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Higher stroke incidence in the patients with pancreatic cancer

A nation-based cohort study in Taiwan

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Abstract

No study has investigated the role of pancreatic cancer in the stroke risk using population data. We used claims data obtained from a universal health insurance program of Taiwan to evaluate the stroke risk in pancreatic cancer patients.

From the catastrophic disease registry of the insurance, we identified 7479 patients with pancreatic malignancy without stroke history from 2000 to 2009. The comparison cohort consisted of 29,916 individuals identified from 1 million insured people without cancer and stroke history, matching with the cancer cohort by propensity score. We followed each selected individual until stroke was diagnosed or until being censored for death or withdrawal from insurance, or for a maximum of 3 follow-up years, or the end of 2011.

The pancreatic cancer cohort had a 2.3-fold greater incident stroke than comparisons had (28.5 vs 12.3 per 1000 person-years), with an adjusted hazard ratio (aHR) of 2.74 (95% confidence interval (CI) = 2.31–3.24) after controlling for covariates, or a subdistribution hazard ratio (SHR) of 2.04 (95% CI = 1.74–2.40) accounting for the competing risk of deaths. During the follow-up period, stroke events occurred constantly in comparisons, but declined rapidly in the cancer cohort. The pancreatic cancer cohort had a stroke incidence of 46.6 per 1000 person-years within 6 months postdiagnosis, with an aHR of 4.37 (95% CI = 3.45–5.54) and a SHR of 3.87 (95% CI = 3.08–4.86), relative to comparisons.

Our study suggests that patients with pancreatic cancer are at an elevated risk of stroke, patients deserve sufficient follow-up care, particularly in the first 6 months after the diagnosis of the cancer, and for those with comorbidities.

Abbreviations: aHR = adjusted hazard ratio, CI = confidence interval, CMUH = China Medical University and Hospital, CSM = conventional stroke mechanisms, HR = hazard ratio, ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification, IRB = Institutional Review Boards, NHIAMHW = National Health Insurance Administration Ministry of Health and Welfare, NHIRD = National Health Insurance Research Database, NHRI = National Health Research Institutes, REC = Research Ethics Committee, SAS = Statistical Analysis System, SCMH = Show Chwan Memorial Hospital, SHR = subdistribution hazard ratio, SPSS = statistical analysis in social science.

Keywords: pancreatic cancer, population-based retrospective cohort study, stroke, Taiwan

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P-CC and C-HY contributed equally to this study.

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1. Introduction

Cerebrovascular disease is the most common neurological disease and one of leading causes of death and serious disability worldwide.[1] The mortality in the first 30 days after stroke ranges from 9% to 23%.[2] Approximately 50% of stroke survivals suffer from mild hemiparesis, and 26% of the others have to be placed in care facilities due to their inability to perform daily living.[3]

Cancer has been proven to be a risk factor for thromboembolic disease, which reduces the survival rate and has become one of the main causes of deaths in cancer patients.[4,5] However, whether those cancer patients are at a higher risk of cerebrovascular disease remains an important issue for studies. An autopsy study as early as 3 decades ago showed that ischemic cerebral infarcts were found in 14.6% of cancer patients.[6] A large Korean nationwide longitudinal study including 820,491 cancer patients demonstrated various cancers might underlie an increasing risk of hemorrhagic and ischemic strokes.[7] Cancer-related causes of stroke have been postulated, including direct tumor-related vessel compressing or infiltration, tumor occlusion, coagulopathy by tumor cell-derived cytokines, and treatment-related adverse effects.[8]

Based on the 2011 estimates from global cancer statistics, about 138,100 men and 127,900 women died from pancreatic cancer, which respectively represented the eighth and ninth leading cause of cancer deaths for male and female populations in that year.[9] Cancer has been ranked as the first leading cause of death for more than 30 years in Taiwan. The age-adjust incidence rate for pancreatic cancer were 6.94 and 5.12 per 100,000 persons for male and female population, respectively.[10] The disease has become the sixth and eighth leading cancer death for population in Taiwan.[10]

Clinical studies revealed 17% to 57% patients with pancreatic cancer could develop thromboembolic disease.[11] Patients may have the deep vein thrombosis embolize into brain. Pancreatic cancer patients comorbid with pulmonary embolism, portal vein thrombosis, arterial thromboembolism or disseminated intravascular coagulation, and may further develop other cardiovascular disorders. The pathogenesis of this prothrombotic state seems to be related to the generation of an intrinsic hypercoagulable state initiated by pancreatic cancer cells through a series of complex coagulation cascades.[11] However, whether pancreatic cancer is associated with elevated risk of subsequent cerebrovascular disease has not been well evaluated.

