

Proton Pump Inhibitor Use is Associated With Risk of Pancreatic Cancer: A Nested Case–Control Study

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Abstract

Purpose: To investigate the use of proton pump inhibitors (PPIs) and the risk of pancreatic cancer.

Methods: A nested case–control analysis was conducted. Patients with pancreas cancer were matched with controls by propensity score. Univariate and multivariate logistic regression models were used to determine whether PPIs use affected the risk of pancreas cancer. Dose effect was analyzed based on the cumulative defined daily dose (DDD), which was calculated using the total supply of PPIs to individual patients in terms of days and quantity.

Results: A total of 1087 patients with pancreas cancer were matched with 1087 control patients from the database. The overall adjusted odds ratio (OR) of PPI use associated with pancreas cancer was 1.69 (95% confidence interval [CI], 1.44-2.05). Dose analysis by cumulative DDD, based on all types of PPI combined, revealed a lower adjusted OR of 0.92 (95% CI, 0.64-1.33) for those on <30 cumulative DDD compared with those on ≥ 150 cumulative DDD, whose adjusted OR was 2.19 (95% CI, 1.68-2.85). Compared with PPI nonusers, the risks of pancreas cancer were: OR 0.89 (95% CI, 0.62-1.27) for patients using PPI <30 days and 2.22 (95% CI, 1.68-2.94) for ≥ 150 days.

Conclusions: Risk of pancreas cancer was associated with PPI use in patients with peptic ulcer diseases or gastroesophageal reflux disease.

Keywords

National Health Insurance Research database, pancreas cancer, proton pump inhibitors, nested case–control, population-based

Introduction

In the past few decades, proton pump inhibitors (PPIs) have been very effective in maintaining symptomatic and endoscopic remission of acid peptic disorders, such as gastroesophageal reflux and peptic ulcer.^{1,2} A number of recent studies have investigated the pleiotropic effects of PPIs, including immunomodulation, anti-inflammation, and anticancer or carcinogenesis, and the results have raised concerns about the side effects of PPIs.^{3,4}

Pancreatic adenocarcinoma is a deadly cancer with a poor response to chemotherapy and a dismal outcome.⁵ Risk factors related to pancreas cancer include chronic pancreatitis, smoking, diabetes, and obesity.^{6,7} Carcinogenesis in the pancreas remains poorly understood. Thus, there is an urgent need to identify additional risk factors that could enable a better understanding of the roles played by various drugs in the development of pancreas cancer. These data could prove valuable for preventive modalities such as screening and the development of chemoprevention agents.

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The effects of drugs on the risk of developing pancreas cancer, as well as their preventive effects, are an important area of cancer research. Aspirin, metformin, statins, β -blockers, and bisphosphonates are known to biologically inhibit pancreatic neoplasia.⁸ Most studies concerning aspirin and its role in pancreas cancer have shown that it reduces the risk, and high-dose aspirin, rather than low-dose aspirin, appeared to be associated with decreased risk for pancreatic cancer.⁹ Previous reports on the association of PPI use and pancreatic cancer have yielded conflicting findings.^{10,11} Relatively little research has been conducted on PPI use and pancreas cancer, particularly in Asia. Chien et al demonstrated that the use of PPI was associated with periampullary tumor in a population-based study conducted in Taiwan. Though pancreatic head cancer was included in the analysis, the main focus of the study was the periduodenum.¹² Concerning hepatic cytochrome p450 enzyme, people of Asian descent are more likely to be slow metabolizers of PPIs than people in other ethnic groups.¹³ We conducted a nested case-control study using a population-based data set to determine the risk of pancreas cancer in patients taking PPIs.

