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Diabetes and risk of pancreatic cancer: a pooled analysis of three large case–control studies

Donghui Li,

Department of Gastrointestinal Medical Oncology, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Boulevard, Unit 426, Houston, TX 77030, USA

Hongwei Tang,

Department of Gastrointestinal Medical Oncology, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Boulevard, Unit 426, Houston, TX 77030, USA

Manal M. Hassan,

Department of Gastrointestinal Medical Oncology, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Boulevard, Unit 426, Houston, TX 77030, USA

Elizabeth A. Holly,

Department of Epidemiology and Biostatistics, School of Medicine, University of California San Francisco, San Francisco, CA, USA

Paige M. Bracci, and

Department of Epidemiology and Biostatistics, School of Medicine, University of California San Francisco, San Francisco, CA, USA

Debra T. Silverman

Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD, USA

Abstract

Racial differences in diabetes-associated pancreatic cancer (PC) and the interaction of diabetes with other risk factors are not well established. We determined the association between diabetes and risk of PC in 2,192 cases and 5,113 controls in three large case–control studies conducted at the National Cancer Institute, the University of California San Francisco, and the M.D. Anderson Cancer Center. In multivariable analyses, diabetes was associated with a 1.8-fold risk of PC [95% confidence interval (CI) = 1.5–2.1]. Risk estimates decreased with increasing years with diabetes (< 2 years OR = 2.9, 95% CI = 2.1–3.9; 3–5 years OR = 1.9, 95% CI = 1.3–2.6; 6–10 years OR = 1.6, 95% CI = 1.2–2.3; 11–15 years OR = 1.3, 95% CI = 0.9–2.0; > 15 years OR = 1.4, 95% CI = 1.0–2.0 (p for trend < 0.0001). Among diabetics, risk was higher in insulin ever users compared with nonusers (OR = 2.2, 95% CI = 1.6–3.7) and was restricted to insulin use of < 3 years (OR = 2.4). Insulin use of >10 years was associated with a reduced risk of pancreatic cancer (OR = 0.5, 95% CI = 0.3–0.9; p for trend < 0.0001). Hispanic men and Asians had a higher risk of diabetes-associated PC than did whites and blacks, but the differences were not statistically significant. No significant interaction between diabetes and cigarette smoking, alcohol consumption and body

Correspondence to: Donghui Li.

Paige M. Bracci and Debra T. Silverman share the senior authorship.

mass index was observed. Although reverse causation may explain the association between diabetes diagnosed in close temporal proximity to PC, our results show that long-term diabetes, even though risk diminishes over time, remains a risk factor for PC independent of obesity and smoking.

Keywords

Diabetes; Pancreatic cancer; Case-control study; Epidemiology

Introduction

Type II diabetes is one of the few modifiable risk factors for pancreatic cancer (PC). The risk of type II diabetes-associated pancreatic cancer could be reduced through behavior modifications such as dietary restrictions, exercise, and weight reduction, and possibly through diabetes control. Because diabetes may be an indication of subclinical PC in some cases, it has been a challenge to demonstrate that diabetes is a predisposing factor for this malignancy [1, 2]. Two meta-analyses have investigated the risk of PC in relation to diabetes [3, 4]. The first, conducted in 1995, included 20 of the 30 published case-control and cohort studies and reported an overall estimated relative risk (RR) of 2.1 and a 95% confidence interval (CI) of 1.6–2.8. This value was relatively unchanged when analyses were restricted to diabetes with a duration of at least 5 years, RR = 2.0, 95% CI = 1.2–3.2 [3]. The second, conducted in 2005, included 17 case-control and 19 cohort or nested case-control studies published from 1996 to 2005 and reported an overall odds ratio (OR) of 1.8 and 95% CI (1.7–1.9) [4]. Individuals diagnosed with diabetes within 4 years of their PC had a 50% greater risk than those with diabetes for > 5 years (OR = 2.1, 95% CI = 1.9–2.3 vs. OR = 1.5, 95% CI = 1.3–1.8; $p = 0.005$). These results support a modest association between type II diabetes and PC.

Further support of a relationship between long-standing diabetes and risk of PC is provided by results from biomarker studies. Prediagnostic elevations in post-load plasma glucose [5, 6], serum and plasma glucose [7, 8], insulin [9, 10], and plasma C-peptide levels [11] have been associated with greater risk of PC.

Cigarette smoking and obesity are established risk factors for both type II diabetes and PC. Whether diabetes is a risk factor for PC independent of smoking or body mass index (BMI) has not been clearly defined.

