p for trend.

Abbreviations: cDDD: cumulative defined daily dose; H2RAs: histamine-2 receptor antagonists; HBV: hepatitis B virus; HCV: hepatitis C virus; GERD: gastroesophageal reflux disease; NAFLD: nonalcoholic fatty liver disease; NSAID: nonsteroidal anti-inflammatory drug; OR: odds ratio; PUD: peptic ulcer disease.

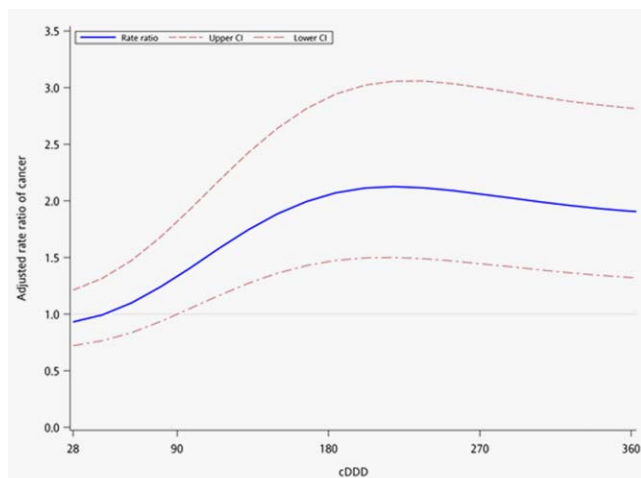


Figure 2. Dose–response curve for the rate ratio (solid line) and 95% CIs (dashed lines) of periampullary cancers as a function of PPI dose (measured in cDDD) estimated by cubic splines model fit by conditional logistic regression. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

gastric ulcer resulted in bacterial overgrowth of gastrointestinal tract. These bacteria alter the metabolism of bile acids through increased deconjugation and fat malabsorption, as evidenced by glycine-1-¹⁴C-labeled glycocholate and breathe analysis studies.^{31,32} A substantial body of evidence suggests that bile acids play a role in the development of intestinal tumors. Evidence reviewed by Bernstein *et al.* suggests that bile acids act as carcinogens in human gastrointestinal cancers.¹⁵ Most benign and malignant tumors of the small intestine and extrahepatic bile ducts arise in the region of the Papilla of Vater. Long-term exposure to bile acids has been known to activate prosurvival stress-response pathways and modulate numerous

genes/proteins associated with chromosome maintenance and mitosis.³³ Therefore, a likely mechanism by which hydrophobic bile acids can induce periampullary cancers involves bile acid induction of reactive oxygen species (ROS), reactive nitrogen species (RNS) and DNA damage in cells of the gastrointestinal tract. These stresses, if too much, can overwhelm cellular defenses resulting in cell death.³⁴

Our results show that patients, who received a large amount of PPI for reasons unrelated to *H. pylori* eradication therapy, were more likely to have periampullary cancers. Previous studies have demonstrated that PPI treatment has a prominent acid-suppressive effect in *H. pylori*-positive patients compared to *H. pylori*-negative patients.³⁵ Furthermore, studies have also reported better symptomatic control and enhanced healing of mucosal lesions with PPI in patients with *H. pylori* and GERD versus *H. pylori*-negative patients. One randomized double-blind trial showed that a total of 44% of *H. pylori*-negative subjects with PPI therapy group developed dyspepsia in comparison with 9% in the placebo group ($p < 0.01$).³⁶ This suggests a correlation between symptoms and acid-rebound hypersecretion. Patients, who develop *H. pylori* infection and undergo PPI treatment, have been shown to have gastritis affecting the antrum and fundus regions of the stomach.³⁷ Many have proposed that the enhanced acid-secretory potency of PPI in *H. pylori* patients may be due to this gastritis.³⁸ Although an earlier study⁵ suggested that inflammation of mucosa in fundal region is associated with gastric cancer, it is generally agreed that patients with *H. pylori* infection should take PPI for *H. pylori* eradication.

