Diabetes Mellitus and Pancreatic Cancer in a Population-Based Case-Control Study in the San Francisco Bay Area, California

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Abstract

Background: **Diabetes has been postulated to be both a risk factor and a consequence of pancreatic cancer, but the degree of risk and associated clinical factors remain unclear.**
Methods: **We conducted a population-based case-control study of pancreatic cancer in the San Francisco Bay Area between 1995 and 1999. Rapid case ascertainment through the Surveillance, Epidemiology and End Results registry for cases and random selection from the general population for controls were employed to identify study participants with no proxy interviews.**
Results: **Five hundred thirty-two cases and 1,701 controls were interviewed. Participants with pancreatic cancer were more likely to report a history of diabetes (13%) than were controls [9%; odds ratio (OR), 1.5; 95% confidence interval (95% CI), 1.1-2.1]. Compared with diabetics in the control group, diabetics in the case group had a shorter duration of diabetes (P = 0.0003) and a larger proportion of insulin users (P = 0.002). Risk for pancreatic cancer varied with duration of diabetes (OR, 2.4; 95% CI, 1.4-4.0 for 1-4 years; OR, 2.0; 95% CI, 1.2-3.4 for 5-9 years; and OR, 0.86; 95% CI, 0.52-1.4 for ≥10 years diabetes duration; P_{trend} = 0.004). Among diabetics, use of oral diabetes medication or insulin for ≥5 years was not associated with pancreatic cancer, but insulin use of <5 years was associated with a 6.8-fold risk for pancreatic cancer (95% CI, 3.7-12).**
Conclusion: **Recent-onset diabetes may be a complication or an early marker of pancreatic cancer. Diabetes of short duration with insulin use conferred a substantially elevated risk for pancreatic cancer and may reflect insulin resistance that is elicited by pancreatic cancer.** (Cancer Epidemiol Biomarkers Prev 2006;15(8):1458–63)

Introduction

Pancreatic cancer is diagnosed in nearly 34,000 individuals per year in the United States, and the overall 5-year survival rate is <4% (1). Although 5-year survival of 15% has been shown in highly selected clinic populations among patients who have localized disease (1), pancreatic cancer is difficult to diagnose at an early, resectable stage, and candidates for surgery comprise <15% of all cases (2). Chemoradiotherapy offers limited benefit (3). Newer molecular therapies, including gene therapy, antiangiogenic agents, immunotherapy, and inhibitors of cell signaling potentially, may be effective but still are under development (4). The relative improvement in duration of survival associated with earlier stage of pancreatic cancer motivates the search for effective early detection tools. Identification of individuals at high risk for pancreatic cancer and prevention by identification of modifiable risk factors may allow for early interventions that will decrease pancreatic cancer morbidity and mortality.

Diabetes has been postulated to be both a risk factor for and a consequence of pancreatic cancer (5-22). Meta-analyses of cohort and case-control studies with >10 years of follow-up have shown that patients with prevalent diabetes have approximately twice the risk of developing pancreatic cancer compared with those without diabetes after censoring of pancreatic cancer diagnosed in the first year of follow-up (5, 13).

Data also suggest that pancreatic cancer may be a cause of new-onset diabetes. Case-control studies show that patients with pancreatic cancer have an increased risk for new diagnoses of diabetes, especially within 3 years before their cancer diagnosis (6, 23). Other cohort studies have reported an association between new-onset diabetes and cancer, but conclusions about the strength of this association are limited by the small number of incident cases of pancreatic cancer in cohort studies (21-23).

Overall, prior data suggest that diabetes may be a marker for pancreatic cancer in some individuals and a risk factor for others. If diabetic individuals at highest risk for pancreatic cancer could be identified through knowledge of epidemiologic and clinical characteristics, targeted surveillance of this population might potentially identify early-stage, resectable pancreatic cancer and thereby improve pancreatic cancer-associated survival.

Few large population-based studies have compared the characteristics (including clinical features) of diabetics with pancreatic cancer to those without cancer. We conducted the current analyses as part of a large, population-based case-control study in the San Francisco Bay Area to examine the relationship between diabetes and pancreatic cancer with particular attention to duration of diabetes and treatment requirements.