Surveillance Epidemiology and End Results (SEER) age-adjusted incidence rates (per 100,000) for PC in 2002–2006 were 13.1 and 10.2 for white men and women; 16.6 and 14.6 for black men and women; 11.1 and 10.2 for Hispanic men and women; and 10.1 and 8.2 for Asian men and women, respectively [12]. The challenges of conducting epidemiological studies of PC in minorities have been exacerbated by the relatively low incidence rates and the rapid fatality of this disease. One of the three studies included in the current pooled analysis is one of the few studies that has been large enough to examine racial differences between whites and blacks/African-Americans in risk factors for PC [13]. Risk factors for PC in other racial/ethnic groups and their interaction with diabetes have not been thoroughly

investigated in large epidemiologic studies PC [14]. In a pooled analysis of data from three large case–control studies (2,192 cases, 5,113 controls), we examined whether the association between diabetes and risk of PC differed by race/ethnicity or sex and whether smoking, alcohol and body mass index (BMI) modified the association between PC and diabetes.

Materials and methods

Study populations

The M.D. Anderson Cancer Center Study (MDACC)—A hospital-based case–control study of PC was conducted between 2001 and 2008 at MDACC. The detailed methodology has been described previously [15–18]. Cases were patients with pathologically confirmed pancreatic adenocarcinoma, United States' residents, able to communicate in English, and who had no prior history of cancers except non-melanoma skin cancer. There was no age or sex restriction in patient recruitment. Eligible patients were identified among patients who were treated at the Gastrointestinal Cancer Clinic of the MDACC. A total of 1,788 patients were approached, and 1,501 were consented to the study (response rate 84%) with the strong support of attending physicians and clinical staff. A total of 1,167 cases were included in these analyses after excluding 234 cases determined not to have pancreatic adenocarcinoma and 100 cases who did not complete the personal interview. Controls were recruited from among spouse, friends, and in-laws of patients who accompanied cancer patients (other than PC, gastrointestinal malignancies, lung cancer, and head and neck smoking-related cancers) who attended the institution's Central Diagnostic Radiology Clinics. Controls were not genetically related to the patients. Controls met the same criteria as cases except that they had no prior history of cancer and were cancer-free at the time of interview. Controls were frequency-matched to cases by age (± 5 years), sex, and race/ethnicity. A total of 1,266 eligible controls (84% response rate) were included in the final analyses. Because information on BMI was not collected until 2004, it is missing from 412/1,167 (35%) of cases and 490/1,266 (39%) of controls.

The University of California San Francisco Bay Area Study (SFBA)—A population-based case–control study was conducted in the SFBA using rapid case ascertainment with a goal to identify patients within one month of diagnosis. Detailed methods have been published [19–27]. Briefly, eligible patients were diagnosed between 1995 and 1999 with incident adenocarcinoma of the exocrine pancreas, were between 21 and 85 years old, resided in one of the six Bay Area counties, were alive at the time of first attempted contact, and could complete an interview in English. A total of 532 eligible cases completed the interview (67% response rate) [19–27]. Patient diagnoses were confirmed by participants' physicians and by SEER abstracts that included histologic confirmation of disease. Eligibility criteria for controls were identical to those for cases except for PC status. Random-digit-dial methods supplemented by random sampling of the Health Care Finance Administration (HCFA, now the Centers for Medicare & Medicaid Services) lists for those 65 years of age were used to identify control participants within the six San Francisco Bay Area counties. Controls were frequency-matched to cases by sex and by five-year age-

groups for an approximate 1:3 case-to-control ratio. A total of 1,701 eligible control participants (67% response rate) completed inperson interviews [19–27].

The National Cancer Institute Study (NCI)—This population-based case–control study [13, 28–34] was conducted from August 1986 to April 1989 in three US geographical areas covered by population-based SEER cancer registries located in Atlanta (DeKalb and Fulton counties), Detroit (Macomb, Oakland and Wayne counties), and New Jersey (ten counties). Cases were patients newly diagnosed with carcinoma of the pancreas (International Classification of Diseases for Oncology code = 157), aged 21–79 years and were residents of the study areas.

About 90% of the interviewed cases had a tissue-confirmed diagnosis and 10% by an in-depth medical chart review [35]. Because of the rapidly fatal course of PC, 471 of the 1,153 patients initially identified for study died before the interview could be conducted even though the median time from diagnosis to interview was seven weeks. Of the 682 living cases identified for study, 526 (77%) were interviewed. Controls under the age of 65 years were selected by random-digit dial from the general population of the study areas, and those 65 years or older were selected from the HCFA lists of the population 65 years or older in each study area. Controls were frequency-matched to cases by age, race, sex, and geographic area. Of the 17,746 households telephoned, 86% provided a household census that served as the sampling frame for selection of controls. Of the 1568 controls under age 65 years and 1,232 controls older than 65 years who were selected, 1,227 (78%) and 926 (75%) were interviewed, respectively. After exclusion of participants with incomplete data or who did not meet study eligibility criteria, a total of 493 cases and 2,146 controls were included in the final data analysis.

