Original Article

Use of Proton Pump Inhibitors Correlates with Increased Risk of Pancreatic Cancer: A Case-Control Study in Taiwan

Shih-Wei Lai[1,2], Fung-Chang Sung[3,4], Cheng-Li Lin[3,4], Kuan-Fu Liao[5,6]

[1]School of Medicine, and [3]Department of Public Health, China Medical University, Taichung, Taiwan

[2]Department of Family Medicine, and [4]Management Office for Health Data, China Medical University Hospital, Taichung, Taiwan

[5]Graduate Institute of Integrated Medicine, China Medical University, Taichung, Taiwan

[6]Department of Internal Medicine, Taichung Tzu Chi General Hospital, Taichung, Taiwan

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ABSTRACT

Objective: To investigate whether use of proton pump inhibitors (PPIs) enhances the risk of pancreatic cancer

Design: Retrospective case control study

Settings: Department of Public Health, China Medical University, Taiwan

Subjects: We identified 977 patients aged 20 years or older with newly diagnosed pancreatic cancer as the case group between 2000 and 2010. The control group consisted of 3908 subjects without pancreatic cancer selected from the same sample.

Intervention: Use of Proton pump inhibitors

Main Outcome Measure: History of using PPIs and other comorbidities were compared between cases and controls

Results: After adjustment for confounders, multivariable logistic regression analysis showed that pancreatic cancer had strong association with PPIs use (OR 9.28, 95% CI 7.77 - 11.08). Among PPI drugs, those using esomeprazole were at the highest risk with an odds ratio of 12.1 (95% CI 9.76 - 15.0).

Conclusions: Taking PPIs correlates with increased risk of pancreatic cancer. The risk may greater for those taking esomeprazole.

KEYWORDS: pancreatic cancer; proton pump inhibitor

INTRODUCTION

Pancreatic cancer is an important global burden of cancer because of low survival rate. Among cancer related deaths, it is the eighth most common cause of death (266,000 deaths, 3.5% of the total) worldwide, the fourth in the US and the eighth in Taiwan[1-3]. The etiology of pancreatic cancer remains unclear. Studies have implicated smoking, drinking alcohol, consuming coffee, obesity, family history, medications and pancreatitis as factors associated with this disease[4-6]. Lowenfels *et al* in an European international cohort study found that the incidence ratio of pancreatic cancer in patients with pancreatitis was 26.3 times higher than expected[4]. A recent study found the risk of pancreatic cancer increased in patients with gastric ulcer[7].

Proton pump inhibitors (PPIs), a class of drugs that reduce gastric acid secretion, are commonly prescribed to manage peptic ulcer diseases. Their long-term effects on cancer risk have been widely discussed. Long-term omeprazole treatment may lead to hypergastrinemia and profound hypochlorhydria in response to the reduced gastric acid secretion[8,9]. Hypergastrinemia is found to be associated with digestive tract malignancies[8,10-12]. The earlier experimental studies have identified gastrin receptors in human pancreatic cancer cells, and gastrin can stimulate the growth of human pancreatic cancer cells in culture[13,14]. Thus, we hypothesized that use of PPIs may lead to hypergastrinemia, which might correlate with increased risk of pancreatic cancer. To date, no evidence is available about the role of PPIs on pancreatic cancer risk in Taiwan. Therefore, we conducted a case-control study to explore whether there is an association between PPIs use and pancreatic cancer risk.

MATERIALS AND METHODS

Study population

This case-control study used the claims data of the National Health Insurance of Taiwan. The program

Address correspondence to:

Kuan-Fu Liao, Department of Internal Medicine, Taichung Tzu Chi General Hospital, No.66, Sec. 1, Fongsing Road, Tanzi District, Taichung City, 427, Taiwan, Phone: 886-4-2205-2121, Fax: 886-4-2203-3986, E-mail: kuanfuliao@yahoo.com.tw

has been detailed in previous studies[15-17]. In brief, this universal insurance program has a coverage rate of more than 99% in this country[17]. The database consists of a random sample with 1,000,000 insured persons, being established by the Taiwan National Health Research Institute. The database included information on insured demographic status, ambulatory care and inpatient care, and medicine prescribed. International Classification of Diseases (ICD) 9th Revision-Clinical Modification (ICD-9) was used to identify diagnosis. Data files can be linked with scrambled identification to secure privacy of patients.