In this study, we hypothesized that pancreatic cancer patients exhibit increased incidence of stroke compared to those noncancer counterparts. We used the claims data in the National Health Insurance Research Database (NHIRD) of Taiwan to conduct a population-based retrospective cohort study to investigate the stroke risk in newly diagnosed pancreatic cancer patients.

2. Materials and methods

2.1. Data sources

In 1995, the Taiwan government launched a universal single-payer health insurance, the Taiwan National Health Insurance program, which currently covers almost 99% of the entire 23.7 million population of Taiwan.[12] The National Health Insurance Administration Ministry of Health and Welfare (NHIAMHW) in Taiwan authorized the National Health Research Institutes (NHRI) to manage the claims data and establish NHIRD for research. For the present study, we obtained 2 longitudinal health insurance databases from NHRI. These 2 databases contain all medical records including inpatient and outpatient claims from 1996 to 2011. One database was for catastrophic illness patients and another one contained records of 1 million insured people randomly selected from the year 2000 registry for beneficiaries. Cancer patients could apply a catastrophic illness certificate for exempting from copayment under NHIAMHW guideline. In Taiwan, patient with disease diagnosis without valid supporting clinical findings may be considered a medical fraud, and the treating physician or hospital can be punished with a penalty by NHIAMHW. Diseases were coded using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM).

To protect patient privacy, the NHRI scrambled identification numbers of insured people and replaced with anonymous identification numbers for linking data files. This study was approved by the Institutional Review Boards at Show Chwan Memorial Hospital (SCMH IRB No. 1020401) and the Research Ethics Committee at China Medical University and Hospital, in Taiwan (CMUH104-REC2-115).

2.2. Sampled subjects

From the medical claims of catastrophic illness patients, we identified 11,304 patients newly diagnosed with pancreatic malignancy from 2000 to 2009. From these patients, 7479 persons were included in the pancreatic malignancy cohort, after excluding patients with other type of malignancy history [including head and neck (ICD-9-CM: 140–149), other digestive (ICD-9-CM: 150–156 and 158–189), respiratory (ICD-9-CM: 160–165), bone, connective tissue, skin and breast (ICD-9-CM: 170–176), genitourinary (ICD-9-CM: 179–189), lymphatic and hematopoietic tissue (ICD-9-CM: 200–208), and unspecified site (ICD-9-CM: 190–199, n = 682)], stroke history (ICD-9-CM: 430–438, n = 3022), and <20 years of age (n = 121). The date with the diagnosis of pancreatic malignancy was defined as index date.

The comparison cohort consisted of adult individuals (age ≥ 20 years) without the history of malignancy (ICD-9-CM: 140–208) and stroke, randomly selected from population without cancer matched by propensity score, with the sample size 4-fold of the pancreatic malignancy cohort. We used a logistic regression to calculate propensity score by estimating the probability of patients with pancreatic malignancy assignment based on age, sex, index date, and baseline comorbidities by greedy algorithm.

2.3. Outcome measures and comorbidities

Individuals were monitored from the date entering the study cohorts until the date with stroke diagnosed, or censored because of death or withdrawal from the insurance program, or until a maximum of 3 follow-up years by the end of 2011, whichever came first. Sums of follow-up person-years were calculated for both cohorts. We evaluated both hemorrhagic stroke (ICD-9-CM: 430–432) and ischemic stroke (ICD-9-CM: 433–438). In addition to sex and age, we also incorporated the baseline comorbid diseases as potential confounding factors. The comorbidity included hypertension (ICD-9-CM codes 401–405), diabetes (ICD-9-CM code 250), hyperlipidemia (ICD-9-CM code 272), coronary artery disease (ICD-9-CM codes 410–413, 414.0, 414.8), and atrial fibrillation (ICD-9-CM code 427.31).