Study conduct and data collection

In all three studies, trained interviewers conducted in-person interviews at the participants' homes or at a convenient location (for the SFBA Study and the NCI study) and at the clinic (for the MDACC Study). No proxy interviews were conducted in any of the three studies. Each study was reviewed and approved by its site-specific institutional review board, the University of Texas MDACC, the University of California San Francisco, and the National Cancer Institute. In all three studies, a written informed consent was obtained from participants prior to interview.

Each study used a structured questionnaire that included demographic factors, smoking, alcohol, medical, occupational, and dietary history. Participants were asked whether they ever had been diagnosed with diabetes by a physician, their age at diagnosis or the year of diagnosis, whether they had used insulin and/or oral anti-diabetic medications for the treatment of diabetes and the duration of insulin use. Age was categorized in five-year age-groups for multivariable analyses. Potential confounding factors considered in the analyses included education, cigarette smoking, alcohol consumption, and BMI. Smokers were defined as those participants who had smoked > 100 cigarettes in their lifetime or had smoked a pipe or cigar at least once per month for ≥ 6 months. Former smokers were those who had quit smoking for at least a year at the time of recruitment. Lifetime alcohol

consumption for those who reported ever having consumed more than one drink per month of beer, wine or liquor was categorized as: 0 to <0.1, 0.1–7, 8–14, 15–21, 22–36, and >36 drinks per week. To assess interaction between diabetes and other risk factors, analyses were stratified by race/ethnicity (white, black, Asian and Hispanic), sex, age (50, 51–60, 61–70, and >70 years), education (<high school, high school, some college, college degree, and graduate school), and BMI (<25, 25–30, >30). To assess the temporal association between diabetes and pancreatic cancer, we computed diabetes duration as the difference in years between age first diagnosed with diabetes and age at pancreatic cancer diagnosis (or interview for controls). For analyses, duration was grouped as 2, 3–5, 6–10, 11–15, and >15 years to diminish the potential effects of reverse causation and for comparability with other published studies.

Statistical methods

Available data from each study were pooled using the SPSS software (version 15; SPSS Inc., Chicago). The crude associations between PC status and demographic characteristics and potential risk factors were assessed using a chi-square test for categorical variables. Analyses of the pooled data were conducted using multivariable unconditional logistic regression models to compute OR as estimates of the relative risk and 95% confidence intervals. The final model included age, sex, race, smoking, alcohol consumption, BMI, and study site. Heterogeneity among studies and among racial/ethnic groups was evaluated using the Q and I^2 statistics [36]. Trend in duration of diabetes and duration of insulin use was tested using logistic regression to model the median value of each category as an ordinal variable. Statistical interaction between diabetes and other risk factors was evaluated based on a log-likelihood ratio test comparing nested models with and without the cross-product term of interest included in a multivariable logistic regression model. Results were considered statistically significant for two-sided p -values that were less than 0.05.

Results

The demographic characteristics and selected risk factors for each study population are provided in Table 1. In the pooled dataset, statistically significant differences in the distribution of race, education, smoking, alcohol, and BMI were observed between cases and controls. Controls were less likely to have been black/African-American, to have smoked cigarettes, to have been heavy consumers of alcohol, to have been overweight/obese, and to have had fewer years of education compared with cases. Heterogeneity was observed for race, sex, and education among studies (Table 1).

In the pooled data, a total of 448 cases (20.4%) and 561 controls (11%) reported a history of diabetes that was associated with a 1.8-fold increased risk of PC (Table 2), consistent with the study-specific estimates. A total of 276 cases (12.6%) and 456 controls (8.9%) had diabetes of >2 years duration [adjusted OR (AOR) = 1.6, 95% CI = 1.3–1.9]. There were 171 of 448 cases (38%) and 100 of 561 controls (18%) whose diabetes was diagnosed 2 years before their cancer diagnosis for cases or interview for controls (1 case and 5 controls had missing information on duration of diabetes). Risk of PC decreased with increased duration of diabetes. Among those whose diabetes was diagnosed 2 years before their

pancreatic cancer/interview, risk was substantially higher than in participants whose diabetes was diagnosed > 2 years before diagnosis/interview (< 2 years: OR = 2.9, 95% CI = 2.1–3.9; 3–5 years: OR = 1.9, 95% CI = 1.3–2.6; 6–10 years: OR = 1.6, 95% CI = 1.2–2.3; 11–15 years: OR = 1.3, 95% CI = 0.9–2.0; >15 years: OR = 1.4, 95% CI = 1.0–2.0; trend $p < 0.0001$). Diabetics who used oral diabetes medications had a somewhat decreased risk of PC compared with those who did not use oral diabetes medications (AOR = 0.8, 95% CI = 0.6–1.2 among all diabetic individuals, AOR = 0.7, 95% CI = 0.4–1.1 among insulin nonusers). Insulin users had a higher risk of PC compared with diabetics who did not use insulin (AOR = 2.2, 95% CI = 1.6–3.7). Risk of PC decreased with increased duration of insulin use (trend $p < 0.0001$). Diabetics who used insulin for < 3 years or 3–10 years had a 2.4-fold or 20% higher risk of PC, respectively, than diabetics who did not use insulin, whereas a 50% reduced risk was observed among those who had used insulin for >10 years (Table 2).