Inclusion criteria

First, during the period of 2000 - 2010, subjects aged 20 years or older who had newly diagnosed pancreatic cancer were defined as the study cases (based on ICD-9 codes 157). A total of 977 cases were selected as the case group. Second, for each pancreatic cancer case, four subjects without pancreatic cancer from the same database were randomly selected as the study controls (case / control ratio = 1:4). A total of 3908 subjects were selected as the control group. Both groups were matched by gender, age (per 5 years) and index year of diagnosing pancreatic cancer. The date of diagnosing pancreatic cancer was defined as the index date. Subjects with pancreatic cancer or any other cancer (ICD-9 codes 140 - 208) before index date were excluded.

Exposure definition

Patients with early-undiagnosed pancreatic cancer initially presenting with abdominal symptoms might have been treated with PPIs. To reduce misclassification, cases receiving the PPIs therapy only within two years before the index date were excluded from the data analyses. In order to explore the effect of medications on pancreatic cancer risk, histamine-2 receptor antagonists, statins, non-statin lipid-lowering drugs, aspirin, other non-steroidal anti-inflammatory drugs, and cyclooxygenase-2 inhibitors before index date were included.

Co-morbidities potentially associated with pancreatic cancer risk

Co-morbidities before index date potentially associated with pancreatic cancer risk were as follows: acute pancreatitis, chronic pancreatitis, diabetes

Table 1: Characteristics between pancreatic cancer cases and control subjects

Characteristics of subjects	Pancreatic cancer				p-value
	No N = 3908		Yes N = 977		
	n	%	n	%	
Gender					
Men	2368	60.59	592	60.59	0.99
Women	1540	39.41	385	39.41	
Age group (years)					
20-39	5	0.13	1	0.10	0.94
40-64	1296	33.16	329	33.67	
≥ 65	2607	66.71	647	66.22	
Age (mean and SD, years)*	68.11	11.16	68.38	11.24	0.50
Co-morbidities before index date					
Acute pancreatitis	34	0.87	153	15.66	<0.0001
Chronic pancreatitis	11	0.28	58	5.94	<0.0001
Diabetes mellitus	773	19.78	370	37.87	<0.0001
Obesity	38	0.97	41	4.20	<0.0001
Gallstones	176	4.50	56	5.73	0.11
Hepatitis C	78	2.00	23	2.35	0.48
Medications (ever used)					
Proton pump inhibitors	521	13.33	619	63.36	<0.0001
Duration of using proton pump inhibitors (mean ± SD, months) *	4.45	6.67	9.50	14.75	<0.0001
Histamine-2 receptor antagonists	2459	62.92	824	83.34	<0.0001
Statins	808	20.68	337	34.49	<0.0001
Non-statin lipid-lowering drugs	524	13.41	212	21.70	<0.0001
Aspirin and cyclooxygenase-2 inhibitors					
Aspirin only	725	18.55	146	14.94	<0.0001
Cyclooxygenase-2 inhibitors only	772	19.75	254	26.00	
Both of above	1040	26.61	372	38.08	

Data are presented as the number of subjects in each group, with relevant percentages. Chi-square test, and *t-test comparing subjects with and without pancreatic cancer

Table 2: Odds ratio and 95% confidence interval of pancreatic cancer associated with use of proton pump inhibitors and co-morbidities