Materials and Methods

Data Source

Taiwan's universal, single-payer National Health Insurance (NHI) program was established in 1995 and offers comprehensive medical coverage for over 99% of the population (approximately 23.5 million in 2018).¹⁴ The National Health Research Institutes is in charge of the entire insurance claims database, or the NHIRD, which contains registration files and original medical claims data of all beneficiaries. The data are encrypted with unique personal identifications in accordance with strict privacy protocols. The NHIRD has been used extensively in many epidemiologic studies conducted in Taiwan. The diagnostic codes used in NHIRD are based on the *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)*. Patients on the Registry of Catastrophic Illness Database (RCIPD), a subset of the NHIRD, comprised the case group. The RCIPD includes data from insured residents with severe diseases, as defined by the NHI program, such as malignancies, transplant, or autoimmune diseases. The longitudinal health insurance database (LHID2000) is a data set containing the original claims data of 1 000 000 individuals randomly sampled from the "2000 Registry for Beneficiaries" database, which is a part of the NHIRD. The LHID2000 contains the registration data of everyone who was a beneficiary in the NHI program during the period 1996 to 2000. There was no significant difference in gender distribution between patients in the LHID2000 and those in the original NHIRD.

Ethics Statement

The NHIRD encrypts patients' personal information to protect their privacy and provides researchers with anonymous

identification numbers associated with relevant claims information, including sex, date of birth, medical services received, and prescriptions. Therefore, patient consent is not required to access the NHIRD. This study was approved by the institutional review board of China Medical University (CMUH104-REC2-115-CR2), which also waived the requirement for patient consent.

Data Availability Statement

The data set used in this study is managed by Taiwan's Ministry of Health and Welfare (MOHW). Researchers can request access to this data set by submitting an application form to the MOHW. Please contact the MOHW (email: stcarolwu@mohw.gov.tw) for further details (address: No. 488, Sec 6, Zhongxiao E. Rd, Nangang Dist, Taipei City 115, Taiwan, ROC). Phone: +886-2-8590-6848). All relevant data analyzed in this article are presented herein.

Study Populations and Disease Codes

Patients diagnosed with gastroesophageal reflux disease (GERD; *ICD-9* codes 530.81, 530.11) or peptic ulcer diseases (*ICD-9* codes 531-534) formed the base population. We also included patients with newly diagnosed pancreatic cancer (*ICD-9-CM* 157) between January 1, 2006, and December 31, 2011, from the RCIPD. The date of diagnosis of pancreatic cancer was defined as the index date. Patients were excluded if they had other malignancy (*ICD-9-CM* codes 140-208) before the index date, were younger than 20 years, or had missing information on age or sex. Control patients in the nonpancreatic cancer group were randomly selected from the patients with GERD or peptic ulcer disease without cancer. The control patients were randomly assigned an index date within the same index year of the matched pancreatic cancer cases. We also excluded patients who were diagnosed with pancreatic cancer during the 6-month period following first-time use of PPIs. To reduce selection bias, propensity score was applied to select the 2 groups with and without pancreatic cancer in a 1:1 ratio. The propensity score was calculated using logistic regression to estimate the probability of developing pancreatic cancer based on the baseline variables including gender, age, year of pancreatic cancer diagnosis, medications (H₂-receptor antagonist [H₂RA], aspirin, metformin), and comorbidities (gastric polyp, gastritis, cirrhosis, diabetes, chronic pancreatitis, hepatitis B infection, hepatitis C infection, inflammatory bowel disease, biliary tract disease, stroke, coronary arterial disease, chronic obstructive pulmonary disease, and alcohol-related illness). In order to avoid possible bias caused by differences in the observation period, each patient was only retrospectively observed for 5 years. A total of 1087 cases with pancreatic cancer and 1087 controls without pancreatic cancer were included in the final analysis (Figure 1).