Materials and Methods

Study Population. Detailed methods for this case-control study have been published elsewhere (24-28). A brief summary

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of methods follows. Cases were individuals with newly diagnosed pancreatic cancer identified by the Northern California Cancer Center between 1995 and 1999 in the San Francisco Bay Area using rapid case ascertainment. Diagnoses of pancreatic cancer were confirmed by participants' physicians and by the Surveillance, Epidemiology and End Results abstracts that included histologic confirmation of cancer. All pancreatic cancer patients in the six counties of the San Francisco Bay Area, alive at first contact, 21 to 85 years of age, and able to complete an interview in English were eligible to be cases. Additional pancreatic cancer patients were included who were seen in the oncology clinics at the University of California San Francisco and who met all eligibility criteria except for residence.

Control participants were selected from the target population using random-digit dial and were frequency matched to cases by sex and age within 5-year categories. Controls older than 65 years were supplemented by random selection from the Health-Care Finance Administration lists. Sixty-seven percent of eligible cases and 67% of eligible controls completed an in-person interview and answered questions in standardized questionnaires. No proxy interviews were done. Written consent was obtained from each study participant before the interview. This study was reviewed and approved by the University of California institutional review board.

Data on Diabetes Mellitus. The structured interview contained extensive questions about diabetes, including presence or absence of diabetes diagnosed by a physician that lasted 1 year or longer before pancreatic cancer diagnosis, age of diabetes diagnosis, use of insulin for glycemic control, first age, last age, and total duration of insulin use if present, use of oral hypoglycemic medication, first age, last age, and total duration of oral hypoglycemic use. Duration of diabetes was grouped as 1 to 4, 5 to 9, and ≥10 years. Total years of treatment was categorized as <5 and ≥5 years for both insulin and oral diabetic medication.

Statistical Methods. Odds ratios (OR) and 95% confidence intervals (95% CI) were used as an estimate of the relative risk (hereafter called risk) for pancreatic cancer associated with diabetes and diabetes-related factors. Unconditional logistic regression was applied to compute ORs and 95% CIs. All statistical tests were two sided with $\alpha \leq 0.05$ considered as significant and all analyses were done using SAS V8.0 (SAS Institute, Inc., Cary, NC).

Potential confounders that were considered included race, adult body-mass index, physical activity, cigarette smoking, and alcohol consumption. Race was categorized as white, black/African American, and Asian/Pacific Islander/Other. Body-mass index was estimated from adult weight and height [weight (kg)/height (m^2)]. Body-mass index was categorized by quartiles among controls: ≤22.1, 22.2-24.2, 24.3-26.5, and ≥26.6; and by WHO categories: ≤25, 25.1-30, and >30. Frequency of non-occupation-related physical activity that lasted at least 30 minutes each episode was recorded as never or <1/mo, 1-2/mo, 3-4/mo, 2-3/wk, and daily or almost daily. Participants were defined as smokers if they had smoked ≥100 cigarettes, cigars at least once a month for ≥6 months, or pipes at least once a month for ≥6 months in their lifetime. Cigarette smokers were defined as never smoker, former smoker, and current smoker. Because one can, bottle, or 12-oz. glass of beer, one 4-oz. glass of wine, and one shot of liquor contain approximately the same amount of alcohol, each was defined as one drink. Alcohol consumption was computed as the average drinks weekly over the past two decades and the current decade, and was categorized as never drinker, ≤21, and >21 drinks per week. As none of the factors mentioned above was a confounder for the association between pancreatic cancer and diabetes mellitus, the final model was adjusted only for sex and age.