Variables	Crude		Adjusted†	
	OR	(95%) CI	OR	(95%) CI
Gender (men vs. women)	1.00	(0.87, 1.15)	-	-
Age (per one year)	1.00	(0.99, 1.01)	-	-
Co-morbidities before index date (yes vs. no)				
Acute pancreatitis	21.16	(14.48, 30.91)	16.32	(10.24, 26.02)
Chronic pancreatitis	22.33	(11.68, 42.70)	2.27	(1.00, 5.15)
Diabetes mellitus	2.47	(2.13, 2.88)	1.54	(1.27, 1.87)
Obesity	4.46	(2.85, 6.98)	2.59	(1.54, 4.36)
Gallstones	1.29	(0.95, 1.76)	-	-
Hepatitis C	1.18	(0.74, 1.90)	-	-
Medications				
Proton pump inhibitors	11.24	(9.58, 13.18)	9.28	(7.77, 11.08)
Histamine-2 receptor antagonists	3.17	(2.64, 3.82)	1.90	(1.53, 2.35)
Statins	2.02	(1.73, 2.35)	0.97	(0.79, 1.32)
Non-statin lipid-lowering drugs	1.79	(1.50, 2.14)	1.15	(0.91, 1.45)
Single treatment on aspirin and/or cyclooxygenase-2 inhibitors (vs. non-use of aspirin and non-use of cyclooxygenase-2 inhibitors)				
Aspirin only	1.35	(1.07, 1.70)	1.02	(0.79, 1.32)
Cyclooxygenase-2 inhibitors only	2.20	(1.79, 2.70)	1.04	(0.81, 1.34)
Both of above	2.39	(1.98, 2.89)	0.83	(0.65, 1.06)

† Adjusted for acute pancreatitis, chronic pancreatitis, diabetes mellitus, obesity, and histamine-2 receptor antagonists, statins, non-statin lipid-lowering drugs, and both of aspirin and cyclooxygenase-2 inhibitors. OR = odds ratio, CI = confidence interval

mellitus, obesity, gallstones, and hepatitis C infection. All were identified with ICD-9 codes.

Statistical analysis

Data analysis first compared between cases and controls for distribution of demographic status, comorbidities and medications received. The Chi-square test and t-test were used to examine the differences. Only the factors found significant in the crude analysis were further included in multivariable logistic regression analysis to estimate odds ratio (OR) and 95% confidence interval (CI) for pancreatic cancer. The risk of the cancer was estimated by individual PPI with the adjustment of acute pancreatitis, chronic pancreatitis, diabetes mellitus, obesity, histamine-2 receptor antagonists, statins, non-statin lipid-lowering drugs, and both of aspirin and cyclooxygenase-2 inhibitors. A p- value < 0.05 was considered statistically significant (SAS software version 9.1, SAS Institute Inc., Cary, North Carolina, USA).

RESULTS

Characteristics of the study population

There were 977 patients with pancreatic cancer as cases and 3908 subjects without pancreatic cancer as controls. Table 1 shows that the case group had higher proportions of acute pancreatitis, chronic pancreatitis, diabetes mellitus, obesity, PPIs use, histamine-2 receptor antagonists use, statins use, non-statin lipid-lowering drugs use, and cyclooxygenase-2 inhibitors use. The mean duration of using PPIs was longer in case group than in the control group (9.50 Vs 4.45 months, p-value < 0.0001). Because more than 98% of subjects in both groups had used other non-steroidal anti-inflammatory drugs, these drugs were excluded from further analysis (data not shown).

Association between co-morbidities, medications and pancreatic cancer risk

After adjustment for multiple confounders that were found significant in the crude analysis, multivariable logistic regression analysis showed that the adjusted OR of pancreatic cancer was 9.28 for the group with PPIs use (95% CI 7.77, 11.08), as compared to the group with non-use of PPIs. In addition, acute pancreatitis (OR 16.32, 95% CI 10.24, 26.02), chronic pancreatitis (OR 2.27, 95% CI 1.00, 5.15), diabetes mellitus (OR 1.54, 95% CI 1.27, 1.87), obesity (OR 2.59, 95% CI 1.54, 4.36), and use of histamine-2 receptor antagonists (OR 1.90, 95% CI 1.53, 2.35), were significantly associated with pancreatic cancer risk (Table 2).