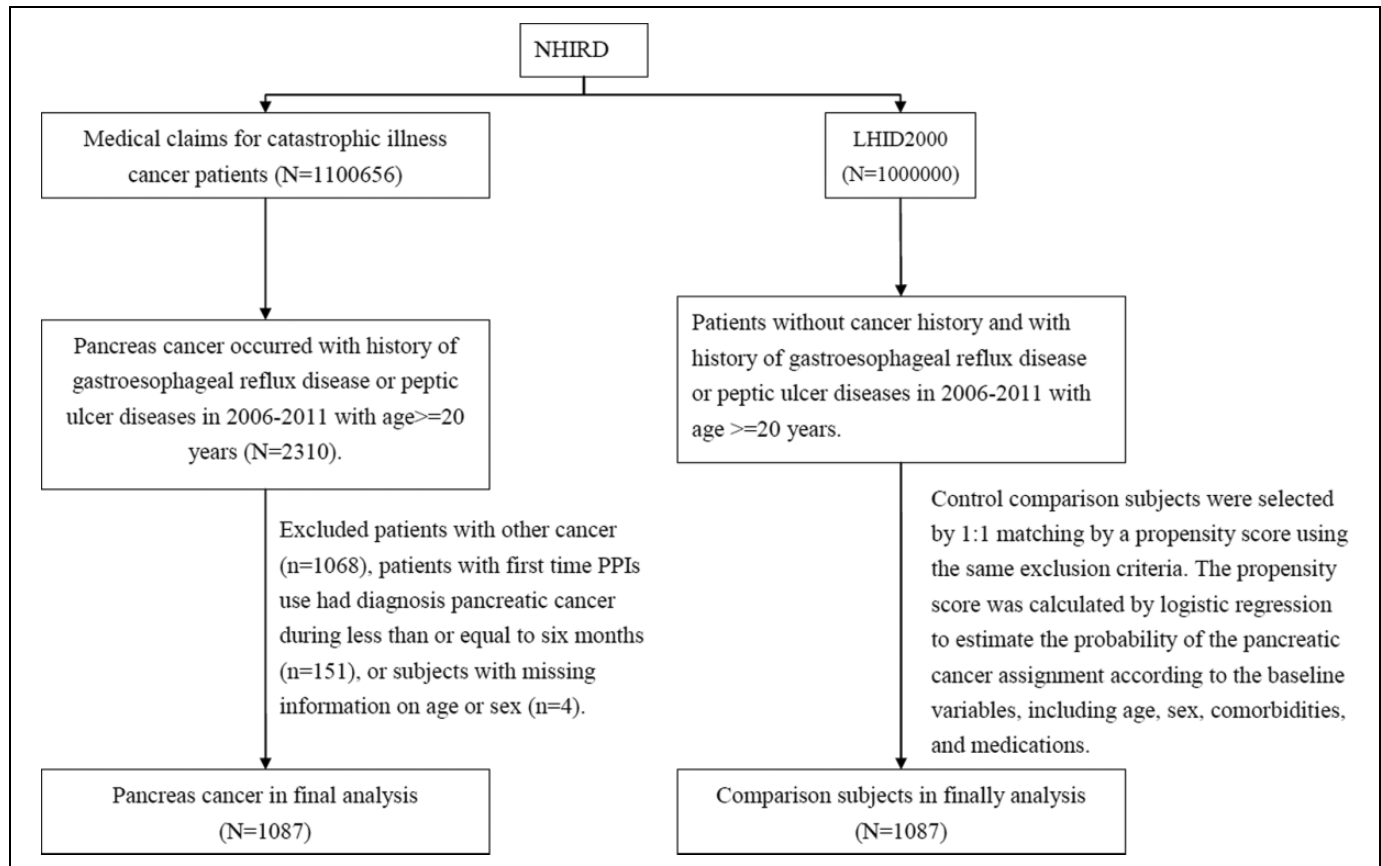


Figure 1. Study flow diagram. CCA indicates cholangiocarcinoma; GERD, gastroesophageal reflux disease; LHD2000, longitudinal health insurance database; NHIRD, National Health Insurance Research Database; PUD, peptic ulcer disease.