Table 1

Demographic characteristics and comorbidities of pancreatic cancer patients and subjects in the comparison cohort.

	Comparison cohort (N = 29916)		Pancreatic cancer cohort (N = 7479)		
Variable	**n**	**%**	**n**	**%**	**Standardized difference**
Gender					
Male	17706	59.2	4402	58.9	0.007
Female	12210	40.8	3077	41.1	0.017
Age, y					
20–54	7186	24.0	1783	23.8	0.004
55–64	6735	22.5	1770	23.7	0.027
65–74	8332	27.9	2132	28.5	0.015
75+	7663	25.6	1794	24.0	0.038
Mean (SD)	65.0	(13.6)	64.7	(13.2)	0.024
Comorbidities					
Hypertension	3422	45.8	13774	46.0	0.006
Diabetes	9410	31.5	2499	33.4	0.042
Hyperlipidemia	7347	24.6	1714	22.9	0.039
CAD	6206	20.7	1544	20.6	0.002
AF	177	1.97	520	1.74	0.017

AF = atrial fibrillation, CAD = coronary artery disease, SD = standard deviation.

2.4. Statistical analysis

The proportionate distributions of demographic characteristics (sex and age) and comorbidities were compared between cohorts with and without pancreatic cancer. We used standardized difference to present the difference of distributions of sex, age, and comorbidities between the 2 cohorts. When the absolute value of standardized difference is less than 0.1, the distribution was in balance between the 2 cohorts. We also estimated the stroke risk by the follow-up time (0–6, 7–12, 13–24, >24 months) and stroke type. We used Kaplan–Meier analysis to calculate and plot the cumulative incidence of stroke for the 2 cohorts, and the difference was tested using log-rank test. Ischemic stroke and hemorrhagic stroke were also evaluated. Incidence density rates (per 1000 person-years) of stroke were calculated for the 2 study cohorts. Incidence was the new stroke cases divided by the sum of follow-up person-years during the study period. Cox proportional hazards regression analysis was used to assess the pancreatic cancer cohort to the comparison cohort hazard ratio (HR) of stroke with 95% confidence interval (CI). Multivariable model was used to calculate the adjusted HR after controlling for sex, age, and all comorbidities. Because pancreatic cancer patients had a higher mortality, we further used Cox model to estimate the Fine and Gray's subdistribution hazard ratio (SHR) of stroke accounting for the competing risk of death.[13] We used the scaled Schoenfeld residuals to test the Cox proportional hazards assumption, the assumption was not violated. We managed and analyzed the data using SAS 9.4 software (SAS Institute, Cary, NC) and draw the cumulative incidence curve using SPSS statistical software (version 18.0 for windows; IBM Corp, New York, NY). Statistical significance was defined at 2-tailed *P*-value less than .05.

3. Results

This study included 7479 patients in the pancreatic cancer cohort and 29,916 individuals without the cancer in the comparison cohort, with similar distributions in sex, age, and comorbidities (Table 1). There were more men than women and more than half of them were the elderly. In both cohorts, hypertension (near 46.0%) was the most prevalent comorbidity, followed by diabetes, hyperlipidemia and coronary artery disease, and least prevalent with atrial fibrillation (<2.0%).

After a 3-year of follow-up period, the cumulative incidence of all stroke was 1.8% greater in pancreatic cancer patients than in comparisons (5.5% vs 3.7%), mainly for the hemorrhagic stroke ($P < .001$, log-rank test) (Fig. 1). The incidence density of all