In stratified analyses (Table 3), risk estimates for PC associated with diabetes before adjustment for BMI were higher in Hispanics (AOR = 2.9) and Asians (AOR = 2.9) than in whites (AOR = 1.6) and blacks (AOR = 1.4). However, none of the differences in risk estimates among racial/ethnic groups was statistically significant. The p value (Q test) for the comparison of ORs was 0.16 and 0.10, respectively, for Hispanics versus whites and Hispanics versus blacks. When BMI was included in the model, the AOR decreased to 1.5 in Hispanics but increased to 4.3 in Asians. Individuals with BMI <25 or >30 kg/m² had similar ORs for diabetes-associated PC (Table 3).

Further stratification by sex showed that the AOR decreased in Hispanic women (AOR = 1.4, 95% CI = 0.3–6.4) but not in men (AOR = 3.3, 95% CI = 1.0–10.9). Black women in the NCI control group had a higher than expected prevalence of diabetes (20%), contributing to the observed null association between diabetes and PC in this group (AOR = 0.9, 95% CI = 0.5–1.5). Diabetes was associated with increased risk of PC among black women when the NCI data were excluded (AOR = 2.5, 95% CI = 1.5–3.9). Risk estimates were comparable between those with early-onset PC (age ≥ 55 years, AOR = 1.7, 95% CI = 1.2–2.5) compared with those with later-onset (age <55 years, AOR = 1.9, 95% CI = 1.6–2.3). There was no significant interaction between diabetes and sex, race, education, smoking, alcohol, or BMI (P for interaction terms: 0.28, 0.52, 0.22, 0.95, 0.36 and 0.35, respectively).

Discussion

Results from our large pooled analysis of data from three previously published case–control studies confirm the previously reported association between diabetes and risk of PC. Diabetes was associated with a 1.6-fold (among those with diabetes duration of >2 years) to 1.8-fold (all diabetes) increased risk of PC. Risk decreased with increased duration of diabetes but remained elevated at a 1.4-fold borderline significant risk 15 years after diagnosis with diabetes. In addition, age, sex, race/ethnicity, education, smoking, alcohol, and BMI did not markedly modify the observed association between diabetes and risk of PC in our pooled population.

Odds ratios from our pooled analyses (unadjusted OR = 2.1, AOR = 1.6–1.8) of diabetes and PC risk are consistent with those reported in two published metaanalyses (summary OR =

2.1 and 1.8) [3, 4]. The second meta-analyses included the NCI study [4]. Because diabetes could be an indication of subclinical PC, a short duration between the diagnosis of diabetes and the diagnosis of PC usually indicates that PC caused the diabetes [37, 38]. In our analyses of diabetes duration, we observed a decreasing trend in ORs with increased duration. Although it is likely that the higher risk of PC among individuals with a shorter duration of diabetes (< 2 years) was mainly due to reverse causality, risk of PC remained significantly elevated in longer-term diabetes (>5 years of duration). Even 10 or 15 years after diabetes diagnosis, the risk of PC remained non-significantly elevated. Because PC is a rapidly fatal disease, it is unlikely that a person with PC-caused diabetes would live for many years without being diagnosed with cancer [36, 37]. Thus, the increased risk of PC among those with long-term diabetes is unlikely to be explained by reversed causality.

The decreasing risk of PC along with increasing duration of diabetes may partially be related to lifestyle changes after diabetes diagnosis or to use of certain anti-diabetic medications. Previous studies [18, 39, 40] have suggested that use of the anti-diabetic drug, metformin, reduced risk, and use of insulin or insulin secretagogues increased the risk of cancer including PC among individuals with diabetes. Because information on the various types of oral anti-diabetic medication used was not available in the SFBA and the NCI studies, the current analyses focused on ever use of oral medication and use of insulin only. In our analyses, risk of PC was slightly reduced for diabetics who used oral diabetes medications compared with those who did not take oral medications (OR = 0.8). The observed difference was not confounded by insulin use, because restriction of the analyses to those who did not use insulin yielded a similar risk estimate for diabetics who used oral medication compared to those who did not use oral medication (AOR = 0.7). Insulin use was associated with a higher risk of PC, and the risk was restricted to those with a shorter duration of use (<3 years). Long-term insulin use (>10 years) was associated with a reduced risk of PC, whereas the risk among those who used insulin for 3–10 years was 20% higher than the risk of PC among diabetics who did not use insulin. Among insulin users, >70% of the patients with PC began using insulin < 2 years before their cancer diagnosis [18]. The increased risk of PC associated with short-term insulin use has been consistently reported in all four case-control studies that examined the duration of insulin use [15, 23, 29, 41]. If insulin use was a result of worsening of their diabetes caused by the cancer, the association between short-term insulin use and PC suggests reverse causality. Of these 4 studies, the 3 studies included in this pooled analysis previously reported no association or reduced risk of PC for those used insulin for >5 years [15, 23, 29]. There is no experimental evidence showing that better glycemic control with insulin use actually reduces the risk of cancer. Our analysis of PC risk among diabetics who used insulin >3 years was based on a limited number of exposed participants, requires validation and further investigation.

