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ORIGINAL PAPER

Diabetes and risk of pancreatic cancer: a pooled analysis from the pancreatic cancer cohort consortium

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Abstract
Purpose Diabetes is a suspected risk factor for pancreatic cancer, but questions remain about whether it is a risk factor or a result of the disease. This study prospectively examined the association between diabetes and the risk of pancreatic adenocarcinoma in pooled data from the NCI pancreatic cancer cohort consortium (PanScan).
Methods The pooled data included 1,621 pancreatic adenocarcinoma cases and 1,719 matched controls from twelve cohorts using a nested case–control study design. Subjects

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who were diagnosed with diabetes near the time (<2 years) of pancreatic cancer diagnosis were excluded from all analyses. All analyses were adjusted for age, race, gender, study, alcohol use, smoking, BMI, and family history of pancreatic cancer.

Results Self-reported diabetes was associated with a forty percent increased risk of pancreatic cancer (OR = 1.40, 95 % CI: 1.07, 1.84). The association differed by duration of diabetes; risk was highest for those with a duration of 2–8 years (OR = 1.79, 95 % CI: 1.25, 2.55); there was no association for those with 9+ years of diabetes (OR = 1.02, 95 % CI: 0.68, 1.52).

Conclusions These findings provide support for a relationship between diabetes and pancreatic cancer risk. The absence of association in those with the longest duration of diabetes may reflect hypoinsulinemia and warrants further investigation.

Keywords Diabetes · Risk factor · Cohort consortium · Pancreatic cancer

Introduction

Pancreatic adenocarcinoma is the fourth leading cause of cancer death in the United States [1] and annually accounts for more than 227,000 deaths worldwide [2]. It is a highly fatal disease with a five-year survival rate of less than 5 % [1]. Several risk factors have been identified including age, smoking, race, sex, diabetes, alcohol intake, ABO blood group, body mass index (BMI), and family history of pancreatic cancer [3–9]. Pancreatic cancer risk is higher in Blacks than Whites, men than women, obese than normal weight, and diabetics compared to non-diabetics [3]. Smoking is the most studied and well-characterized risk factor; other possible risk factors are less established [3, 4, 10].

Type 2 diabetes, generally discovered during adulthood, is usually marked by an initial period of relative hyperinsulinemia, in which the mass of the β-cells of the pancreatic islets of Langerhans is reduced but insulin secretion increased as partial compensation for increased insulin resistance due to overweight and lack of physical activity, followed later by a period of relative hypoinsulinemia, reflecting further reduction of the mass of the β-cells [11]. Hyperglycemia is associated with altered glucose metabolism, chronic inflammation, oxidative stress, and the activation of insulin signaling cascades that may increase the risk of pancreatic cancer [12]. Diabetes can also be an early manifestation of pancreatic cancer, so it is important to determine whether diabetes is an independent risk factor for pancreatic cancer or instead a consequence of the disease. Pancreatic cancer progresses without significant early symptoms and is generally diagnosed at late stages. The development of diabetes within a few years of a pancreatic cancer diagnosis is more likely to suggest an effect of the tumor, whereas diabetes of longer duration is more likely to contribute to the development of cancer [13].

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Two meta-analyses concluded that diabetes is associated with an increased risk of pancreatic cancer [14, 15]; however, many of the studies included in these analyses were limited by low numbers of pancreatic cancer cases, were likely to involve secondary effects of pancreatic cancer including the induction of diabetes, and had limited numbers of prospective studies with an evaluation of the long-term effects of diabetes. In addition, these studies generally did not evaluate the effect of diabetes duration. Thus, additional investigations with adequate numbers of cases in prospective studies are needed to discern this complicated relationship, especially in light of the increasing prevalence of diabetes in many Western countries.

This report examines the association between type 2 diabetes and subsequent pancreatic adenocarcinoma risk by pooling data from 12 cohort studies in the NCI Pancreatic Cancer Cohort Consortium (PanScan) using a nested case–control study design. These cohorts have long-term follow-up and include 1,621 pancreatic adenocarcinoma cases, making this one of the largest prospective analyses to date of type 2 diabetes and pancreatic cancer.

