Risk of Malignant Neoplasm of the Pancreas in Relation to Diabetes

A population-based study in Taiwan

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OBJECTIVE—We prospectively assessed the age- and sex-specific incidence and relative risk of malignant neoplasm of the pancreas in Taiwan's diabetic population.

RESEARCH DESIGN AND METHODS—A total of 615,532 diabetic patients and 614,871 age- and sex-matched control subjects were linked to inpatient claims (2000–2006) to identify the admissions for malignant neoplasm of the pancreas (ICD-9: 157). The Cox proportional hazards regression model was used to estimate the age- and sex-specific relative risk of pancreatic neoplasm.

RESULTS—Compared with the control group, the diabetic patients had a significantly increased risk of pancreatic cancer (hazard ratio [HR] 1.54 [95% CI 1.39–1.71]). The higher and significant age-specific HRs were observed in diabetic men (1.91) and women (1.80) aged 45–65 years.

CONCLUSIONS—Middle-aged diabetic men and women were associated with the most increased risk of malignant neoplasm of the pancreas.

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Malignant neoplasm of the pancreas, a cancer with a high case-fatality rate (1), has been observed to be associated with diabetes. Some studies (2–6) reported that diabetes is a risk factor for pancreatic cancer, but others (7,8) concluded that diabetes is simply a consequence of pancreatic cancer. As a result of fewer cases of pancreatic cancer included in previous studies, most of the previous analyses were unable to provide reliable estimates of the incidence rate and relative risk of malignant neoplasm of the pancreas in diabetes, according to different age and sex stratifications. The current study used a national cohort retrieved from Taiwan's National Health Insurance database to prospectively investigate the age- and sex-specific incidence rates and relative risks of pancreatic cancer in Taiwan's diabetic population between 2000 and 2006.

RESEARCH DESIGN AND METHODS

—Details of claim data and methods of selection of diabetic and control groups were described in our previous report (9). In brief, an individual was classified as a diabetic patient if she or he had an initial diabetes diagnosis (ICD-9: 250 or a code 181) at any time in 2000 and then experienced another one or more diagnoses within the subsequent 12-month follow-up periods. The first and last outpatient visits within 1 year must be >30 days apart to avoid accidental inclusion of miscoded patients. We further excluded those patients admitted for malignant neoplasm (ICD-9: 140–208) during 1997–1999, resulting in the final diabetic cohort of 615,532 patients, and the index date was the date of their first outpatient visit for diabetes in 2000.

A total of 614,871 age- and sex-matched control subjects were randomly selected from the registry of beneficiaries after excluding those who were included in the diabetic ambulatory care claim or hospitalized for any kind of malignancy between 1997 and 1999. The index date for control subjects was the first day (for those enrolled prior to 2000) or the first date of enrollment to the National Health Insurance in 2000.

We linked study subjects in both diabetic and control groups to the inpatient claim data from 2000 to 2006 to identify the possible onset of primary or secondary diagnoses of malignant neoplasm of the pancreas (ICD-9: 157). To account for the biologically relevant link between diabetes and pancreatic cancer, we retrieved only pancreatic neoplasm admission 1 year after the index date. The date of encountering pancreatic cancer was the 1st day of hospitalization.

The age- and sex-specific hazard rates were determined under the Poisson assumption. To assess the independent effects of diabetes on the risks of malignant neoplasm of the pancreas, we conducted Cox proportional hazards regression models with age, sex, geographic area, urbanization statuses, and various gastric and hepatobiliary comorbidities adjusted simultaneously in the model. All statistical analyses were performed with SAS (version 9.1; SAS Institute, Cary, NC). A P value <0.05 was considered statistically significant.

RESULTS

—The overall incidence density for diabetic men and women was 3.34 and 2.58 per 10,000 patient-years, respectively, whereas the corresponding figures for control men and women were 1.88 and 1.71 per 10,000 patient-years, respectively. Irrespective of sex, the incidence density increased with age in both diabetic and control groups, and the highest incidence density was observed in those aged >65 years.

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Compared with the control subjects, diabetic patients showed significantly increased risks of malignant neoplasm of the pancreas, with an adjusted hazard ratio (HR) of 1.54 (95% CI 1.39–1.71). The adjusted HR was higher in diabetic men (1.66 [1.44–1.91]) than in diabetic women (1.43 [1.23–1.65]). Because there was a significant interaction of diabetes with age ($P < 0.0001$) for both men and women, we performed the stratified analyses to estimate the age-specific HRs for each sex. The higher and significant age-specific adjusted HRs were observed in diabetic men and women aged 45–65 years (1.91 [1.52–2.39] and 1.80 [1.37–2.36], respectively) (Table 1).