Exposure to PPIs

The primary exposures of interest were PPI use since the date of entry into the database until 2 years prior to the index date. The PPI data were defined according to the Anatomical, Therapeutic and Chemical/Defined Daily Dose (ATC/DDD) system of the World Health Organization Collaborating Centre for Drug Statistics and Methodology. Patients with claims for PPIs including omeprazole (ATC A02BC01), pantoprazole (ATC A02BC02), lansoprazole (ATC A02BC03), rabeprazole (ATC A02BC04), and esomeprazole (ATC A02BC05) before the index date were assigned to the exposure to PPI group. The cumulative DDD of each type of PPIs prescribed for the pancreatic cancer group and control group was determined. The DDD is a unit that is used to measure a prescribed amount of drug and was defined according to the abovementioned ATC/DDD system. This is the assumed average maintenance dose per day of a drug consumed by the patient.¹⁵ All types of PPI were compared based on the same standard according to the following formula: total amount of drug/amount of drug in a DDD = number of DDDs. Cumulative DDD was estimated as the sum of the dispensed DDDs of any PPI. The overall cumulative duration of PPI was also calculated by summing the daily supply of each type of PPI before the index date.

Statistical Analysis

All analyses were performed using SAS statistical software (version 9.4; SAS Institute, Inc, Cary, New Carolina). The χ^2 test was used to determine the difference in categorical variables between the pancreatic cancer and control groups, while the 2-sample Student *t* test was used to determine the differences in continuous variables. Univariable and multivariable logistic regression were used to estimate the effect of PPI treatment and comorbidities on the risk of pancreatic cancer, as indicated by the odds ratio (OR) with 95% confidence interval (CI). Results were considered statistically significant when 2-tailed *P* values were less than .05.

Results

Demographics and Characteristics of Study Patients

The demographic data of both study groups are shown in Table 1. There were no statistically significant differences in the distributions of gender, age, H2RA medications, aspirin, and metformin, and comorbidities. The pancreatic cancer groups had a higher rate of chronic pancreatitis. The mean age of the pancreatic cancer group was 67.4 (± 11.5) and compared with 68.3 (± 13.6) years in the controls. Patients with

Table 1. Baseline Characteristics of Patients With and Without Pancreatic Cancer.^a

	Pancreatic Cancer				P Value ^b
	No, N = 1087		Yes, N = 1087		
	n	%	n	%	
Gender					.60
Women	425	39.1	437	40.2	
Men	662	60.9	650	59.8	
Age (year)					
Mean (SD) ^b	68.3	13.6	67.4	11.5	.09
Medications					
PPI	320	29.4	454	41.8	<.001
H2RA	908	83.5	934	85.9	.12
Aspirin	603	55.5	602	55.4	.97
Metformin	331	30.5	342	31.5	.61
Baseline comorbidities					
Gastritis	757	69.6	739	68.0	.40
Acute pancreatitis	126	11.6	155	14.3	.06
Chronic pancreatitis	67	6.16	93	8.56	.03
Diabetes	344	31.7	340	31.3	.85
Hypertension	733	67.4	699	64.3	.12
COPD	482	44.3	477	43.9	.83
CAD	432	39.7	416	38.3	.48
Heart failure	91	8.37	89	8.19	.88
Cirrhosis	558	51.3	550	50.6	.73
Hepatitis B infection	108	9.94	115	10.6	.62
Hepatitis C infection	78	7.18	75	6.90	.80
Inflammatory bowel disease	55	5.06	46	4.23	.36
Biliary tract disease	278	25.6	283	26.0	.81
Stroke	138	12.7	120	11.0	.23
Gastric polyp	12	1.10	17	1.56	.35
Alcohol-related disease	115	10.6	108	9.94	.62

Abbreviations: CAD, coronary arterial disease; COPD, chronic obstructive pulmonary disease; H2RA, H2-receptor antagonist; PPI, proton pump inhibitor; SD, standard deviation.

^aData are presented as the number of patients in each group, with percentages given in parentheses.

^b χ^2 test and t test comparing patients with and without pancreatic cancer.

pancreatic cancer tended to have a higher prevalence of PPI use compared with the control group (P values <.001).