Methods

Study population

PanScan is an initiative that was funded jointly by the National Cancer Institute's Division of Cancer Control and Population Sciences and the Division of Cancer Epidemiology and Genetics in 2006. PanScan includes investigators from 12 prospective epidemiologic cohorts and one case–control study, the Mayo Clinic Study. It was created to investigate environmental, lifestyle, and genetic causes of pancreatic cancer. Studies in the pooled analysis included: The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Trial (ATBC) [16], CLUE II [17], Cancer Prevention Study II (CPS II) [18], European Prospective Investigation into Cancer and Nutrition (EPIC) [19], the Health Professionals Follow-up Study (HPFS) [20], the Mayo Clinic study (MAYO) [21], the New York University Women's Health Study (NYUWHS) [22], the Nurses' Health Study (NHS) [20], the Physicians' Health Study (PHS I) [20], the Prostate, Lung, Colorectal, Ovarian Cancer Screening Trial (PLCO) [23], Shanghai Men's and Women's Health Studies (SMWHS) [24, 25], the Women's Health Initiative (WHI) [26], and the Women's Health Study (WHS) [27]. Characteristics of these studies have been summarized previously including the years of recruitment, age range of participants, racial composition, years of follow-up, and matching criteria [16–27]. The Mayo study was excluded from these analyses due to its case–control study design. A total of 120 cases and 79 controls had missing data on diabetes and thus were excluded from analysis. We have also excluded participants diagnosed with diabetes less than 2 years before pancreatic cancer diagnosis or selection as a control ($n = 36$) and also any participants diagnosed with diabetes after cancer/selection ($n = 4$) in our analyses. A total of 1,621 cases and 1,719 controls were included in the current analysis.

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Case ascertainment and data collection

Cases included all incident primary pancreatic adenocarcinoma (ICD-O-3 codes C25.0-C25.3, C25.7-C25.9). Endocrine pancreatic tumors (ICD-O-3 code C25.4, histology types 8,150, 8,151, 8,153, 8,155, 8,240, and 8,246) were excluded because the etiology of these cancers is thought to be different from that of exocrine tumors, which account for the vast majority of pancreatic tumors. Case ascertainment varied between studies but included linking participants to cancer registries and national death indices, and using self and next of kin reports. Most cases were histologically confirmed (ATBC, CLUE II, EPIC, NYUWHS, SMWHS, WHI) or confirmed through cancer registries (ATBC, CPS II, EPIC, SMWHS), death certificates (CPS II, EPIC), or review of medical records by medical personnel (ATBC, CPS II, EPIC, NHS, PHS I, PLCO, SMWHS).

Controls were incidence density-sampled with a 1-to-1 control-to-case ratio and were alive and cancer-free on the date of diagnosis of the matched case. At a minimum, controls were matched to cases by calendar year of birth (±5 years), gender, race and ethnicity. Some cohorts employed more stringent matching on age such as age at baseline or age at blood draw (±5 years), and additionally, on other relevant factors such as smoking, date/time of day of blood draw, fasting blood draw (for comparisons of blood levels of analytes of interest), and length of follow-up. Detailed descriptions of data collection methods have been published previously by the individual studies [16–27]. Baseline information on BMI, waist circumference, waist-to-hip ratio, history of cigarette smoking, gender, age, race, family history of pancreatic cancer in a first-degree relative, alcohol consumption, pancreatitis, and history of diabetes was requested from the cohorts that collected this information. Data on diabetes, demographics, and possible confounders were collected through self-administered written questionnaires or in-person interviews from baseline and/or follow-up questionnaires, with the most recent data available used in analysis. Self-reported diabetes status was ascertained based on a physician's diagnosis of diabetes and/or treatment for diabetes with the use of insulin or oral hypoglycemic drugs. The duration of diabetes was assessed by the reported age at diagnosis, when available, and the reported follow-up period. When the age of diagnosis was not available, it was estimated from the date of the follow-up examination that first reported the presence of diabetes. Three cohorts (ATBC, PLCO, and WHI) did not query age at diabetes diagnosis; these data were missing for 22 % of participants in the remaining cohorts. Individual datasets were checked for consistency with previously published results. The Special Studies Institutional Review Board (SSIRB) of the National Cancer Institute approved the pooled PanScan study. Each study also was approved by its local IRB.

Statistical analysis

Odds ratios (ORs) and 95 % confidence intervals (95 % CIs) for pancreatic cancer risk were calculated using unconditional logistic regression. Several multivariate models were used to assess the effects of potential confounders. Unless otherwise noted, models were adjusted for age (<=50, 51–60, 61–70, 71–80, and 81+ years), gender, race (European, African, Asian, other, unknown), study, continuous BMI, alcohol use (never, ever current status unknown, former drinker, light current drinker, heavy current drinker, unknown), smoking (never, former, current, unknown), and family history of pancreatic cancer. Indicator variables were used in all analysis for variables with missing responses. No adjustment was made for pancreatitis because few cohorts had this information. Several approaches, including visual representation and splines, were used to evaluate the duration of diabetes when modeling the effect of diabetes on pancreatic cancer risk but did not change results appreciably. We used cut points of 2–8 years and nine or more years based on the numbers of responses to ensure adequate cell size for analysis.