CONCLUSIONS—Compared with the age- and sex-matched control group, the incidence of malignant neoplasm of the pancreas was higher in the diabetic patients in all age and sex stratifications. In addition, the incidence densities of pancreatic neoplasm increased with age irrespective of age and those aged >65 years had the highest incidence density in both sexes. Meanwhile, the overall relative risk of pancreatic neoplasm was significantly increased in both male and female diabetic patients, even after adjustment for potential confounders. Generally, the relative risk of diabetic patients noted in our study was comparable with those of population-based cohort studies (2,3,5,6). Although Chow et al. (2) indicated that diabetic women had slightly higher HRs of pancreatic cancer, our study found that diabetic men had a higher relative risk of pancreatic neoplasm, which was consistent with the results from some previous studies (3,5). Because 69% of pancreatic cancers are diagnosed after the age of 65 years (1), there were fewer cases of pancreatic cancers in the middle-aged population. Thus, the higher HR observed in middle-aged patients (i.e., 45–64 years) could be attributed to a low incidence density of pancreatic cancer in middle-aged control subjects, which also may be a valid argument for a high but insignificant HR in young (aged <45 years) patients.

Although we could not differentiate between type 1 and type 2 diabetes in our study, type 1 diabetes constitutes only 1.8% of all diabetes in Taiwan (10). Therefore, the majority of diabetic patients in our study are likely to be type 2 diabetic patients. The possible underlying biologic mechanism with which type 2 diabetes may cause malignant neoplasm

Table 1—*Overall and age- and sex-specific incidence densities and relative hazards of malignant neoplasm of pancreas (ICD-9: 157) in diabetic and control groups*

	Control group			Diabetic group				
Variables*	Patients (*n*)	Events (*n*)	Incidence density (per 10,000 patient-years) (95% CI)†	Patients (*n*)	Events (*n*)	Incidence density (per 10,000 patient-years) (95% CI)†	Crude HR (95% CI) in association with diabetic group‡	Adjusted HR (95% CI) in association with diabetic group§
Men								
Age (years)								
<45	40,537	7	0.26 (0.07–0.45)	40,537	14	0.54 (0.26–0.83)	2.10 (0.85–5.81)	1.92 (0.76–4.89)
45–65	141,899	120	1.28 (1.05–1.51)	141,899	222	2.46 (2.14–2.78)	1.93 (1.55–2.41)	1.91 (1.52–2.39)
>65	113,127	193	2.66 (2.28–3.03)	113,129	256	3.71 (3.25–4.16)	1.40 (1.16–1.69)	1.47 (1.21–1.77)
Total	295,563	320	1.88 (1.68–2.07)	295,566	492	3.34 (3.08–3.60)	1.62 (1.40–1.86)	1.66 (1.44–1.91)
Women								
Age (years)								
<45	29,080	2	0.10 (−0.04 to 0.25)	29,079	10	0.54 (0.21–0.87)	5.15 (1.13–23.50)	4.46 (0.96–20.70)
45–65	154,911	83	0.81 (0.63–0.98)	154,911	142	1.43 (1.20–1.67)	1.78 (1.36–2.34)	1.80 (1.37–2.36)
>65	135,317	232	2.62 (2.28–2.95)	135,318	274	3.23 (2.85–3.61)	1.24 (1.04–1.47)	1.26 (1.06–1.51)
Total	319,308	317	1.71 (1.54–1.89)	319,310	426	2.58 (2.36–2.80)	1.40 (1.21–1.62)	1.43 (1.23–1.65)
Overall	614,871	637	1.79 (1.66–1.92)	615,532	918	2.94 (2.77–3.11)	1.51 (1.36–1.67)	1.54 (1.39–1.71)

Data are HR (95% CI) unless otherwise indicated. *Inconsistency between total population and population summed for individual variable was a result of missing information. †Based on the Poisson assumption. ‡Based on Cox proportional hazards regression without adjustment. §Based on Cox proportional hazards regression with adjustment for age, sex, and geographic area and urbanization status; status of hepatitis B, hepatitis C, cholecystitis, cholangitis, cholelithiasis, choledocholithiasis, cholecystectomy, gastric ulcer, and duodenal ulcer; and gastrectomy.

of the pancreas has not been fully elucidated. Insulin resistance and accompanying compensatory hyperinsulinemia might increase local blood flow and cell division in the pancreas (11). They also might promote the growth of pancreatic cell lines (12).

In conclusion, over a 7-year study period, diabetic men and women in Taiwan were observed to experience significantly increased risks of malignant neoplasm of the pancreas. Diabetic men and women aged 45–65 years were found to experience the most increased age-specific HRs.

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H.-F.C. wrote the manuscript and researched data. P.C. contributed to the discussion and reviewed and edited the manuscript. C.-Y.L. researched data and reviewed and edited the manuscript.

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