Sub-analysis of association between individual proton pump inhibitors and pancreatic cancer risk

In sub-analysis, use of omeprazole (OR 7.88, 95% CI 5.46, 11.4), pantoprazole (OR 10.9, 95% CI 8.61, 13.9), lansoprazole (OR 10.4, 95% CI 7.78, 13.9), rabeprazole (OR 8.71, 95% CI 6.28, 12.1), or esomeprazole (OR 12.1, 95% CI 9.76, 15.0), could be associated with increased risk of pancreatic cancer (Table 3).

Table 3: Risk of pancreatic cancer associated with individual proton pump inhibitors

Non-use of PPIs as a reference	Case/N 358/3745	Crude odds ratio	(95% CI)	Adjusted odds ratio†	(95% CI)
Omeprazole	66/137	8.80	(6.18, 12.5)	7.88	(5.46, 11.4)
Pantoprazole	309/492	16.0	(12.9, 19.8)	10.9	(8.61, 13.9)
Lansoprazole	164/272	14.4	(11.0, 18.7)	10.4	(7.78, 13.9)
Rabeprazole	116/205	12.3	(9.16, 16.6)	8.71	(6.28, 12.1)
Esomeprazole	412/639	17.2	(14.1, 20.9)	12.1	(9.76, 15.0)

†Adjusted for acute pancreatitis, chronic pancreatitis, diabetes mellitus, obesity, histamine-2 receptor antagonists, statins, non-statin lipid-lowering drugs, and both of aspirin and cyclooxygenase-2 inhibitors

DISCUSSION

So far, only one observational study with large sample size from UK general practice research database (GPRD) has reported that PPIs use was not associated with pancreatic cancer risk (OR 1.02, 95% CI 0.85-1.22), no matter what the duration or dosage had been[18]. Because some subjects might have underlying early-undiagnosed pancreatic cancer who initially presented with abdominal symptoms and received PPIs treatment, to reduce this confounding effect, subjects who have used PPIs only within two years before index date were excluded from this present study. In the present study, we found that the overall risk of pancreatic cancer might be increased up to 9-fold among PPIs-users. To date, only few studies can be referenced. Therefore, we cannot provide a plausible explanation about the strong discrepancies of the above results. The postulated pathophysiological basis linking hypergastrinemia and pancreatic cancer is that there are gastrin receptors in human pancreatic cancer cells, and gastrin can stimulate the growth of human pancreatic cancer cells in culture[13,14]. Additionally, bacterial overgrowth and generation of nitrosamines secondary to gastric acid suppression may also contribute to human pancreatic carcinogenesis *in vitro*[19]. Therefore, our finding is compatible with the prior hypothesis that use of PPIs might cause hypergastrinemia and gastric acid suppression, which might correlate with increased risk of pancreatic cancer. Nevertheless, one point needs to be discussed. Because of the lag time between diagnosing date of pancreatic cancer and onset of pancreatic cancer, we could not make sure whether PPIs use was before or after onset of pancreatic cancer, even though subjects who have used PPIs only within two years before index date were excluded from the analysis. Thus, whether PPIs use is really causality for pancreatic cancer risk or only a coincidence for treating abdominal symptoms of early-undiagnosed pancreatic cancer cannot be determined in this present study.

Some limitations should be discussed. First, there was no record of body mass index due to inherited limitation of this database. Thus, we defined obesity by using ICD-9 codes. This could lead to underestimation of the prevalence of obesity. Second, because there is no other study supporting such an association between PPIs use and pancreatic cancer, interpretation of our findings should be careful. Third, it is not clear whether our findings can be extrapolated to a Caucasian population.

CONCLUSION

We conclude that although residual confounding may have affected the results, PPIs use is associated with a markedly increased risk of pancreatic cancer in Taiwan. Further studies are needed to confirm the role of PPIs on pancreatic cancer risk.

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Conflict of Interest Statement: The authors disclose no conflicts of interest

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