We modeled multiplicative interaction terms between diabetes and gender, age, cigarette smoking status (never, former, current), and continuous BMI and compared p values for the likelihood ratio tests (<0.05) for the models with and without interaction terms. We also evaluated heterogeneity across studies by fitting models with and without multiplicative interaction terms between diabetes and study and calculating a p value for heterogeneity

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using the likelihood ratio statistic. All analyses were conducted using SAS version 9.1.3 (SAS Institute Inc, Cary, North Carolina).

Results

Table 1 describes each study in the PanScan study included in these analyses, including the study location, numbers of participants, age range, method to assess diabetes status, and the prevalence of diabetes among cases and controls, while Table 2 presents the baseline characteristics of the participants included. There were approximately equal numbers by age, gender, and race among cases and controls. There were small numbers of Asians and Africans, and most of the participants were between the ages of 60 and 80. Cases were more likely to identify as current smokers than controls (28 vs. 22 %) and were more likely to be overweight or obese. Cases were more likely to report being diagnosed with diabetes than controls (10 vs. 7 %). A history of pancreatitis and/or family history of pancreatic cancer were slightly more common among cases as compared to controls. However, many cohorts did not collect this information and approximately one-half of the participants lacked these data. The mean age at pancreatic adenocarcinoma diagnosis was 68.9 years (SD 8.5), whereas the mean age at diabetes diagnosis was 58.5 years (SD 12.4).

Diabetes was associated with an increased risk of pancreatic cancer (Odds ratio (OR) = 1.37, 95 % CI: 1.06, 1.77); adjustment for age, gender, study, and race had a minor effect on the odds ratio (OR = 1.49, 95 % CI: 1.14, 1.94), as did adjustment for the full model including age, race, gender, study, alcohol use, smoking, BMI, and family history of pancreatic cancer (OR = 1.40, 95 % CI: 1.07, 1.84). Because a consequence of pancreatic cancer can be the development of diabetes, all analyses excluded pancreatic cancer cases with diabetes diagnosed within 2 years of the pancreatic cancer diagnosis, as well as controls diagnosed with diabetes within 2 years of the diagnosis date of the matched case. When those cases diagnosed/controls enrolling within 2 years of a diabetes diagnosis were included, the odds ratio was modestly higher (OR = 1.50, 95 % CI: 1.18, 1.91).

We also examined whether the duration of diabetes was associated with the risk of pancreatic adenocarcinoma (Table 3). Due to the limited number of cases for some time periods, several time periods were grouped together to ensure adequate numbers of cases for analysis. The optimal groupings were cases with a duration of 2–8 years and 9+ years of duration. Changing the periods of duration within the grouping yielded similar results (Table 4). The risk of pancreatic adenocarcinoma was elevated when the duration of diabetes ranged from 2–8 years (OR = 1.79, 95 % CI: 1.25, 2.55). Interestingly, the risk of pancreatic adenocarcinoma decreased with a duration of diabetes of 9+ years (OR = 1.02, 95 % CI: 0.68, 1.52) as compared to a duration of diabetes from 2–8 years. Similar results were found for men (OR = 1.79, 95 % CI: 1.00, 3.21) and women (OR = 1.81, 95 % CI: 1.15, 2.87) for those with a duration of diabetes for 2–8 years. In a fully adjusted model, we adjusted for the potential confounders of age, gender, race, study, BMI, alcohol use, smoking, and family history of pancreatic cancer. Examination of possible effect modification with BMI, age, and smoking did not reveal any statistically significant interactions. In addition, we tested for heterogeneity among the studies included in these analyses using Cochran's Q test and found no evidence of heterogeneity ($p = 0.317$ for 2–8 years and $p = 0.923$ for 9+ years duration).

