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Diabetes mellitus correlates with increased risk of pancreatic cancer: A population-based cohort study in Taiwan

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Abstract

Background and Aim: This study investigated whether diabetes mellitus (DM) increased the risk of pancreatic cancer and whether anti-diabetic drugs reduced the risk in Taiwan.
Methods: We designed a population-based cohort study using the Taiwan National Health Insurance Database, which consisted of 49 803 patients aged 20 years and older with newly diagnosed DM as the diabetic group and 199 212 people without DM as the non-diabetic group during 1998–2007.
Results: The incidence of pancreatic cancer was higher in patients with diabetic duration less than 2 years, as compared to the non-diabetic group (27.81 *vs* 6.96 per 10 000 person-years, 95% confidence interval = 2.11–7.54). Age (aged 40–64, hazard ratio [HR] = 5.22, and aged 65 and older, HR = 7.59, respectively), chronic pancreatitis (HR = 19.40), gallstones (HR = 2.56), and hepatitis C infection (HR = 3.08) were also significant factors predicting pancreatic cancer. Patients with concurrent DM and chronic pancreatitis had an appreciably elevated risk of developing pancreatic cancer (HR = 33.52), as compared with subjects without these comorbidities. The association was not statistically significant between use of anti-diabetic drugs and the risk of pancreatic cancer.
Conclusions: Diabetes < 2 years' duration is associated with pancreatic cancer and could be an early manifestation of pancreatic cancer. Long-standing diabetes was not found to be a risk factor for pancreatic cancer in Taiwan's patients. Old age, chronic pancreatitis, gallstones and hepatitis C infection are other risk factors for pancreatic cancer. These high-risk patients should undergo close follow-up programs for pancreatic cancer.

Introduction

Pancreatic cancer is a relatively fatal disease with a poor prognosis and a high mortality rate because it is usually diagnosed in the advanced stage and is usually surgically unresectable.[1,2] A 10-year study in the USA found that the resectable rate of pancreatic cancer is only 4.8%.[1] A 30-year study in France found that the 5-year survival rate is less than 5% after diagnosis.[2] In a review by Michaud,[3] over 200 000 people die of pancreatic cancer in the world annually. In 2009, pancreatic cancer ranked the ninth leading cause of cancer death in Taiwan.[4] It accounted for approximately 1354 deaths in 2007, 1364 deaths in 2008, and 1480 deaths in 2009.[4] There is an increased trend of death caused by pancreatic cancer in Taiwan.

The cause of pancreatic cancer is not well established, but prior epidemiological studies have indicated that cigarette smoking, diabetes mellitus (DM), chronic pancreatitis, obesity, alcohol consumption, hepatitis B virus infection, family history of pancreatic cancer, and genetic disorders are significantly associated with pancreatic cancer.[3,5–9] As there is no available screening tool for pancreatic cancer, it seems to be very important to find the risk factors of pancreatic cancer early. Thus, early-targeted intervention can be performed to reduce the risk and suffering of pancreatic cancer.

The prevalence of DM in Taiwan increased approximately from 2.9% in 1996 to 11.4% in 2002.[10,11] In 2009, DM was the fifth leading cause of death in Taiwan.[4] Previous studies have proven that diabetic patients presented with an approximate two- to three-fold risk of pancreatic cancer in Western countries.[7,12,13] To the best of our knowledge, only one case–control study in Taiwan has revealed that there is a 2.8-fold risk of pancreatic cancer in diabetic patients.[5] Another cohort study, also from Taiwan, has observed the metformin effect, a frequently used anti-diabetic drug, in reducing the risk of pancreatic cancer (HR = 0. 15).[14] To clarify the role of diabetes, comorbidities and anti-diabetic drugs on the risk of developing pancreatic cancer in Taiwan, we designed this nationwide population-based cohort study, taking advantage of a

large dataset available from the Taiwan National Health Insurance program, to examine this association.