Risk of Pancreatic Cancer Associated With PPIs and Covariates

The ORs of estimated pancreas cancer risk based on PPI use are shown in Table 2. The PPI use was associated with an increased risk of pancreas cancer and the association was statistically significant (adjusted OR [aOR] = 1.69, 95% CI, 1.42-2.03]. A comparison of the 2 groups based on age revealed that patients aged 65 to 74 years had a higher risk for pancreatic cancer (aOR = 1.25, 95% CI, 1.01-1.55). The crude ORs were not significant for other medications, including H2RA, aspirin, and metformin, or for comorbidities, except for chronic pancreatitis.

Table 2. Odds Ratios and 95% Confidence Intervals of Pancreatic Cancer Associated With Proton Pump Inhibitor and Covariates.

Variable	Crude		Adjusted ^a	
	OR	95% CI	OR	95% CI
Gender				
Women	1	Reference	1	Reference
Men	0.96	0.80, 1.13		
Age (years)				
≤64	1.17	0.96, 1.43	1.15	0.93, 1.41
65-74	1.26	1.02, 1.56 ^b	1.25	1.01, 1.55 ^b
≥75	1	Reference	1	Reference
Medications				
PPI	1.72	1.44, 2.05 ^c	1.69	1.42, 2.03 ^c
H2RA	1.20	0.95, 1.52		
Aspirin	1.00	0.84, 1.18		
Metformin	1.05	0.87, 1.26		
Baseline comorbidities				
Gastritis	0.93	0.77, 1.10		
Acute pancreatitis	1.27	0.99, 1.63		
Chronic pancreatitis	1.42	1.03, 1.97 ^b	1.26	0.90, 1.76
Diabetes	0.98	0.82, 1.18		
Hypertension	0.87	0.73, 1.04		
COPD	0.98	0.83, 1.16		
CAD	0.94	0.79, 1.12		
Heart failure	0.98	0.72, 1.32		
Cirrhosis	0.97	0.82, 1.15		
Hepatitis B infection	1.07	0.82, 1.42		
Hepatitis C infection	0.96	0.69, 1.33		
Inflammatory bowel disease	0.83	0.56, 1.24		
Biliary tract disease	1.02	0.85, 1.24		
Stroke	0.85	0.66, 1.11		
Gastric polyp	1.42	0.68, 3.00		
Alcohol-related disease	0.93	0.71, 1.23		

Abbreviations: CAD, coronary arterial disease; COPD, chronic obstructive pulmonary disease; H2RA, H2-receptor antagonist; PPI, proton pump inhibitor. ^aAdjusted for age group and chronic pancreatitis.

^b $P < .05$.

^c $P < .001$.

Dosage of PPIs and Risk of Pancreatic Cancer

Dose analysis by cumulative DDD was performed. Table 3 shows the dose-response relationship between PPI use and pancreatic cancer risk, compared with controls. For all types of PPIs combined, the OR increased was 1.68 (95% CI, 1.14-2.49) for patients on <30 cumulative DDD compared with 2.19 (95% CI, 2.68-2.85) for those on ≥150 cumulative DDD. Compared with controls, the risks of pancreatic cancer were: OR 0.89 (95% CI, 0.62-1.27) for use of PPI <30 days and 2.22 (95% CI, 1.68-2.94) for ≥150 days.

Table 4 shows cumulative DDD for individual PPIs and the risk of pancreatic cancer. Dose analysis showed the highest risk for patients using <70 cumulative DDD of rabeprazole (aOR = 6.31, 95% CI, 2.41-16.5), followed by <60 cumulative DDD of lansoprazole (aOR = 2.26, 95% CI, 1.45-3.53), ≥60 cumulative DDD of lansoprazole (aOR = 2.59, 95% CI, 1.67-4.03), ≥50 cumulative DDD of pantoprazole (aOR = 1.98, 95% CI, 1.13-3.34), and ≥85 cumulative DDD of esomeprazole (aOR = 1.76, 95% CI, 1.11-2.79; Table 4).