The ORs for each of the 12 cohorts are shown in a Forest plot for those with the duration of diabetes of 2–8 years (Fig. 1) and nine or more years (Fig. 2). Four cohorts (HPFS, PHS, WHS, and NYU) were not included in the summary estimates and are not displayed because these cohorts contained too few cases with diabetes that matched these criteria to calculate meaningful estimates. For diabetes duration of 2–8 years, the ORs are consistent across the cohorts indicating a positive association of diabetes with pancreatic cancer, with a range of ORs from 1.06 to 12.0 with the exception of NHS (OR = 0.43, 95 % CI: 0.04, 5.07). The risks seen in Fig. 1 are attenuated for each cohort in Fig. 2, with risk estimates for most studies being approximately null. The wide confidence limits seen were a consequence of low case numbers in many cohorts.

Discussion

The purpose of the current study was to examine the association between diabetes and pancreatic adenocarcinoma risk by pooling data from nested case–control studies included in the NCI Pancreatic Cancer Cohort Consortium (PanScan). Diabetes appears to be a moderate risk factor for pancreatic cancer risk with 40 % higher risk seen in diabetics than non-diabetics. Those with a duration of diabetes of 2–8 years were at the highest risk, being 1.8 times as likely to develop pancreatic cancer as non-diabetics. No increased risk was observed for those with the longest duration of diabetes (>9 years). The association between diabetes and pancreatic adenocarcinoma was not modified by gender, smoking, age, or BMI.

Diabetes was established as a possible risk factor for pancreatic cancer based primarily on two well-conducted meta-analyses [14, 15] that produced summary estimates that are very similar to ours. The first meta-analysis of nine cohort studies and 11 case–control studies reported a

Table 1 Characteristics of the 12 cohort studies included in the pooled analysis of diabetes and pancreatic cancer

Cohort	Center	Center location	Years of data collection	Age range at enrollment, Years	Cases		Controls		How diabetes status was assessed
					Diagnosed with diabetes				
					Yes	No	Yes	No	
Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study	National Cancer Institute; the National Public Health Institute	Finland	1985–1988	57–85	15	195	10	201	*Baseline Questionnaire*: Have you ever had any of the following diseases [diabetes mellitus] confirmed by a physician?
CLUE II	John Hopkins Bloomberg School of Public Health	United States	1989	42–94	16	30	17	56	*Follow-up questionnaire*: Have you ever been told by a doctor or other health professional that you have any of the following conditions [diabetes] listed below? How old were you when you were first told you had this condition [diabetes]?
Cancer Prevention Study II	American Cancer Society	United States	1997	64–90	8	157	9	156	*Baseline and Followup Questionnaires*: Has a physician ever diagnosed you with any of the following conditions: Diabetes (Yes/No) Year first diagnosed queried in categorical intervals.
European Prospective Investigation into Cancer and Nutrition	International Agency for Research on Cancer; Imperial College London	Europe	1992–2000 (varied by center)	37–84	24	346	19	391	*Baseline and Followup Questionnaires:* Self-reported response to whether participant has received a diagnosis of diabetes, in what year, by whom, and what treatment was received. (*Exact question varied by EPIC site*)
Health Professionals Follow-up Study	Harvard School of Public Health	United States	1986-	40–75	2	53	0	55	*Baseline Questionnaire:* Please mark any professionally diagnosed diseases or clinical procedures and year of first occurrence: [Diabetes Mellitus]. Years are categorical. *Followup questionnaires*: Since [last followup year] have you had any of the following professionally diagnosed conditions? [Diabetes mellitus] and year of diagnosis.
New York University Women's Health Study	New York University	United States	1991–1994	48–82	8	80	8	80	*Followup questionnaire:* Did a doctor ever tell you that you had any of the medical problems listed below? Diabetes (sugar disease) No/Yes and year first diagnosed.
Nurses' Health Study	Harvard School of Public Health	United States	1976-	30–55	2	8	0	13	*Baseline Questionnaire:* Have you ever had any of the following conditions? [Diabetes mellitus] (Yes/No). If yes, specify date of diagnosis (month/year). *Followup Questionnaires:* Since [DATE], have you had any of the following illnesses diagnosed: [Diabetes mellitus] (yes/no); Month/Year of diagnosis.

