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Parkinson's disease and risk of pancreatic cancer: a population-based case-control study in Taiwan

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Abstract

Background: The aim of this study was to investigate whether there is a relationship between Parkinson's disease and pancreatic cancer in Taiwan. *Methods:* This was a case-control study using claim data of the Taiwan National Health Insurance Program. There were 13,861 subjects aged 20-84 with newly diagnosed pancreatic cancer as cases and 55,444 randomly selected subjects without pancreatic cancer as controls from 1998 to 2011. Cases and controls were matched by sex, age and index year of diagnosing pancreatic cancer. The association of pancreatic cancer with Parkinson's disease was evaluated by the multivariable logistic regression model to estimate the adjusted odds ratio (OR) and 95% confidence interval (95% CI). *Results:* After adjusting for confounding factors including acute pancreatitis, chronic pancreatitis, diabetes mellitus, biliary stone, alcoholism, hepatitis B and hepatitis C, the multivariable logistic regression analysis showed the adjusted OR of pancreatic cancer was 0.82 for subjects with Parkinson's disease (95% CI 0.55, 1.21), as compared with subjects without Parkinson's disease.
Conclusion: No association is detected between Parkinson's disease and pancreatic cancer.

INTRODUCTION

Epidemiological evidence suggests a lower incidence of many common cancers among patients with Parkinson's disease.[1-4] Although not fully understood, a hypothesis is postulated that a hypothesized process drives cells to opposite directions.[5] That is, in cancer, cells have uncontrolled proliferation and/or survival. In Parkinson's disease, conversely, cells have progressive degeneration and/or death.[5,6] This opposite direction partially explains why inverse association exists between cancer and Parkinson's disease.

In our published and unpublished studies, after controlling for confounding factors, no significant association is detected between Parkinson's disease and lung cancer or hepatocellular carcinoma in Taiwan.[7] So far, pancreatic cancer is a major public concern due to its poor prognosis. It is the eighth most common cause of cancer- related deaths in Taiwan in 2011 (1,607 deaths, 3.8% of the total).[8] However, there is no conclusive evidence linking Parkinson's disease and pancreatic cancer in Taiwan. Hence, we conducted a population-based case-control study to investigate this issue by analyzing the database from the Taiwan National Health Insurance Program.

METHODS

Data sources

This population-based case-control study used claim data of the Taiwan National Health Insurance Program. The insurance program also includes a catastrophic illness program to protect vulnerable beneficiaries (including pancreatic cancer patients) by exempting them from co-payments for the corresponding medical services. The insurance program has been well described in previous studies in details.[9-12]

Study design and criteria

The International Classification of Disease, 9th Revision of Clinical Modification (ICD-9 code) is available in the claims data to define disease status. The index date was defined as the date of diagnosing pancreatic cancer. Subjects aged 20 or older with new diagnosis of pancreatic cancer between 1998 and 2011 (ICD-9 code 157)

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were selected as the case group. For each case identified, four subjects without pancreatic cancer were randomly selected as the control group. Both groups were matched by sex, age (every 5 year) and index year of diagnosing pancreatic cancer. Cases with pancreatic cancer were identified from the Registry of Catastrophic Illnesses Patient Database (RCIPD), a dataset containing health claims data for treatment of catastrophic illness, which consists of thirty categories of diseases that require long-term care. Claims data were used to identify comorbidities including Parkinson's disease (ICD-9 code 332.0), acute pancreatitis (ICD-9 code 577.0), chronic pancreatitis (ICD-9 code 577.1), diabetes mellitus (ICD-9 code 250), biliary stone (ICD-9 code 574), alcohol-related disease (ICD-9 codes 291, 303, 305.00, 305.01, 305.02, 305.03, 790.3 and V11.3), hepatitis B infection (ICD-9 codes V02.61, 070.20, 070.22, 070.30 and 070.32) and hepatitis C infection (ICD-9 codes V02.62, 070.41, 070.44, 070.51 and 070.54). The diagnosis accuracy of comorbidities based on ICD-9 codes, such as Parkinson's disease, acute pancreatitis, biliary stone, diabetes mellitus, hepatitis B infection and hepatitis C infection, has been well reviewed in previous studies.[10,12,13] In order to avoid being mistakenly diagnosed or being mistakenly coded by accident, we defined that subjects should have at least 3 consensus same diagnoses during outpatient visits and/or hospitalization to ensure the validity of diagnosis. Therefore, Parkinson's disease and other comorbidities were recorded for 3 or more outpatient visits and/or hospitalization. To reduce biased results, subjects who were diagnosed with Parkinson's disease or other comorbidities only within 5 years of diagnosing pancreatic cancer were excluded from this study. That is, only those whose pancreatic cancer was diagnosed > 5 years after Parkinson's disease diagnosis were included in the study. Subjects who had any cancer (ICD-9 codes 140-208) or secondary Parkinsonism (ICD-9 code 332.1) before the index date were excluded from the study.