According to American Diabetes Association, 11% of adults aged 20 years or older and 23% of adults aged 60 years or older in the United States have diabetes. African- Americans, Hispanic/Latino Americans, Native Americans, and some groups of Asian Americans, Native Hawaiians and other Pacific Islanders have a particularly high risk of type 2 diabetes and its complications, especially among women. A higher risk estimate for diabetes-associated PC was observed for Hispanic men and Asians than for Caucasians and African-Americans in this pooled analysis, even though the differences were not statistically

significant. However, the number of Asians was small, and the observation needs to be verified in larger studies. Furthermore, the higher risk among Hispanic women diminished when BMI was included in the model, suggesting a possible confounding effect of BMI in this group. The lack of association between diabetes and PC risk among black/African-American women was probably due to an unexplained high prevalence of diabetes (20%) among the black/African-American women controls in the NCI study that contributed the majority of the African-American study participants in this pooled analysis. The NCI study previously had shown that cigarette smoking and diabetes contributed to a higher risk of PC for black/African-American men compared to white men, whereas alcohol consumption and excess body weight contributed to the racial disparity of PC risk among women [13]. Results from the current pooled analyses support the finding that diabetes is a major risk factor for black/African-American men. However, the role of diabetes in PC among black/African-American women needs further investigation with a thorough exploration of BMI. The observed results for diabetes-associated PC risk in minorities require validation in further large studies, as the subgroup sample sizes were small and the risk estimates were imprecise.

The strengths of our study include the large sample size, the detailed information about diabetes history, and other known risk factors for PC. The large size of our pooled study also enabled us to examine the effects of diabetes-associated PC that have been inadequately assessed in earlier studies including differences by race/ethnicity and sex, and the interaction of diabetes with other risk factors.

The limitations of our pooled analyses include some heterogeneity among studies and possible recall bias inherent from the case-control design, as well as the slightly unbalanced matching on age between cases and controls. Relative to the NCI and SFBA studies, the case population recruited from the tertiary referral hospital in the MDACC study was of higher socioeconomic status and had fewer racial/ethnic minority and elderly patients. The three studies pooled for this analysis were conducted at different time periods spanning 22 years (1986 to 2008). During the last 20 years, there was a dramatic increase in the prevalence of obesity, and the definition of diabetes was changed in 1998 from fasting glucose level of 140 to 126 mg/dl, which may have contributed to the higher prevalence of diabetes among the more recently conducted studies. The majority of the black/African-American participants were recruited in the NCI study during a time when the prevalence of diabetes was lower than in recent years. Therefore, it is possible that the differences in susceptibility to diabetes-associated PC observed between blacks/African-Americans and other ethnic groups could be related to a cohort effect thereby making our risk estimates conservative.

Because PC is rapidly fatal, patients with the most aggressive disease were likely to have died before the initial contact for recruitment. Also, according to the ADA, about 25% of people with diabetes are undiagnosed. Therefore, non-differential misclassification of diabetes as non-diabetes in both cases and controls may have biased our risk estimates towards the null value, particularly for non-white women. Although history of diabetes was not confirmed by medical record in these pooled studies, assessment of recall of diabetes has been shown to be accurate [42].

In conclusion, our results provide convincing evidence that diabetes is a risk factor for PC in US populations, independent of smoking and BMI. Our results also suggest that risk of PC associated with diabetes may vary by race/ethnicity and by time since diagnosis of diabetes. Confirmation of these results is required in further large pooled studies. More detailed investigation is warranted to help clarify the suggested disparities by race/ethnicity including the role of access to care, genetic factors, and other modifiable lifestyle factors.