Table 3. Odds Ratio and 95% Confidence Intervals of Pancreatic Cancer Associated With Cumulative DDD Dose and Cumulative Use Day of Proton Pump Inhibitors.

Nonuse of PPI	Case Number/Control Number 633/767	Crude Odds Ratio 1.00	95% CI Reference	Adjusted odds ratio ^a 1.00	95% CI Reference
PPI^b					
<30 DDD	55/72	0.93	0.64, 1.34	0.92	0.64, 1.33
30-65 DDD	64/46	1.69	1.14, 2.50 ^c	1.68	1.14, 2.49 ^c
65-150 DDD	148/100	1.79	1.36, 2.36 ^d	1.77	1.34, 2.33 ^d
≥150 DDD	187/102	2.22	1.71, 2.89 ^d	2.19	1.68, 2.85 ^d
<i>P</i> for trend		<0.001		<0.001	
PPI^b					
<30 day	58/79	0.89	0.62, 1.27	0.89	0.62, 1.27
30-65 day	84/52	1.96	1.36, 2.81 ^d	1.94	1.35, 2.78 ^d
65-150 day	144/99	1.76	1.34, 2.32 ^d	1.75	1.33, 2.31 ^d
≥150 day	168/90	2.26	1.72, 2.98 ^d	2.22	1.68, 2.94 ^d
<i>P</i> for trend		<0.001		<0.001	

Abbreviation: DDD, defined daily dose.

^aAdjusted for age group and biliary tract disease.

^bThe cumulative DDD dose is partitioned into 2 segments by third quartile.

^c*P* < .01.

^d*P* < .001.

Table 4. Odds Ratio and 95% Confidence Intervals of Pancreatic Cancer Associated With Cumulative DDD Dose of Individual Proton Pump Inhibitors.

Nonuse of PPI	Case Number/Control Number 633/767	Crude Odds Ratio 1.00	95% CI Reference	Adjusted Odds Ratio ^a 1.00	95% CI Reference
Omeprazole^b					
<40 DDD	69/68	1.23	0.87, 1.75	1.24	0.87, 1.76
≥40 DDD	65/54	1.46	1.00, 2.12 ^c	1.46	1.00, 2.12
<i>P</i> for trend		<0.001		<0.001	
Pantoprazole^b					
<50 DDD	30/27	1.35	0.79, 2.29	1.37	0.80, 2.34
≥50 DDD	34/21	1.96	1.13, 3.41 ^c	1.98	1.13, 3.44 ^c
<i>P</i> for trend		<0.001		<0.001	
Lansoprazole^b					
<60 DDD	60/32	2.27	1.46, 3.53 ^d	2.26	1.45, 3.53 ^d
≥60 DDD	66/31	2.58	1.66, 4.00 ^d	2.59	1.67, 4.03 ^d
<i>P</i> for trend		<0.001		<0.001	
Rabeprazole^b					
<70 DDD	26/5	6.30	2.41, 16.5 ^d	6.31	2.41, 16.5 ^d
≥70 DDD	16/10	1.94	0.87, 4.30	1.93	.87, 4.29
<i>P</i> for trend		<0.001		<0.001	
Esomeprazole^b					
<85 DDD	40/39	1.24	0.79, 1.96	1.24	0.79, 1.95
≥85 DDD	48/33	1.76	1.12, 2.78 ^c	1.76	1.11, 2.79 ^c
<i>P</i> for trend		<0.001		<0.001	

Abbreviation: DDD, defined daily dose.

^aAdjusted for age group and biliary tract disease.

^bThe cumulative DDD dose is partitioned into 2 segments by median.

^c*P* < .05.

^d*P* < .001.