Methods

Data source and inclusion criteria

This was a population-based cohort study using data from Taiwan National Health Insurance Database. This insurance program began in March 1995 and covered more than 99% of the entire population of Taiwan (23 million residents) in 2008.[15] The insurance program details can be found in previous studies.[16,17] This study was exempted from a full review by the Institution Review Board.

The criteria of diseases were defined according to the International Classification of Diseases (ICD) 9th Revision. This cohort design would investigate whether patients with DM were at an increased risk of pancreatic cancer (ICD-9 codes 157.0, 157.1, 157.2, 157.3, 157.4, 157.8, 157.9, 157.90 and A096). In addition to ICD-9 codes to define diseases, the A-code was also used because it had been used before ICD-9 was adapted in Taiwan. Patients aged 20 and older, newly diagnosed with DM (ICD-9 codes 250 and A181) and currently using anti-diabetic drugs in 1998–2007 were included in diabetic group. For each diabetic case, we randomly selected four persons without medical claims for diabetes individually matched for age (every 5-year span) and sex in the same time period as the non-diabetic group. We defined each subject's index date as the date at which the subject was identified from the claims data. Both the diabetic group and the non-diabetic group were followed up to measure the incidence of pancreatic cancer until the end of 2007 or to be censored because of death or withdrawal from the insurance program.

The anti-diabetic drugs included metformin, sulfonylureas, thiazolidinediones, alpha-glucosidase inhibitors, D-phenylalanine derivatives, dipeptidyl peptidase 4 inhibitors, incretin mimetic agents and insulins. Subjects with cancers prior to the index date (ICD-9 codes 140 -208 and A08-A14) were excluded from this study. Other comorbidities were defined as obesity (ICD-9 codes 278.00 and 278.01 and A183), chronic pancreatitis (ICD-9 codes 577.1), alcoholism (ICD-9 codes 303, 305.00, 305.01, 305.02, 305.03, V11.3 and A215), gallstones (ICD-9 codes 574.00, 574.01, 547.10, 574.11, 574.20, 574.21 and A348), 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).

Statistical analysis

We estimated the incidence density of pancreatic cancer by the sociodemographic status and comorbidities. Crude and adjusted hazard ratios (HR) and 95% confidence intervals (CI) for factors associated with pancreatic cancer were calculated using Cox proportional hazard analyses. The statistical significance level was set at two-sided probability value of < 0.05. All analyses were measured with SAS version 9.2 (SAS Institute, Cary, NC, USA).

Results

Baseline characteristics of the study population

This study consisted of 49 803 subjects in the diabetic group and 199 212 subjects in the non-diabetic group, with similar sex and age distributions and mean age of 55.9 years (Table 1). The diabetic group had higher prevalence of obesity, chronic pancreatitis, alcoholism, gallstones, hepatitis B and hepatitis C infections at the baseline ($P < 0.001$).

During the follow-up period, the incidence of pancreatic cancer was 1.79-fold greater in the diabetic group than in the non-diabetic group (1.78 *vs* 1.00 per 10 000 person-years, 95%CI = 1.53–2.10) (Table 2). This further translated into approximately eight additional cases of pancreatic cancer per 100 000 diabetic patients each year. Regardless of sex or age groups, the incidence of pancreatic cancer was still higher in subjects with DM. The incidence of pancreatic cancer was higher in patients with diabetic duration less than 2 years, as compared to the non-diabetic group (27.81 *vs* 6.96 per 10 000 person-years, 95%CI = 2.11–7.54). After 2 years of diabetes diagnosis, however, there was no statistical significance in the incidence between the diabetic group and the non-diabetic group (1.21 *vs* 0.86 per 10 000 person-years, 95%CI = 0.96–2.03).