Results

Five hundred thirty-two cases and 1,701 control participants completed the interview and were included in the final analysis. Thirteen percent of cases (68 of 532) and 9% of controls (150 of 1,701) reported a history of diabetes. Sex, body mass index, and family history of diabetes were similarly distributed among cases and controls with diabetes (Table 1). Diabetics in the case group had a shorter duration of diabetes (mean, 7.6 versus 12.1 years; $P = 0.0003$) and older age at diagnosis of diabetes (mean, 60 versus 57 years; $P = 0.05$) than

Table 1. Characteristics of diabetes mellitus patients, population-based case control study of pancreatic cancer, San Francisco Bay Area, California

Characteristic	Diabetics with pancreatic cancer (n = 68)	Diabetics without pancreatic cancer (n = 150)	P
Sex			
Men	40 (59%)	91 (61%)	
Women	28 (41%)	59 (39%)	0.80
Race			
White	47 (69%)	128 (85%)	
Black	14 (21%)	10 (7%)	
Asian/Pacific Islander/other	7 (10%)	12 (8%)	0.007
Body-mass index, kg/m^2 (range)			
Mean ± SD	27.7 ± 4.5	27.3 ± 4.6	0.52
Quartile 1 (≤22.1)	3 (4%)	20 (13%)	
Quartile 2 (22.2-24.2)	14 (21%)	21 (14%)	
Quartile 3 (24.3-26.5)	16 (24%)	30 (20%)	
Quartile 4 (≥26.6)	35 (51%)	79 (53%)	0.17
Diabetes duration, y			
Mean ± SD	7.6 ± 5.6	12.1 ± 9.4	0.0003
Diabetes diagnosis age, y			
Mean ± SD	60.4 ± 10.1	57.0 ± 12.5	0.05
≥50 y old at diagnosis	58 (85%)	110 (73%)	0.05
Insulin use			
Yes	39 (57%)	53 (35%)	0.002
Years of use (mean ± SD)	2.9 ± 4.1	9.2 ± 7.5	<0.0001
Years between diabetes diagnosis and initial use of insulin (mean ± SD)	4.2 ± 5.2	5.7 ± 6.2	0.23
Family history of diabetes	25 (38%)	53 (36%)	0.83

Table 2. ORs and 95% CIs for pancreatic cancer and history of diabetes mellitus, population-based case control study, San Francisco Bay Area, California

	All			Men			Women		
	Case	Control	OR* (95% CI)	Case	Control	OR* (95% CI)	Case	Control	OR* (95% CI)
Diabetes									
No †	455	1,538	1.0 (reference)	245	785	1.0 (reference)	210	753	1.0 (reference)
Yes	68	150	1.5 (1.1-2.1)	40	91	1.4 (0.96-2.2)	28	59	1.7 (1.0-2.7)
Borderline	8	11	2.4 (0.97-6.1)	5	6	2.7 (0.82-9.0)	3	5	2.1 (0.50-8.9)
Diabetes diagnosis age (y)									
<50	10	40	0.85 (0.42-1.7)	5	21	0.76 (0.28-2.0)	5	19	1.0 (0.37-2.8)
50-59	20	40	1.7 (0.97-2.9)	15	24	2.0 (1.0-3.9)	5	16	1.1 (0.4-3.0)
≥60	38	70	1.8 (1.2-2.8)	20	46	1.5 (0.84-2.6)	18	24	2.5 (1.3-4.8)
Diabetes duration (y)									
1-4	25	35	2.4 (1.4-4.0)	14	19	2.4 (1.2-4.9)	11	16	2.4 (1.1-5.3)
5-9	23	38	2.0 (1.2-3.4)	12	26	1.5 (0.75-3.0)	11	12	3.2 (1.4-7.5)
≥10	20	77	0.86 (0.52-1.4)	14	46	1.0 (0.54-1.9)	6	31	0.68 (0.28-1.6)
Trend *P*		*P* = 0.004			*P* = 0.06			*P* = 0.03	

*Adjusted for age and sex.
†Reference group for all comparisons.

diabetics in the control group. A greater proportion of diabetic cases (57%) reported insulin use than diabetic controls (35%; $P = 0.002$) and diabetic cases had a shorter duration of insulin use (2.9 years) than diabetic controls (9.2 years; $P < 0.0001$). The interval between diabetes diagnosis and insulin use was shorter for the diabetic case group (mean, 4.2 years) than the diabetic control group (mean, 5.7 years).