By using a dose–response curve to track the relative risk of periampullary cancers as a function of PPI use (measured in cDDD), we found that the risk of periampullary cancers

Table 3. Subgroup analysis of the odds of PPI exposure of periampullary cancer cases and matched controls by *H. Pylori* eradication therapy

Group	PPI exposure	Cancer cases	Matched controls	Adjusted OR (95% CIs) ¹	<i>p</i> Values
		<i>N</i> (%)	<i>N</i> (%)		
With <i>H. Pylori</i> eradication therapy					
	Non-PPI user	1,086(84.3)	8,601(86.3)	1.00(Ref.)	
	PPI user	203(15.7)	1,363(13.7)	1.14(0.80–1.64)	0.469
	cDDD				
	0–27	1,086(84.3)	8,601(86.3)	1.00(Ref.)	0.592 ²
	28–90	38(2.9)	363(3.6)	1.10(0.67–1.81)	
	91–180	78(6.1)	480(4.8)	1.31(0.85–2.02)	
	>180	87(6.7)	520(5.2)	1.02(0.65–1.60)	
Without <i>H. Pylori</i> eradication therapy					
	Non-PPI user	6,058(94.8)	63,712(95.4)	1.00(Ref.)	
	PPI user	334(5.2)	3,086(4.6)	1.33(1.11–1.60)	0.003
	cDDD				
	0–27	6,058(94.8)	63,712(95.4)	1.00(Ref.)	0.015 ²
	28–90	58(0.9)	573(0.9)	1.36(0.96–1.93)	
	91–180	143(2.2)	1,304(2.0)	1.44(1.14–1.82)	
	>180	133(2.1)	1,209(1.8)	1.23(0.97–1.55)	

¹Adjusted for choledochal cysts, cholangitis, cholelithiasis, cholecystitis, cirrhosis, alcoholic liver disease, NAFLD, HBV, HCV, diabetes, chronic pancreatitis, inflammatory bowel disease, PUD, GERD, cardiovascular disease, H2RAs, aspirin, NSAIDs, statins, metformin, insulins, other antidiabetic drugs and *H. pylori* eradication therapy.

²*p* for trend.

Abbreviations: cDDD: cumulative defined daily dose; H2RAs: histamine-2 receptor antagonists; HBV: hepatitis B virus; HCV: hepatitis C virus; GERD: gastroesophageal reflux disease; NAFLD: nonalcoholic fatty liver disease; NSAID: nonsteroidal anti-inflammatory drug; OR: odds ratio; PUD: peptic ulcer disease.

Table 4. Sensitivity analysis

PPI exposure	Cancer cases	Matched controls	Adjusted OR (95% CIs) ¹	<i>p</i> Value
	<i>N</i> (%)	<i>N</i> (%)		
Use a 3-year washout period to select cancer cases				
Non-PPI user	6,206(92.2)	62,935(93.5)	1.00(Ref.)	
PPI user	527(7.8)	4,346(6.5)	1.27(1.09–1.48)	0.003
Use the lung cancer as a negative cancer cases				
Non-PPI user	50,126(94.8)	502,499(95.1)	1.00(Ref.)	
PPI user	2,750(5.2)	26,117(4.9)	1.03(0.97–1.09)	0.360

¹Adjusted for choledochal cysts, cholangitis, cholelithiasis, cholecystitis, cirrhosis, alcoholic liver disease, NAFLD, HBV, HCV, diabetes, chronic pancreatitis, inflammatory bowel disease, PUD, GERD, cardiovascular disease, H2RAs, aspirin, NSAIDs, statins, metformin, insulins, other antidiabetic drugs and *H. pylori* eradication therapy.

Abbreviations: cDDD: cumulative defined daily dose; H2RAs: histamine-2 receptor antagonists; HBV: hepatitis B virus; HCV: hepatitis C virus; GERD: gastroesophageal reflux disease; NAFLD: nonalcoholic fatty liver disease; NSAID: nonsteroidal anti-inflammatory drug; OR: odds ratio; PUD: peptic ulcer disease.

peaked at cDDD levels near 180 days and decreased as cDDD levels increased. We believe this decrease in periampullary cancer risk as cDDD levels increase beyond 180 days

is partly attributed to mechanism of PPI tolerance. Studies on H2RAs (another medication commonly used for GERD and PUD) have found that tolerance of the drug decreases

after previous drug treatments, especially intravenous medication.^{39,40} It is possible that patients on long-term PPI use encounter similar tolerance problems with PPI just as patients experience with H2RAs. Further investigations are needed to confirm this unproven mechanism.