Pancreatic cancer and comorbidities by univariate and multivariate Cox proportional hazard analysis

Adjusted hazard ratios and 95%CI of pancreatic cancer associated with DM and comorbidities are shown in Table 3. The adjusted HR of pancreatic cancer for patients with DM was 1.77 (95%CI = 1.29–2.43). Chronic pancreatitis (HR = 19.40, 95%CI = 10.36–36.30), gallstones (HR = 2.56, 95%CI = 1.71–3.82), and hepatitis C infection (HR = 3.08, 95%CI = 1.74–5.44)

Table 1 Baseline characteristics between diabetic group and non-diabetic group identified in 1998–2007

	Diabetes				*P*-value†
	No (*n* = 199 212)		Yes (*n* = 49 803)		
	n	%	*n*	%	
Sex					1.000
Women	91 984	46.17	22 996	46.17	
Men	107 228	53.83	26 807	53.83	
Age group (years)					1.000
20–39	17 060	8.56	4 265	8.56	
40–64	132 688	66.61	33 172	66.61	
≥ 65	49 464	24.83	12 366	24.83	
Mean (SD)	55.92	(12.23)	55.92	(12.23)	1.000
Comorbidities					
Obesity	1 249	0.63	1 208	2.43	< 0.001
Chronic pancreatitis	322	0.16	262	0.53	< 0.001
Alcoholism	2 251	1.13	930	1.87	< 0.001
Gallstones	9 637	4.84	3 145	6.31	< 0.001
Hepatitis B	5 256	2.64	1 689	3.39	< 0.001
Hepatitis C	3 374	1.69	1 319	2.65	< 0.001

†χ^2-test comparing patients with and without diabetes.

Table 2 Incidence density of pancreatic cancer estimated by sex, age, and follow-up years for diabetic group and non-diabetic group in 1998–2007

	Non-diabetes				Diabetes					
	n	Case	Person-years	Incidence rate†	*n*	Case	Person-years	Incidence rate†	IRR‡	(95%CI)
All	199 212	125	1 255 365	1.00	49 803	56	313 732	1.78	1.79	(1.53–2.10)
Sex										
Women	91 984	61	616 911	0.99	22 996	25	154 184	1.62	1.64	(1.03–2.61)
Men	107 228	64	638 453	1.00	26 807	31	159 547	1.94	1.94	(1.26–2.98)
Age group (years)										
20–39	17 060	1	90 479	0.11	4 265	2	22 614	0.88	8.00	(0.73–88.22)
40–64	132 688	72	793 226	0.91	33 172	33	198 238	1.66	1.83	(1.21–2.77)
≥ 65	49 464	52	371 659	1.40	12 366	21	92 879	2.26	1.62	(0.97–2.68)
Follow-up years										
< 2	27 594	19	27 298	6.96	6 911	19	6 831	27.81	3.99	(2.11–7.54)
≥ 2	171 574	106	1 228 067	0.86	42 881	37	306 901	1.21	1.40	(0.96–2.03)

†Incidence rate: per 10 000 person-years.
‡IRR: diabetes *vs* non-diabetes (95%CI).
CI, confidence interval; IRR, incidence rate ratio.

Table 3 Crude and adjusted HR and 95%CI of pancreatic cancer associated with diabetes and covariates during 1998–2007

Variable	Crude HR	95%CI	Adjusted HR†	95%CI
Sex (women *vs* men)	1.23	0.91–1.65	—	—
Age group (years)‡				
20–39	1.00		1.00	
40–64	5.37	1.32–21.75	5.22	1.29–21.17
≥ 65	8.10	1.99–33.01	7.59	1.86–31.00
Diabetes (yes *vs* no)	1.93	1.41–2.65	1.77	1.29–2.43
Comorbidities				
Obesity (yes *vs* no)	2.06	0.66–6.44	—	—
Chronic pancreatitis (yes *vs* no)	28.12	15.27–51.76	19.40	10.36–36.30
Alcoholism (yes *vs* no)	0.50	0.07–3.57	—	—
Gallstones (yes *vs* no)	3.52	2.39–5.19	2.56	1.71–3.82
Hepatitis B (yes *vs* no)	0.92	0.34–2.49	—	—
Hepatitis C (yes *vs* no)	3.85	2.19–6.77	3.08	1.74–5.44