Compared with participants without diabetes, the risk for pancreatic cancer among participants with diabetes was 1.5 (95% CI, 1.1-2.1; Table 2). Similar results were seen in men and women. The association between the two diseases was notable after age 50 in men and after age 60 in women. The risk for pancreatic cancer was 2.4 for diabetics with 1 to 4 years of diabetes, 2.0 for 5 to 9 years, and 0.86 for ≥10 years of diabetes. Increasing duration of diabetes was significantly associated with decreasing risk for pancreatic cancer ($P_{trend} = 0.004$). Risk for the overall association between pancreatic cancer and diabetes mellitus may differ by race as a nearly 3-fold increased risk was observed among black/African Americans (95% CI, 1.1-7.3; Table 3).

Most participants with diabetes in this study reported oral medication use alone or in combination with insulin for treatment of diabetes. The risk for pancreatic cancer among diabetics who reported sole use of oral medication was not different from participants without diabetes (Table 4). The risk for diabetics treated with insulin alone was elevated (OR, 1.9) but 95% CI overlapped unity. Diabetics who reported the use of a combination of oral medication and insulin had 2.5 times the risk for pancreatic cancer compared with controls (95% CI, 1.6-4.0). There was a nearly 7-fold elevation in risk for pancreatic cancer among diabetics who took insulin alone or with oral medication for <5 years (95% CI, 3.7-12) but no elevation of risk among diabetics who took insulin alone or with oral medication for ≥5 years.

Separate analyses for diabetic patients stratified by whether or not they were treated with insulin showed that among insulin-treated diabetics, the risk for pancreatic cancer was 10-fold for 1 to 4 years of diabetes, 4.8 for 5 to 9 years of diabetes, and 1.2 for ≥10 years of diabetes ($P_{trend} = 0.0003$; Table 5). However, among diabetic patients not treated with insulin, no notable trend was observed based on duration of diabetes.

Discussion

Our population-based case-control study has identified that recent-onset diabetes, but not diabetes of ≥10-year duration, is associated with an increased risk for pancreatic cancer. Additionally, increased severity of diabetes, as reflected by requirement for insulin therapy alone or insulin plus oral antiglycemic-agent therapy, conferred an increased risk for pancreatic carcinoma, particularly among persons with diabetes of recent onset.

The current estimation of the overall risk of pancreatic cancer among diabetics is consistent with the up to 2-fold increase in risk reported by other investigators (5-22) and supports previous work that has identified an inverse temporal relationship between diabetes and pancreatic cancer with cancer-associated risk decreasing with increasing duration of diabetes (5, 13, 16, 29-32) Because of rapid case ascertainment, use of in-person interviews rather than proxy, and population-based sampling, our observations are robust

Table 3. ORs and 95% CIs for pancreatic cancer and prior history of diabetes mellitus by race, population-based case control study, San Francisco Bay Area, California

	White			Black/African American			Asian/Pacific Islander/other		
	Case	Control	OR* (95% CI)	Case	Control	OR* (95% CI)	Case	Control	OR* (95% CI)
Diabetes									
No †	388	1,333	1.0 (reference)	31	65	1.0 (reference)	36	140	1.0 (reference)
Yes	47	128	1.2 (0.87-1.8)	14	10	2.9 (1.1-7.3)	7	12	2.1 (0.76-5.9)
Diabetes duration (y)									
1-4	17	28	2.1 (1.1-3.8)	5	3	3.4 (0.75-15)	3	4	2.6 (0.55-13)
5-9	16	31	1.7 (0.93-3.2)	5	3	3.7 (0.81-17)	2	4	1.7 (0.29-9.9)
≥10	14	69	0.68 (0.38-1.2)	4	4	2.0 (0.47-8.8)	2	4	2.0 (0.35-12)
Trend *P*		*P* = 0.007			*P* = 0.62			*P* = 0.69	

*Adjusted for age and sex.
†Reference group for all comparisons.