Discussion

Our results showed that the use of PPI was associated with the risk of pancreatic cancer (aOR = 1.69, 95% CI, 1.42-2.03). For all types of PPI combined, the OR was 1.68 (95% CI, 1.14-2.49) for patients on <30 cumulative DDD compared with 2.19

(95% CI, 2.68-2.85) for those on ≥150 cumulative DDD. The cumulative DDD of individual PPIs was also associated with risk of pancreatic cancer.

The present study is, to the best of the authors' knowledge, the largest investigation of the effects of PPIs on risk of pancreatic cancer in an Asian population. A previous report

conducted in Europe (United Kingdom) showed that anti-acid treatment (H2RA and PPI) was not associated with risk of pancreatic cancer.¹⁰ However, recent data showed that PPI therapy may be associated with pancreatic cancer risk and PPI users recently started on treatment had slightly worse survival.¹¹ The use of PPI was associated with an increased risk of periampullary cancers, including pancreas head cancer, in a population-based study from NHIRD.¹² The association of PPI use and pancreatic cancer risk requires further investigation in order to establish the precise nature of the relationship as well as the underlying mechanism. Furthermore, ethnicity appears to play a role as East Asians are known to be slow metabolizers of PPIs as a result of a lower expression of hepatic cytochrome p450.¹³ Our results demonstrated that PPI use was associated with pancreatic cancer risk in our population-based database.

Gastrin has 2 physiological roles related to meal-stimulated gastric acid secretion and as a trophic hormone for epithelial and enterochromaffin cells.¹⁶ Gastrin and its receptors are coexpressed in pancreatic cancer.^{17,18} Hypergastrinemia has been shown to be associated with carcinogenesis, and thus it is reasonable to postulate that PPI-induced hypergastrinemia could be considered a factor in the development of pancreatic cancer.^{12,17,19,20} It is possible that gastrin and PPIs interact, resulting in a cellular microenvironment that is more conducive to pancreatic carcinogenesis in susceptible patients. However, the aOR for developing periampullary cancers in patients taking PPIs was 1.35 (95% CIs, 1.16-1.57), and for pancreatic cancer was 1.69 in the present study. Thus, the risk of periampullary cancers and pancreatic cancer in PPI users, although not high, was nonetheless statistically significant. Compared with the risk of developing gastric cancer in patients without GERD or PPI use, the risk of gastric cancer in patients with GERD taking PPIs was also moderate and seemed to be higher than that for pancreatic cancer in our previous report.^{20,21}

To evaluate the potential dose-response relationship, we summed up the doses of PPIs and stratified PPI use into less than 30, 30 to 65, 65 to 150, and more than 150 cumulative DDDs. We demonstrated a statistically significant trend between the dose and the cumulative incidences of pancreatic cancer. Therefore, taken together, our results revealed a significant association between use of PPIs and risk of pancreatic cancer.

This study had several limitations. First, patients' compliance with medication could not be confirmed in the NHIRD. Second, patients' lifestyle behaviors, such as alcohol and smoking habits, were not collected in the NHIRD. Third, most patients may have taken more than one type of PPI, so the interaction of different PPIs could not be completely accounted for. In addition, use of over-the-counter PPIs could not be evaluated. Fourth, this study employed a retrospective case-control design and thus it was not possible to definitively establish any cause-effect relationships between use of PPIs and pancreatic cancer. As such, further research using randomized controlled trials is needed to determine whether PPI use causes pancreatic cancer.

Conclusion

The PPI use was associated with the risk of pancreatic cancer in patients taking PPIs for peptic ulcer diseases or GERD. Further investigations with a prospective and randomized controlled study design are warranted to explore the relationship between PPI use and pancreatic cancer risk.

Authors' Note

Y.-C.P. and C.-H.K. contributed to conceptualization, investigation, resource, supervision, and project administration; Y.-C.P., C.-L.L., W.-Y.H., I.-T.L., H.-Z.Y., C.-S.C., and C.-H.K. contributed to methodology, data curation, validation, and formal analysis and wrote original draft (preparation and visualized, review and editing); C.-L.L. and C.-H.K. contributed to software; and C.-H.K. did funding acquisition.


Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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