†Adjusted HR: adjusted for age, chronic pancreatitis, gallstones and hepatitis C infection.
‡Tests for trend in hazard ratios across age group in univariate and multivariate Cox proportional hazard models ($P = 0.0005$ and $P = 0.001$).
CI, confidence interval; HR, hazard ratio.

were also significant factors predicting pancreatic cancer. When compared with subjects aged 20–39, subjects aged 40–64 and subjects aged 65 and older also had higher HR of pancreatic cancer (HR = 5.22, 95%CI = 1.29–21.17 and HR = 7.59, 95%CI = 1.86–31.00, respectively).

Interaction between diabetes and comorbidities

The case number was too small for hepatitis C infection. Therefore, we combined the status of hepatitis C infection together. Table 4 shows stratified analyses by the status of DM, chronic pancreatitis, gallstones and/or hepatitis C infection for hazards associated with pancreatic cancer controlling for age. There were synergistic effects on the pancreatic cancer hazards between factors. Subjects comorbid with DM and chronic pancreatitis had the highest HR of pancreatic cancer, as compared with subjects without these comorbidities (HR = 33.52, 95%CI = 10.61–105.94).

Influence of anti-diabetic drugs on the risk of pancreatic cancer

Table 5 shows the effects of anti-diabetic drugs on the risk of pancreatic cancer. After adjustments for potential confounders, there was no significant association between use of anti-diabetic drugs and the risk of pancreatic cancer.

Discussion

This study is not novel as many data on the risk of pancreatic cancer in diabetics have already been published, but it brings into this knowledge a very large sample from Taiwan. Prior studies have demonstrated that DM patients are at a 2.37- to 3.22-fold

Table 4 Interaction effect on pancreatic cancer between diabetes and comorbidities in 1998–2007

Diabetes	Chronic pancreatitis	Gallstones	Hepatitis C	Adjusted HR†	(95%CI)
No	No	No	No	1.00	(Reference)
No	No	No	Yes	2.83	(1.15–6.94)
No	No	Yes	No	1.73	(0.90–3.31)
No	No	Yes	Yes	14.38	(5.86–35.31)
No	Yes	No	No/Yes	29.28	(10.77–79.59)
No	Yes	Yes	No/Yes	16.79	(2.34–120.35)
Yes	No	No	No	1.48	(1.01–2.17)
Yes	No	No	Yes	5.01	(1.59–15.81)
Yes	No	Yes	No	6.44	(3.53–11.72)
Yes	No	Yes	Yes	8.02	(1.12–57.51)
Yes	Yes	No	No/Yes	33.52	(10.61–105.94)
Yes	Yes	Yes	No/Yes	32.36	(4.51–232.04)

†Adjusted for age.
CI, confidence interval; HR, hazard ratio.

Table 5 Cox proportional HR and 95%CI of pancreatic cancer associated with anti-diabetic drugs during 1998–2007

	n	Case	Person-years	Incidence rate†	Crude HR	95%CI
Insulins						
Non-use	38 000	43	218 057	1.97	1.00	
Use	11 803	13	95 675	1.36	0.68	0.36–1.27
Metformin						
Non-use	7 049	7	34 004	2.06	1.00	
Use	42 754	49	279 728	1.75	0.85	0.39–1.89
Sulfonylureas						
Non-use	8 032	6	31 721	1.89	1.00	
Use	41 771	50	282 011	1.77	0.96	0.41–2.26
Thiazolidinediones						
Non-use	37 544	40	216 413	1.85	1.00	
Use	12 259	16	97 319	1.64	0.89	0.50–1.59
Alpha-glucosidase inhibitors						
Non-use	37 502	37	220 933	1.67	1.00	
Use	12 301	19	92 799	2.05	1.22	0.70–2.13

†Incidence rate: per 10 000 person-years.
CI, confidence interval; HR, hazard ratio.

increased risk of pancreatic cancer,[7,12,13] which is consistent with our observation (HR = 1.77). Although the risk varied moderately among studies, DM really correlates with increased risk of pancreatic cancer.