Table 4. ORs and 95% CIs for pancreatic cancer and treatment for diabetes mellitus, population-based case control study, San Francisco Bay Area, California

	Case	Control	OR* (95% CI)
No diabetes †	455	1,538	1.0 (reference)
Treatment for diabetes			
Exercise and/or diet alone	2	6	1.1 (0.23-5.6)
Medication alone	27	91	0.98 (0.63-1.5)
Insulin alone	4	7	1.9 (0.55-6.5)
Medication and insulin combined	35	46	2.5 (1.6-4.0)
Total years of medication alone			
<5	19	48	1.3 (0.77-2.3)
≥5	8	43	0.62 (0.29-1.3)
Total years of insulin ‡			
Men + women			
<5	33	16	6.8 (3.7-12)
≥5	6	37	0.54 (0.23-1.3)
Men			
No diabetes	245	785	1.0 (reference)
<5	19	12	5.2 (2.5-11)
≥5	5	20	0.81 (0.30-2.2)
Women			
No diabetes	210	753	1.0 (reference)
<5	14	4	12 (3.9-37)
≥5	1	17	0.21 (0.03-1.6)

*Adjusted for age and sex.
†Reference group for all comparisons.
‡Combined with or without oral medication.

and lend further support to the hypothesis that diabetes may often be a consequence rather than a cause of pancreatic cancer, or an early marker of the disease (6, 10, 16, 20-23, 33, 34).

Our results extend the results of prior case-control and cohort studies by assessing the association between medication use for diabetes and pancreatic cancer risk. Few studies have closely examined the potential interaction of the presence, type, and intensity of diabetes medication use with risk for pancreatic carcinoma. An Italian hospital–based case-control study with 720 case and 720 control participants documented similar proportions of participants who used insulin or oral diabetic medication (16). For oral medications, it is possible that the use of hospital-based controls (who, if diabetic, might be expected to have more severe diabetes) may have biased results towards the null. A population-based case-control study with direct interviews in the United States, similar in scope and methods to our study, reported that treatment for diabetes, including oral medications or insulin, did not confer increased risk for pancreatic cancer diagnosis (35). However, similar to our results, this study reported that shorter duration of insulin use was associated with pancreatic cancer, with a nearly 3-fold increased risk for <4 years of use, a 2-fold increase risk for 5 to 9 years of use, and no association with longer use (35), although their risk estimates were not as high as ours. Another population-based case-control study found no association between diabetes and pancreatic cancer, or interaction between type of diabetes medication and risk of pancreatic cancer, except among men with diabetes treated with insulin, although this study included few cases or controls with diabetes (36). A cohort study of diabetics who were insulin dependent at baseline identified an increased risk for pancreatic cancer in the cohort. However, because all study participants were insulin dependent at study outset, the investigators could not evaluate insulin treatment as a potential effect modifier (37). A nested case-control study evaluating the incidence of pancreatic cancer following diabetes diagnosis collected medication data on the 18 diabetic case patients but did not report an analysis of these factors (23). Lastly, a hospital-based case-control study estimated a >6-fold increased risk for pancreatic cancer associated with insulin use and a 2-fold increased risk associated with oral diabetic medication use, as well as evidence of increased risk for pancreatic cancer associated with shorter duration of diabetes (6). Some of these studies contrast with our study that identified a markedly increased risk for cancer among diabetics with <5-year duration of diabetes.

Our in-person detailed interviews allowed us to identify that the requirement for insulin use, particularly in those who were newly diabetic, was associated with a substantially increased risk for pancreatic cancer. We did not find that use of oral medication alone was associated with increased risk for pancreatic carcinoma among diabetics. Notably, one oral diabetes medication, metformin, has been shown in animal studies to inhibit pancreatic cancer development (38). Because metformin is a common diabetic medication, any potential protective benefit against pancreatic cancer is intriguing but will need confirmation in other studies.

We hypothesize that requirement for insulin treatment is an indicator for more severe diabetes, and that, because of its particular association with pancreatic cancer risk among new diabetics, may reflect insulin resistance that is elicited by pancreatic cancer. Our data provide objective support for the clinical impression that diabetics with pancreatic cancer tend to have diabetes of higher severity, and provide another clinical clue that may aid in the identification of diabetic individuals with pancreatic cancer (34, 39).