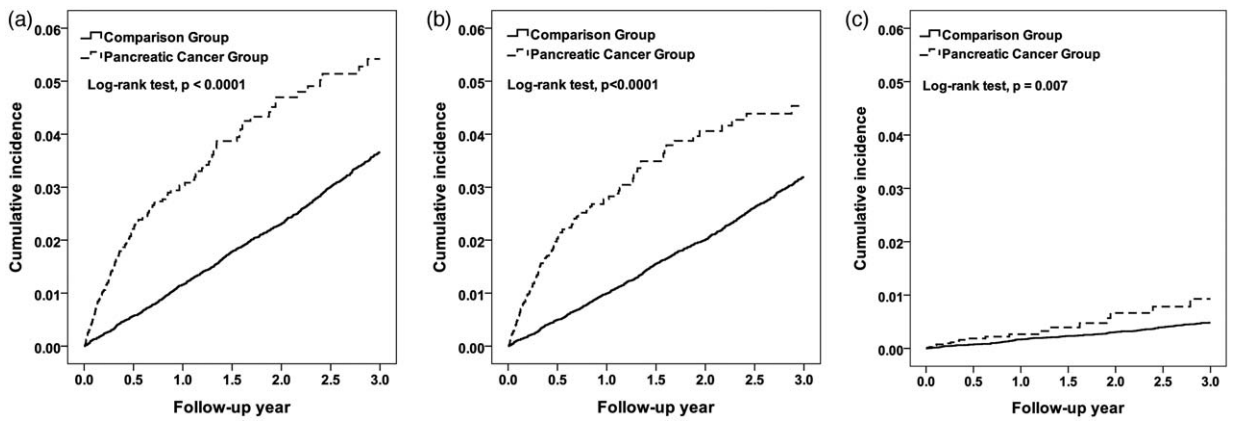

Figure 1. Cumulative incidence for stroke, ischemic stroke, and hemorrhagic stroke between pancreatic cancer and comparison group. (A) Overall stroke, (B) ischemic stroke, and (C) hemorrhagic stroke.

Table 2

Incidence of stroke and pancreatic cancer cohort relative to comparison cohort hazard ratios for stroke.

	Comparison group			Pancreatic cancer group					
	No. of events	PYs	Rate	No. of events	PYs	Rate	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	SHR (95% CI)
All strokes	1000	81,072	12.3	172	6032	28.5	2.23 (1.88–2.63)***	2.74 (2.31–3.24)***	2.04 (1.74–2.40)***
Ischemic stroke	870	81,072	10.7	153	6032	25.4	2.26 (1.90–2.70)***	2.81 (2.35–3.37)***	2.05 (1.72–2.43)***
Hemorrhagic stroke	130	81,072	1.60	19	6032	3.15	1.96 (1.19–3.21)**	2.25 (1.36–3.71)**	1.53 (0.95–2.45)
Gender									
Male	583	47,812	12.19	110	3402	32.34	2.57 (2.08–3.17)***	2.89 (2.33–3.57)***	2.15 (1.76–2.64)***
Female	417	33,260	12.54	62	2630	23.57	1.80 (1.37–2.36)***	2.54 (1.92–3.37)***	1.88 (1.44–2.45)***
Age, y									
20–54	46	20,370	2.26	23	1954	11.77	4.69 (2.80–7.86)***	4.96 (2.94–8.36)***	2.63 (1.68–4.12)***
55–64	137	18,692	7.33	40	1558	25.68	3.29 (2.28–4.76)***	3.27 (2.26–4.73)***	2.24 (1.60–3.15)***
65–74	316	22,724	13.91	55	1574	34.95	2.42 (1.80–3.26)***	2.41 (1.79–3.25)***	1.73 (1.31–2.30)***
75+	501	19,286	25.98	54	946	57.06	2.24 (1.67–3.00)***	2.32 (1.73–3.12)***	1.45 (1.10–1.91)**

Models were adjusted for sex, age, hypertension, diabetes, hyperlipidemia, coronary artery disease, and atrial fibrillation.

CI = confidence interval, HR = hazard ratio, PYs = person-years, rate = incidence rate, per 1000 person-years, SHR = subdistribution hazard ratio.

** $P < .01$.

*** $P < .001$.

strokes was 2.3-fold greater in the pancreatic cancer cohort than in comparisons (28.5 vs 12.3 per 1000 person-years), with an adjusted HR of 2.74 (95% CI = 2.31–3.24) or a SHR of 2.04 (95% CI = 1.74–2.40) (Table 2). The stroke incidence was greater in men than in women and increased with age. Relative to comparisons, younger pancreatic cancer patients were at a greater stroke hazard than older patients.