Statistical analysis

Data analysis first compared cases with controls on the proportional distributions of demographic status and comorbidities using the Chi-square test and Fisher-exact test for categorical variables. Initially, all covariables were examined by the univariable unconditional logistic regression model. Only those observed to be significant in the univariable unconditional logistic regression model were further examined by the multivariable unconditional logistic regression model to estimate the adjusted odds ratio (OR) and 95% confidence interval (95% CI) for pancreatic cancer. Analyses were performed using the SAS 9.2 (SAS Institute Inc., Carey, North Carolina, USA), with P <0.05 considered as statistically significant.

RESULTS

Characteristics of the study population

Table 1 displays the characteristics between two groups. The case group had 13,861 subjects with new diagnosis of pancreatic cancer and the control group had 55,444 subjects without pancreatic cancer. The mean ages (standard deviation) were 65.7 (12.1) years in the pancreatic cancer group and 64.9 (12.3) years in the control group.

The pancreatic cancer group was more likely to have acute pancreatitis, chronic pancreatitis, diabetes mellitus, biliary stone, alcohol-related disease, hepatitis B and hepatitis C than the control group, with statistical significance (P < 0.05 for all). In further analysis, among 31 subjects with Parkinson's disease in the pancreatic cancer group, 30 subjects were aged 65-84 (96.77%) and 1 subject was aged 40-64 (3.23%). Among 139 subjects with Parkinson's disease in the control group, 129 subjects were aged 65-84 (92.81%) and 10 subjects were aged 40-64 (7.19%). There was no significant difference in the proportion of age group between the pancreatic cancer group and control group among subjects with Parkinson's disease (Fisher-exact test for P = 0.69).

Parkinson's disease and comorbidities associated with pancreatic cancer

Table 2 displays the odds ratio of pancreatic cancer associated with Parkinson's disease and other comorbidities. After adjusting for potential confounding factors, the multivariable unconditional logistic regression analysis displayed that the adjusted OR of pancreatic cancer was 0.82 for subjects with Parkinson's disease (95% CI 0.55, 1.21), when compared with subjects without Parkinson's disease. Acute pancreatitis (adjusted OR1.97, 95% CI 1.53, 2.53), chronic pancreatitis (adjusted OR 2.78, 95% CI 1.89, 4.09), diabetes mellitus (adjusted OR 1.35, 95% CI 1.27, 1.43) and biliary stone (adjusted OR 1.16, 95% CI 1.04, 1.29) were other comorbidities significantly associated with pancreatic cancer.

Table 1: Characteristics of pancreatic cancer cases and control subjects

	Pancreatic cancer				
	No N= 13,861		Yes N= 55,444		
	n	(%)	n	(%)	*P* value*
Sex					0.99
Male	32,372	58.39	8,093	58.39	
Female	23,072	41.61	5,768	41.61	
Age group (year)					0.99
20-39	1674	3.02	418	3.02	
40-64	21,954	39.60	5,489	39.60	
65-84	31,816	57.38	7,954	57.38	
Comorbidities before index date					
Parkinson's disease	139	0.25	31	0.22	0.56
Acute pancreatitis	176	0.32	123	0.89	<0.0001
Chronic pancreatitis	57	0.10	62	0.45	<0.0001
Diabetes mellitus	5,079	9.16	1,705	12.30	<0.0001
Biliary stone	1,478	2.67	484	3.49	<0.0001
Alcohol-related disease	158	0.28	59	0.43	0.008
Hepatitis B	724	1.31	215	1.55	0.03
Hepatitis C	454	0.82	144	1.04	0.01