This study also showed that patients with a diabetic duration less than 2 years had higher incidence of pancreatic cancer (27.81 per 10 000 person-years, 95%CI = 2.11–7.54). However, after 2 years of diabetes diagnosis, there was no statistical significance in the incidence between the diabetic group and the non-diabetic group. Prior studies have shown that new-onset diabetes with $\leq$ 2 years' duration is significantly associated with the risk of pancreatic cancer.[18–21] According to the above findings, new-onset DM of $\leq$ 2 years may be an early manifestation of pancreatic cancer, rather than a risk factor. Thus, these patients with a short duration of diabetes should receive close follow up for the potential of pancreatic cancer.

The previous literature has consistently reported the association of pancreatic cancer with other comorbidities, such as chronic pancreatitis, alcoholism, gallstones, and hepatitis B infection.[3,5–9] In fact, our study also demonstrated a strong association with chronic pancreatitis (HR = 19.40), followed by hepatitis C infection (HR = 3.08) and gallstones (HR = 2.56). These findings further confirm that pancreatic cancer is a disease with multifactorial causes. We did not find an association between hepatitis B infection and pancreatic cancer, however, we found that hepatitis C infection increased the risk of pancreatic cancer, which was contrary to the prior study.[22] Hassan *et al*. found that the odds ratio for pancreatic cancer in patients with past exposure to hepatitis B increased to 7.1 (95%CI = 1.7- 28.7), but dropped to 0.9 in patients with past exposure to hepatitis C (95%CI = 0.3–2.8).[22]

In particular, further analysis showed that diabetic patients comorbid with chronic pancreatitis had a 33.5-fold higher risk of developing pancreatic cancer (95%CI = 10.61–105.94), compared with people without DM, chronic pancreatitis, gallstones and hepatitis C infection. These findings further indicate a synergistic effect on the development of pancreatic cancer between DM and

other comorbidities. These high-risk patients should undergo close follow-up programs for pancreatic cancer.

In further analysis, we found no significant association between use of anti-diabetic drugs and a reduced risk of pancreatic cancer. In the study by Hassan *et al*. in the USA,[7] patients using only insulins or using only oral anti-diabetic drugs had 5.9-fold and 1.9-fold risk of pancreatic cancer (95%CI = 1.7–21.1 and 95%CI = 1.3–2.8, respectively). In contrast, although this present study shows a 32% risk reduction in patients using insulins, the association was not statistically significant. Because the role of anti-diabetic drugs on the risk of pancreatic cancer remains unproven and because this is an observational study, we cannot make an expanded explanation of why there was no association between use of anti-diabetic drugs and the risk of pancreatic cancer in Taiwan. More prospective clinical trials are required to definitively address this issue.

The limitations of this present study should be addressed. First, the claims data used in this study do not contain smoking data. The inability to account for this factor may result in certain degrees of bias from confounding. Second, there was no HbA1c data in this claims dataset, a marker of diabetes control, so we could not assess the degree of diabetes control when pancreatic cancer was diagnosed. However, there are marked strengths in this study. Because the incidence of pancreatic cancer is low, it is required to use a large sample to increase the statistical power. This population-based cohort study used the Taiwan National Health Insurance dataset with a large sample size to investigate the natural history of pancreatic cancer development in diabetic patients.

Conclusion

We made five important findings: (i) diabetes of ≤ 2 years' duration is associated with pancreatic cancer and could be an early manifestation of pancreatic cancer; (ii) long-standing diabetes is not found to be a risk factor for pancreatic cancer in Taiwan's patients; (iii) old age, chronic pancreatitis, gallstones and hepatitis C infection are other risk factors for pancreatic cancer; (iv) diabetic patients comorbid with chronic pancreatitis, have a 33.5-fold higher risk of developing pancreatic cancer; and (v) there was no significant association between use of anti-diabetic drugs and the risk of pancreatic cancer.

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