A high incidence of 46.6 per 1000 person-years appeared within 6 months after the cancer diagnosed in the pancreatic cancer cohort, with an adjusted HR of 4.37 (95% CI = 3.45–5.54) or a SHR of 3.87 (95% CI = 3.08–4.86), relative to the comparison cohort (Table 3). The stroke incidence declined with time to 7.54 per 1000 person-years 24 months after the cancer had been diagnosed. On the other hand, the stroke incidence occurred constantly in the comparison cohort during the follow-up period. This temporal pattern of stroke was mainly because of ischemic stroke.

4. Discussion

This nationwide population-based cohort study revealed a substantially increased stroke risk for patients with pancreatic cancer, particularly in the first half year of the follow-up period. To the best of our knowledge, the present study is the first longitudinal study using nation-wide data to investigate the likelihood of higher incidence risk of stroke in association with pancreatic cancer. Our results highlight the crucial role for clinicians of management and therapeutic strategy for pancreatic cancer patients.

Our data revealed a markedly elevated risk of ischemic and hemorrhagic stroke among patients with pancreatic cancer. The

Table 3

Incidence and pancreatic cancer cohort relative to comparison cohort hazard ratio of stroke by stroke type and follow-up duration in multivariable Cox model.

	Comparison group			Pancreatic cancer group				
Follow-up duration, mo	No. of events	PYs	Rate	No. of events	PYs	Rate	HR (95% CI)	SHR (95% CI)
All strokes								
0–6	169	14,806	11.4	119	2553	46.6	4.37 (3.45–5.54)***	3.87 (3.08–4.86)***
7–12	172	14,494	11.9	23	1304	17.6	1.87 (1.21–2.90)**	1.49 (0.97–2.29)
13–24	328	28,071	11.7	24	1379	17.4	2.01 (1.33–3.06)**	1.70 (1.13–2.58)*
>24	331	23,702	14.0	6	795	7.54	0.79 (0.35–1.77)	0.73 (0.32–1.63)
Ischemic stroke								
0–6	147	14,806	9.93	109	2553	42.7	4.65 (3.62–5.98)***	3.97 (3.13–5.04)***
7–12	145	14,494	10.0	21	1304	16.1	2.01 (1.27–3.19)**	1.58 (1.01–2.49)*
13–24	289	28,071	10.3	19	1379	13.8	1.84 (1.15–2.93)*	1.50 (0.95–2.39)
>24	289	23,702	12.2	4	795	5.03	0.61 (0.23–1.65)	0.54 (0.20–1.46)
Hemorrhagic stroke								
0–6	22	14,806	1.49	10	2553	3.92	2.63 (1.23–5.59)*	2.34 (1.13–4.82)*
7–12	27	14,494	1.86	2	1304	1.53	1.07 (0.25–4.51)	0.70 (0.17–2.92)
13–24	39	28,071	1.39	5	1379	3.63	3.30 (1.26–8.31)*	2.48 (0.99–6.23)
>24	42	23,702	1.77	2	795	2.51	1.80 (0.43–7.50)	1.63 (0.40–6.67)

Models were adjusted for sex, age, hypertension, diabetes, hyperlipidemia, coronary artery disease, and atrial fibrillation.

Cox proportional hazard regression assumption $P < .0001$.

CI = confidence interval, HR = hazard ratio, PYs = person-years, rate = incidence rate, per 1000 person-years, SHR = subdistribution hazard ratio.

* $P < .05$

** $P < .01$

*** $P < .001$.

risk is substantially higher during the first 6 months after the diagnosis of pancreatic cancer. Several cohort studies have shown similar findings for patients with other cancers.[6–9,14] Zoller et al[7] conducted a nationwide follow-up study in Sweden and found several cancer types are associated with an increased risk of hemorrhagic and ischemic stroke during the first 6 months after diagnosis of cancers.[7] In addition, a population-based cohort study from Taiwan also revealed that lung cancer is associated with increased risk of subsequent stroke within 1 year after diagnosis for men and 2 years after diagnosis for women.[14] These study results suggest that the pathophysiological mechanisms of stroke might differ between patients with and without cancer.