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

DISCUSSION

In this population-based case-control study, we found that no association could be detected between Parkinson's disease and pancreatic cancer, which is compatible with Moller *et al*.'s study in Denmark showing no association between Parkinson's disease and pancreatic cancer (relative risk = 0.86, 95% CI = 0.5-1.3).[1] However, a study by Kareus *et al*. in USA showed that an association could be detected between Parkinson's disease and pancreatic cancer (relative risk = 0.26, 95% CI = 0.05-0.76).[4] These conflicting findings indicate

Table 2: Odds ratio and 95% confidence interval of pancreatic cancer associated with Parkinson's

Variable	Crude		Adjusted†	
	OR	(95%CI)	OR	(95%CI)
Comorbidities before index date (yes vs. no)				
Parkinson's disease	0.89	(0.60, 1.32)	0.82	(0.55, 1.21)
Acute pancreatitis	2.81	(2.23, 3.54)	1.97	(1.53, 2.53)
Chronic pancreatitis	4.37	(3.05, 6.26)	2.78	(1.89, 4.09)
Diabetes mellitus	1.39	(1.31, 1.48)	1.35	(1.27, 1.43)
Biliary stone	1.32	(1.19, 1.47)	1.16	(1.04, 1.29)
Alcohol-related disease	1.50	(1.11, 2.02)	1.09	(0.80, 1.50)
Hepatitis B	1.19	(1.02, 1.39)	1.11	(0.95, 1.29)
Hepatitis C	1.27	(1.05, 1.54)	1.12	(0.92, 1.36)

†Covariables which were significantly associated with pancreatic cancer in the univariable unconditional logistic regression model were further examined by the multivariable unconditional logistic regression model.
Additionally adjusted for acute pancreatitis, chronic pancreatitis, diabetes mellitus, biliary stone, alcohol-related disease, hepatitis B and hepatitis C

that the relationship between Parkinson's disease and pancreatic cancer remains inconclusive. It also indicates a future research direction that only after controlling for comorbidities, the relationship between Parkinson's disease and any other cancer can be totally elucidated.

The latency from initiating mutation of the pancreatic cell to pancreatic cancer death is relatively long.[14] In the few years before diagnosing pancreatic cancer, the cancer typically becomes low-level symptomatic, creating an important issue of potential reverse causality. This is an important problem for examining that histories of Parkinson's disease and other comorbidities should exist before diagnosing pancreatic cancer. In fact, nobody knows what cut-point is suitable, but any shown relationship would be more convincing if comorbidities were present for a much longer period before diagnosing pancreatic cancer. Therefore, in order to reduce the above-mentioned biased results, patients who were diagnosed with Parkinson's disease or other comorbidities only within 5 years of diagnosing pancreatic cancer were excluded from this study. That is, only those whose pancreatic cancer was diagnosed > 5 years after Parkinson's disease diagnosis were included in the study.

This present study has some limitations inherent to the database. First, body mass index and smoking status were not recorded in this database. Some risk factors of pancreatic cancer, such as obesity and cigarette smoking, cannot be included for analysis. Second, before analysis, nobody knows whether patients with pancreatic cancer have higher prevalence rate of Parkinson's disease. In this present study, there were 31 patients with Parkinson's disease in the pancreatic cancer group (0.22%) and 139 patients with Parkinson's disease in the control group (0.25%), without a statistical significance. The prevalence of Parkinson's disease is lower in this study than that in our previous study (2.8%).[7] The low prevalence could be due to the rigorous inclusion criteria studied. That is, only those whose pancreatic cancer was diagnosed > 5 years after Parkinson's disease diagnosis were included in the study. The statistical power in the multivariable analysis may be questionable. Therefore, further studies with more Parkinson's disease patients are needed to clarify this issue. Third, the diagnosis of comorbidities might be under- or over-estimated according to outpatient visits due to the limitation of this database. In further analysis, we included all patients with Parkinson's disease to compare comorbidities studied between the pancreatic cancer group and non-pancreatic cancer group. There was no significant difference in comorbidities between the pancreatic cancer group and non-pancreatic cancer group (Table not shown). This means that the result is not confounded by comorbidities studied. Fourth, although this is a negative study for investigating the association between Parkinson's disease and pancreatic cancer, it is a clinically relevant topic with some scientific novelty. It provides the updated evidence for this country.

We conclude that no association is detected between Parkinson's disease and pancreatic cancer. Acute pancreatitis, chronic pancreatitis, diabetes mellitus and biliary stone are significantly associated with pancreatic cancer.

DISCLOSURE

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