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Abbreviations

AOR	Adjusted odds ratio
BMI	Body mass index
CI	Confidence interval
HCFA	Health Care Finance Administration
MDACC	The University of Texas M.D. Anderson Cancer Center
NCI	National Cancer Institute
OR	Odds ratio
PC	Pancreatic cancer
SFBA	The University of California San Francisco Bay Area

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Demographic and risk-factor characteristics of the study participants in the MD Anderson Cancer Center (MDACC), National Cancer Institute (NCI) and San Francisco Bay Area (SFBA) case-control studies of pancreatic cancer

Table 1

Variable	MDACC		NCI		SFBA		Pooled		Q test
	Case n = 1167 (%)	Control n = 1266 (%)	Case n = 493 (%)	Control n = 2146 (%)	Case n = 532 (%)	Control n = 1701 (%)	Case n = 2192 (%)	Control n = 5113 (%)	
Sex									<0.001
Women	493 (42.3)	505 (39.9)	243 (49.3)	782 (36.4)	241 (45.3)	818 (48.1)	977 (44.6)	2105 (41.2)	
Men	674 (57.8)	761 (60.1)	250 (50.7)	1364 (63.6)	291 (54.7)	883 (51.9)	1215 (55.4)	3008 (58.8)	
Race/ethnicity									
White	1008 (86.4)	1118 (88.3)	314 (63.7)	1179 (54.9)	426 (80.1)	1369 (80.5)	1748 (79.7)	3666 (71.7)	
Black	71 (6.1)	43 (3.4)	179 (36.3)	967 (45.1)	46 (8.7)	78 (4.6)	296 (13.5)	1088 (21.3)	<0.001
Hispanic	65 (5.6)	93 (7.4)	–	–	16 (3.0)	102 (6.0)	81 (3.7)	195 (3.8)	0.15
Asian	19 (1.6)	8 (0.6)	–	–	35 (6.6)	119 (7.0)	54 (2.5)	127 (2.5)	0.03
Other	4 (0.3)	4 (0.3)	–	–	9 (1.7)	33 (1.9)	13 (0.6)	37 (0.7)	0.63
$p(\chi^2)$	0.001		<0.001		0.001		<0.001		
Age (years)									0.54
Median	62	60	63	62	66	65	63	63	
50	161 (13.8)	252 (19.9)	66 (13.4)	363 (16.9)	52 (9.8)	214 (14.7)	279 (12.8)	829 (16.2)	
51–60	327 (28.0)	383 (30.3)	139 (28.2)	587 (27.4)	128 (24.1)	425 (25.0)	594 (27.1)	1395 (27.3)	0.16
61–70	426 (36.5)	411 (32.5)	159 (32.3)	662 (30.9)	182 (34.2)	508 (29.9)	767 (35.0)	1581 (30.9)	0.02
>70	253 (21.7)	220 (17.4)	129 (26.2)	534 (24.9)	170 (32.0)	554 (32.6)	552 (25.2)	1308 (25.6)	0.10
Education									
<High school	90 (7.7)	36 (2.8)	199 (40.4)	846 (39.6)	71 (13.4)	162 (9.5)	360 (16.4)	1044 (20.5)	
High school	262 (22.5)	274 (21.6)	160 (32.5)	582 (27.2)	164 (30.8)	372 (21.9)	586 (26.8)	1228 (24.1)	<0.001
College	589 (50.5)	730 (57.7)	106 (21.5)	473 (22.1)	200 (37.6)	754 (44.3)	895 (40.9)	1957 (38.3)	0.001
Graduate	226 (19.4)	226 (17.9)	18 (3.7)	185 (8.7)	97 (18.2)	413 (24.3)	341 (15.6)	824 (16.1)	0.36
Other			9 (1.8)	51 (2.4)			9 (0.4)	51 (1.0)	
$p(\chi^2)$	<0.001		0.001		<0.001		<0.001		
Smoking									
Never	490 (42.0)	654 (51.7)	153 (31.2)	844 (39.4)	163 (31.6)	652 (40.1)	806 (37.1)	2150 (42.7)	