Insights into why early insulin use might be associated with pancreatic cancer in new diabetics may come through examination of prior work. Requirement of insulin treatment may be associated with pancreatic cancer because of factors elicited by pancreatic cancer that cause insulin resistance (34, 40-42) or pancreatic cancer–associated β-cell dysfunction in insulin production (42-44). On a cellular level, defects in post-insulin receptor glycogen synthesis and storage in skeletal muscle, as well as impaired insulin action on phosphatidylinositol 3-kinase activity and glucose transport, have been identified as potential contributors to pancreatic cancer–associated insulin resistance (45, 46). Islet amyloid polypeptide and a protein identified through proteome analysis have been cited as candidate pancreatic cancer–associated diabetogenic factors that may induce these functional cellular changes (47, 48).

Older age at diagnosis with diabetes was more common among diabetic cases than diabetic controls, a finding

Table 5. ORs and 95% CIs for pancreatic cancer and duration of diabetes mellitus by insulin use, population-based case control study, San Francisco Bay Area, California

Diabetes duration (y)	Diabetic patients used insulin			Diabetic patients did not use insulin		
	Case	Control	OR*(95% CI)	Case	Control	OR* (95% CI)
No diabetes †	455	1,538	1.0 (reference)	455	1,538	1.0 (reference)
1-4	12	4	10 (3.2-31)	13	31	1.4 (0.73-2.7)
5-9	13	9	4.8 (2.0-11)	10	29	1.1 (0.56-2.4)
≥10	14	40	1.2 (0.62-2.1)	6	37	0.54 (0.23-1.3)
Trend *P*		*P* = 0.0003			*P* = 0.11	

*Adjusted for age and sex.
†Reference group for all comparisons.

consistent with other reports and one that may provide another clinically important indicator of those new diabetics at highest risk for cancer (23). Consistent with other investigators (23, 35), we did not find that body mass index affected the risk for pancreatic cancer among diabetics. In contrast to some (16, 49), but in agreement with others (23, 35), we found no correlation between presence of family history of diabetes and risk for pancreatic cancer among diabetics.

We observed the risk for pancreatic cancer among diabetic compared with nondiabetic African Americans to be higher (OR, 2.9) than the risk for pancreatic cancer among diabetic compared with nondiabetic Whites (OR, 1.2) in a small number of African Americans. The excess risk among African Americans persisted after adjustment for tobacco use and body mass index. Although no statistically significant trend for decreasing pancreatic cancer risk with increasing duration of diabetes was observed among African Americans, the point estimates decreased linearly. We cannot rule out the possibility of residual confounding by other factors associated with African American race and pancreatic cancer. African Americans have a higher prevalence of diabetes than do Whites (13% versus 9%; ref. 50) and a higher annual incidence rate of pancreatic cancer (16.6/100,000 versus 10.7/100,000 for 1995-1999; ref. 51). It is plausible that similar factors may be associated with both diseases among African Americans and may account for the association that we observed. For example, in one large population-based case-control study (52), most of the excess risk for pancreatic cancer among African Americans compared with Whites was explained by other established or suspected risk factors for pancreatic cancer. Our ability to do detailed adjusted analysis was limited by the small number of African American cases. Pooling of our data with other similar studies may allow for better delineation of the degree and character of any association between diabetes and pancreatic cancer among African Americans.

Our study may have several limitations. As with other studies of pancreatic cancer, some pancreatic cancer patients who may have been eligible for our study died before enrollment. It is possible that, if present, this incomplete case ascertainment may have differentially affected nondiabetic participants (who may be less likely to receive regular health care) than diabetic participants, and possibly biased our risk estimates. Additionally, the prevalence of undiagnosed diabetes may be as much as half of that of known diabetes in the general population, suggesting that nondifferential misclassification of cases and controls as nondiabetics when diabetes was indeed present may have occurred (53). Such misclassification would be expected to bias our results towards the null. Further, as in all case-control studies, recall of past diagnoses may be biased. However, diabetes is a serious disease and treatment with insulin is unlikely to be confused with oral diabetic medication use by study participants.

Conclusion

We found that recent-onset diabetes, but not diabetes of ≥10-years duration, was associated with increased risk for pancreatic cancer. Clinical factors that correlated with pancreatic cancer–associated diabetes included recent insulin use and older age, but not body-mass index or family history. Further efforts to identify diabetics at highest risk for pancreatic carcinoma may aid in early diagnosis and improved pancreatic cancer–associated survival.

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