The plausible mechanisms of the association between cancers and stroke, such as cancer-related, treatment-related, and conventional stroke mechanisms (CSM), have been postulated.[8] A recent Korean study has reported that of all stroke cases, 40% were found outside of CSM, indicating that stroke patients without CSM could be regarded as cancer-related stroke patients.[15] Furthermore, cancer-related mechanisms of stroke include direct tumor-related vessel compressing or infiltration, tumor occlusion, and intrinsic hypercoagulable state caused by tumor cells.[8]

There are evidences suggesting an association between ischemic and hemorrhagic stroke and the presence of metastasis, indicating that both tumor burden (tumor emboli, vessel compression, or infiltration) and cancer-associated coagulopathy can underlie or enhance the occurrence of stroke in cancer patients.[7,16] In our study, stroke occurred in a short mean follow-up duration (i.e., 0.8 year), and approximately 80% of pancreatic cancer patients had tumor metastasis (data not shown), suggesting that the metastatic state at least play a partial role in augmenting the risks of stroke in the pancreatic cancer group.[17] Among potential treatment-related mechanisms for stroke occurrence in cancer patients,[8] chemotherapy, instead of surgery, is the main treatment option for most pancreatic cancer patients when diagnosed with distant metastasis. Cytostatic agents could cause not only thrombogenesis but also bleeding through their side effects of thrombocytopenia.[18]

Comorbidities may increase the stroke risk much greater for pancreatic cancer patients than for controls. Our further data analysis showed that the impact was the strongest for the cancer patients with atrial fibrillation, with an incidence of 68.8 per 1000 person-years, which was 2.5-fold greater than those without atrial fibrillation. Cancer patients with hypertension were also at a 2-fold greater stroke risk than those without the comorbidity (40.8 vs 19.8 per 1000 person-years) (Data shown in Supplementary Table 1; http://links.lww.com/MD/C172). It is important to note that near half of the study population had hypertension.

In our study, pancreatic cancer patients also had a higher risk of hemorrhagic stroke within 6 months after cancer diagnosis. However, the mechanisms underlying hemorrhagic stroke could not be clarified in this study, although various possible mechanisms should be considered such as tumor invasion to the vessel system, tumor necrosis, neovascularization, chemotherapy-related thrombocytopenia, and postradiation complications.[7,19] Otherwise, another indirect possibility that should not be ignored is that the majority of tumors (~70%) involving the pancreatic head usually cause obstructive cholestasis,[20] thereby underlying liver dysfunction, malnutrition, and elevated prothrombin time/international normalized ratio, all which could increase the risk of hemorrhagic stroke.[21]

The incidence of stroke declined rapidly beyond 6 months after the diagnosis of pancreatic cancer. The postulated causes could be due to the decreased tumor burden after treatment intervention, cessation of cytostatic agents (decreased chemotherapy-related complications) or death-related selective bias in the cancer group.[18,21] With comprehensive clinical information unavailable in present study, such as surgical intervention, dosage and location of the radiotherapy, treatment duration and regimen of chemotherapy and laboratory data, further research is warranted to clarify these problems.

The strength of this study lies in using the large population data as our data source, which covers more than 99% of the population in Taiwan.[11] With a large sample size and timely tracking period, results of this cohort study are highly representative. However, there are several limitations in our study. First, we used the inpatient data to establish the pancreatic cancer cohort, which means that stroke subjects without admission were not included in our analysis. This could under estimate not only the incidence of stroke but also their comorbidity status. Second, certain lifestyle information or demographic variables as potential confounding factors, such as smoking, alcohol, exercise habit, and body mass index, were not available in the claims data, and thus could not be further adjusted in this study. Alcohol consumption and smoking are suggested to be the risks of many cancers and stroke.[22–24] Ultimately, the NHIRD does not provide the information of cancer stage, and laboratory data, which prevented us from identifying the cancer-related mechanisms of stroke.

5. Conclusions

In this retrospective cohort study, patients with pancreatic cancer were at an elevated risk of ischemic and hemorrhagic stroke. Patients with the cancer diagnosed deserve sufficient follow-up care, particularly during the first 6 months after the diagnosis of cancer and for those with comorbidity. Further studies to clarify the mechanisms of stroke in cancer patients are needed to provide treatment strategies for preventing stroke.

Author contributions

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