Variable	MDACC		NCI		SFBA		Pooled		Q test
	Case $n = 1167$ (%)	Control $n = 1266$ (%)	Case $n = 493$ (%)	Control $n = 2146$ (%)	Case $n = 532$ (%)	Control $n = 1701$ (%)	Case $n = 2192$ (%)	Control $n = 5113$ (%)	
Former	527 (45.2)	479 (37.8)	175 (35.6)	709 (33.1)	222 (43.0)	768 (47.2)	924 (42.5)	1956 (38.8)	0.09
Current	150 (12.9)	133 (10.5)	163 (33.2)	592 (27.6)	131 (25.4)	208 (12.8)	444 (20.4)	933 (18.5)	0.24
$P(\chi^2)$	<0.001		0.001			0.001		<0.001	
Alcohol (drinks/day)									
Never	497 (42.6)	558 (44.2)	192 (39.3)	750 (35.0)	85 (16.1)	305 (17.9)	774 (35.4)	1613 (31.6)	
0.1–7	264 (22.6)	321 (25.4)	98 (20.0)	545 (25.4)	231 (43.7)	804 (47.3)	593 (27.1)	1670 (32.7)	0.12
8–14	133 (11.4)	139 (11.0)	64 (13.1)	302 (14.1)	83 (15.7)	293 (17.2)	280 (12.8)	734 (14.4)	0.63
15–21	81 (6.9)	75 (5.9)	34 (7.0)	167 (7.8)	39 (7.4)	138 (8.1)	154 (7.1)	380 (7.4)	0.26
22–36	75 (6.4)	89 (7.0)	43 (8.8)	197 (9.2)	47 (8.9)	88 (5.17)	165 (7.6)	374 (7.3)	0.17
>36	117 (10.0)	82 (6.5)	58 (11.9)	184 (8.6)	44 (8.3)	73 (4.3)	219 (10.0)	339 (6.6)	0.86
$P(\chi^2)$	0.02		0.03		<0.001		<0.001		
BMI (kg/m ²) ^a									
25	397 (52.6)	476 (61.3)	230 (46.8)	1115 (52.2)	286 (53.8)	1019 (59.9)	913 (51.4)	2610 (56.6)	
25.1–30	275 (36.4)	247 (31.8)	187 (38.1)	823 (38.5)	198 (37.2)	537 (31.6)	660 (37.1)	1607 (34.8)	0.23
>30	83 (11.0)	53 (6.8)	74 (15.1)	198 (9.3)	48 (9.0)	145 (8.5)	205 (11.5)	396 (8.6)	0.02
$P(\chi^2)$	0.001		<0.001		0.04		<0.001		

^aInformation on body mass index (BMI) was not collected before 2004, thus was missing from 412/1,167 (35%) of cases and 490/1,266 (39%) of controls in the MDACC study

Table 2

Odds ratios (OR) and 95% confidence intervals (CI) for risk of pancreatic cancer associated with diabetes and diabetes-related characteristics, data pooled from three case–control studies

Variable	Case (n,%)	Control (n,%)	OR (95% CI)	<i>Q</i> test
Diabetes ^a				
No	1744 (79.6)	4552 (89.0)	1.0	
Yes	448 (20.4)	561 (11.0)	1.8 (1.5–2.1)	
>2 years	276 (12.6)	456 (8.9)	1.6 (1.3–1.9)	0.82
Diabetes duration (years) ^a				
2	171 (7.8)	100 (2.0)	2.9 (2.1–3.9)	0.02
3–5	90 (4.1)	106 (2.1)	1.9 (1.3–2.6)	0.29
6–10	78 (3.6)	121 (2.4)	1.6 (1.2–2.3)	0.87
11–15	52 (2.4)	103 (2.0)	1.3 (0.9–2.0)	0.34
>15	56 (2.6)	126 (2.5)	1.4 (1.0–2.0)	0.74
Missing	1	5		
<i>p</i> for Trend			<0.001	
Antidiabetic medication ^b				
No	93 (4.2)	116 (2.3)	1.0	
Yes	347 (15.8)	440 (8.6)	0.8 (0.6–1.2)	0.35
Missing	8 (0.4)	5 (0.1)		
Antidiabetic medication ^c				
No	35 (1.7)	61 (1.2)	1.0	
Yes	236 (11.7)	323 (6.5)	0.7 (0.4–1.1)	0.119
Missing	2 (0.1)	3 (0.1)		
Insulin use ^b				
No	273 (61.2)	387 (69.0)	1.0	
Yes	173 (38.8)	173 (31.0)	2.2 (1.6–3.0)	<0.001
Missing	2 (0.004)	1 (0.0)		
Insulin use duration (years) ^b				
No	273 (60.9)	387 (69.0)	1.0	
3	60 (13.4)	48 (8.6)	2.4 (1.6–3.7)	<0.001
>3 and 10	34 (7.6)	54 (9.6)	1.2 (0.7–1.9)	0.449
>10	18 (4.0)	67 (11.9)	0.5 (0.3–0.9)	0.029
Missing	63 (14.1)	5 (0.9)		
<i>p</i> for Trend			<0.001	

^aOR adjusted for age, sex, race, education, smoking, alcohol, body mass index, and study site

^bInsulin or antidiabetic medication was mutually adjusted in addition to above variables. The analyses included diabetics only

^cAmong insulin non-users only

Table 3

Odds ratios (OR) and 95% confidence intervals (CI) for risk of pancreatic cancer associated with diabetes by demographic and risk factor groups, data pooled from three case-control studies