The cancer risk of PPI use has been reported in many observational studies. However, consensus remains elusive. For example, a study in UK found that long-term PPI therapy at a regular dose was not associated with colorectal cancer⁴¹; however, another study in Taiwan found that PPI use had a 2.5-fold association risk of colorectal cancer.⁴² Authors of the Taiwan study concluded that patients with occult colorectal cancer had longstanding reflux or upper gastrointestinal symptoms and concomitantly received PPI treatment. The UK researchers found that PPIs/H2RAs use was not associated with pancreatic cancer risk,⁴³ which is consistent with our finding when limited to the cancer site into pancreatic cancer (Supporting Information Table 2). However, we did not restrict our sample to those with pancreatic cancer as it is difficult to clinically distinguish it from periampullary cancers.¹⁸ Besides to further explore the risk of PPI on gastrointestinal tract cancers, we additionally selected the gastric cancer as a case cancer. We found that PPI was associated with the risk of gastric cancers in the body of stomach (Supporting Information Table 3). Long-term PPI use has been reported to be associated with an increase in gastritis and even the development of gastric atrophy in the body portion of the stomach.⁵ Histologic studies in combination with culture confirmed that PPI use is associated with a change in the distribution of gastritis with histological improvement in antrum and worsening of the gastritis in the body portion of the stomach.⁴⁴ These changes have been attributed to alteration in local pH as *H. pylori* are killed at pHs below 4 and above 8, are able to survive but not replicate at pHs between 4 and 6 and only replicate at pHs between 6 and 8.⁴⁵ Kuipers *et al.* also suggested that use of PPI was associated with an increased risk of development of atrophic gastritis, the known primary risk factor for development of gastric adenocarcinoma.⁴⁶

Our study possesses a number of strengths, including a large sample size and homogeneity of the study population. First, the nested case-control design with appropriate matching cases and controls on the observational period is an appropriate design for evaluating drug effect. Second, multi-

ple regression analyses were performed to adjust the potential confounding bias. Third, two sensitivity analyses were used to increase the validity of our main findings.

However, several limitations remain. First, the study was based on the population-based claims that did not have information on risk behaviors, such as smoking and alcoholic consumption. Second, the use of PPI was measured by prescribed claims; thus, we were unable to obtain data on OTC PPI or patient's medication compliance. Third, the healthcare and prescription data we used did not provide the indication for an exposed drug and the severity of comorbidities; therefore we can only adjust the presence of drug use and disease but not for the medication indication and severity. Confounding by indication and disease severity is a bias frequently encountered in observational epidemiologic studies of drug effects.⁴⁷ Because the allocation of treatment in observational studies is not randomized and the indication for treatment may be related to the risk of future health outcomes, the resulting imbalance in the underlying risk profile between case and comparison groups can generate biased results. Besides, in case-control studies, if exposure influences the diagnosis of the disease, detection bias occurs.⁴⁸ For example, PPI users might be more likely to visit their healthcare providers compared to non-PPI users and therefore increased the probability to detect their cancer. Moreover, this study only considered the presence of disease that occurred in the diagnostic claims; however, the time of disease starts to the time of disease is identified or diagnosed is usually lagged. The latency time windows of disease diagnosis might induce confounding of the association with cancer incidence by failure to account for disease duration. Therefore, the results should be interpreted cautiously. Finally, this study was conducted in the Pacific-Asian region, where prevalence of PPI use is relatively low; thus, our results might not be generalized to other populations.

In conclusion, all pharmacological agents (including PPI) carry the risk of potential adverse effects. In this study, we observed an increased risk of periampullary cancers among long-term PPI users. Our findings highlight what may be an underappreciated adverse effect of PPI therapy. Future research is needed to validate and further characterize our findings. In the interim, we suggest physicians weigh potential risks and therapeutic benefits of long-term PPI use.

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