Variable	Case/control (n)		OR (95% CI) ^a	OR (95% CI) ^b	OR (95% CI) ^c	Q test
	Non-diabetes	Diabetes				
Race/ethnicity						
White	1426/3334	322/332	2.3 (1.9–2.7)	1.7 (1.4–2.0)	1.6 (1.3–2.0)	0.06
Black	217/908	79/180	1.8 (1.4–2.5)	1.5 (1.1–2.2)	1.4 (1.0–2.0)	0.07
Hispanic	47/161	34/34	3.4 (1.9–6.1)	2.7 (1.4–5.1)	2.9 (1.3–6.1)	<i>d</i>
Asian	42/115	12/12	2.7 (1.1–6.6)	2.5 (1.0–6.3)	2.9 (0.9–9.1)	–
Sex						
Men	933/2658	282/350	2.3 (1.9–2.7)	1.7 (1.4–2.1)	1.9 (1.5–2.3)	0.14
Women	811/1894	166/211	1.8 (1.5–2.3)	1.4 (1.1–1.8)	1.4 (1.1–1.9)	0.007
Age						
<50	253/787	26/42	4.2 (0.8–21.7)	1.7 (0.9–3.3)	1.4 (0.7–2.9)	0.12
>50–60	476/1259	118/136	1.7 (1.0–2.9)	1.6 (1.2–2.3)	1.8 (1.3–2.6)	0.22
>60–70	582/1386	185/193	2.3 (1.8–3.0)	1.7 (1.3–2.2)	1.8 (1.4–2.4)	0.02
>70	433/1118	119/190	2.3 (1.8–2.9)	1.3 (1.0–1.7)	1.5 (1.1–2.0)	0.87
Education						
<High School	262/868	98/176	1.8 (1.4–2.5)	1.7 (1.2–2.2)	1.7 (1.3–2.4)	0.57
High School	473/1085	113/143	1.8 (1.4–2.4)	1.3 (1.0–1.8)	1.5 (1.1–2.1)	0.006
College	726/1768	169/189	2.2 (1.7–2.7)	1.5 (1.1–1.9)	1.4 (1.0–1.8)	0.43
Graduate School	274/780	67/44	4.3 (2.9–6.5)	3.4 (2.1–5.5)	3.8 (2.2–6.4)	0.15
Smoking						
Never	649/1933	157/217	2.2 (1.7–2.7)	1.6 (1.2–2.1)	1.6 (1.2–2.1)	0.07
Former	711/1710	213/246	2.1 (1.7–2.6)	1.6 (1.2–2.0)	1.7 (1.4–2.3)	0.09
Current	369/847	75/86	2.0 (1.4–2.8)	1.6 (1.1–2.4)	1.7 (1.1–2.7)	0.23
Alcohol						
<0.1	583/1414	191/199	2.3 (1.9–2.9)	1.7 (1.4–2.2)	1.8 (1.4–2.4)	0.28
0.1–7	484/1511	191/199	2.1 (1.6–2.8)	1.6 (1.2–2.1)	1.7 (1.2–2.4)	0.18
8–14	237/664	43/70	1.7 (1.1–2.6)	1.4 (0.9–1.9)	1.4 (0.8–2.5)	0.06

Variable	Case/control (n)		OR (95% CI)	OR (95% CI) ^a (univariable)	OR (95% CI) ^b (multivariable)	OR (95% CI) ^c (multivariable)	Q test
	Non-diabetes	Diabetes					
15-21	129/339	25/41	1.6 (1.2-2.4)	1.2 (0.9-1.9)	1.2 (1.1-2.6)	0.9 (0.4-2.0)	0.14
22-36	139/326	26/48	1.3 (0.8-2.1)	0.8 (0.4-1.5)	1.3 (0.6-2.5)	1.4 (0.7-2.9)	0.11
>36	169/296	51/43	2.1 (1.3-3.3)	1.8 (1.0-3.0)	2.2 (1.2-3.8)	2.0 (1.0-3.7)	0.16
BMI							
25	767/2374	146/236	1.9 (1.5-2.4)	1.5 (1.1-1.9)	1.7 (1.3-2.2)	1.7 (1.3-2.2)	0.29
25.1-30	508/1404	152/203	2.1 (1.6-2.6)	1.5 (1.1-1.9)	1.4 (1.1-1.9)	1.4 (1.1-1.9)	0.06
>30	139/319	66/77	2.0 (1.3-2.9)	1.8 (1.2-2.7)	1.8 (1.1-2.9)	1.8 (1.1-2.9)	0.98

^aWith the exclusion of those with diabetes duration > 2 years

^bAge, sex, race, education, smoking, alcohol, diabetes, and study site were included in the model, and those with diabetes duration > 2 years were excluded from the analysis

^cAge, sex, race, education, smoking, alcohol, BMI, diabetes, and study site were included in the model, and those with diabetes duration > 2 years were excluded from the analysis

^dp value could not be calculated