Table 1 continued

Cohort	Center	Center location	Years of data collection	Age range at enrollment, Years	Cases		Controls		How diabetes status was assessed
					Diagnosed with diabetes				
					Yes	No	Yes	No	
Physicians' Health Study	Harvard School of Public Health	United States	1982-	40–84	2	60	2	60	*Baseline Questionnaire:* Do you have a personal history of any of the following [Diabetes] (yes/no). *Followup Questionnaires*: Since you filled out the last questionnaire, have you been newly diagnosed as having any of the following conditions: [Diabetes mellitus] (yes/no), and Date of Dx (month/year)
Prostate, Lung, Colorectal, Ovarian Cancer Screening Trial	National Cancer Institute	United States	1993–2001	56–84	23	220	20	231	*Baseline Questionnaire:* Has a doctor ever told you that you have any of the following conditions [Diabetes] (Yes/No) *Followup Questionnaire:* Were you ever diagnosed with [Diabetes]? (Yes/No); At what age were you first diagnosed? (categorical)
Shanghai Men's and Women's Health Study	Vanderbilt University	China	1996 (F), 2001 (M)	43–77	12	66	12	67	*Baseline and Followup Questionnaires:* Have you ever been diagnosed with any of the following diseases? (Yes/No); Age at diagnosis (years old)
Women's Health Initiative	Fred Hutchinson Cancer Research Center	United States	1992–1998	53–88	52	231	25	258	*Baseline and Followup Questionnaires:* Treated diabetes (pills for diabetes or insulin shots for diabetes)
Women's Health Study	Harvard School of Public Health	United States	1992–1996	45 and older	6	34	1	39	*Baseline Questionnaire:* Have you ever had any of the following? [Diabetes mellitus] diagnosed prior to age 30?; at 30 or older? (Yes/no) *Followup Questionnaires:* Since you last returned a questionnaire, have you been diagnosed with any of the following: [Diabetes mellitus] (Yes/No)

pooled relative risk (RR) of 2.1 and found higher risk in the cohort studies (RR: 2.6) than the case–control studies (RR: 1.8) [14]. A subsequent meta-analysis of 19 cohort studies and 17 case–control studies also found slightly lower risk for cohort studies (RR: 1.73) than the case–control studies (RR: 1.94), with an overall summary OR of 1.82[15]. Both meta-analyses excluded cases diagnosed with diabetes within 1 year of pancreatic cancer, which could produce slightly higher risk estimates than those provided here excluding those with a duration of diabetes <2 years. However, our risk estimates were quite similar (1.79 vs. 2.1 and 1.71). Since the publication of these meta-analyses, additional epidemiologic studies have been conducted. The vast majority have reported similar positive associations [28–31], with ORs ranging from 1.8 to 3.2. One population-based cohort of approximately 18,000 men observed a nonsignificant association, of diabetes with pancreatic cancer mortality (RR: 2.47, 95 % CI: 0.79, 7.75), but was limited by low numbers of cases [32]. Another study of national hospital and cancer registries for type 2 diabetics hospitalized in Sweden with up to 40 years of follow-up observed elevated standardized incidence ratios (SIR), which were standardized to the general Swedish population, for pancreatic cancer risk, with SIRs of 6.08 overall, 3.57 excluding the first year of follow-up, and 1.80 excluding the first 5 years of follow-up [33]. Nonetheless, interpretation of the association between diabetes and pancreatic cancer has been complicated by the difficulty of developing large prospective studies with sufficient numbers of cases and follow-up periods. Many of

Table 2 Selected baseline characteristics of those included in the pancreatic cancer cohort consortium

	Cases		Controls	
	Number	%	Number	%
Age at baseline (years)				
≤ 50	41	2.9	25	1.5
51–60	213	12.9	184	10.6
61–70	652	39.5	708	40.9
71–80	613	37.2	692	40.0
81+	131	7.9	121	7.0
Gender				
Male	783	47.5	816	47.2
Female	867	52.6	914	52.8
Ancestral race				
European	1,465	88.8	1,574	91.0
African	32	1.9	33	1.9
Asian	102	6.2	105	6.1
Other/Unknown	51	3.1	18	1.0
Smoking status				
Non-smoker	638	38.7	730	42.2
Former smoker	551	33.4	611	35.3
Current smoker	455	27.6	381	22.0
Unknown	6	0.4	8	0.5
Body mass index (kg/m^2) at baseline				
< 18.5	15	0.9	20	1.2
18.5– < 2	623	37.8	726	42.0
25– < 30	676	41.0	657	38.0
30+	329	19.9	322	18.6
Missing	7	0.4	5	0.3
Personal history of diabetes				
Yes	170	10.3	123	7.1
No	1,480	89.7	1,607	92.9
Personal history of pancreatitis				
Yes	21	1.3	2	0.1
No	550	33.3	565	32.7
Missing	1,079	65.4	1,163	67.2
Family history of pancreatic cancer				
Yes	44	2.7	25	1.5
No	729	44.8	760	43.9
Missing	877	53.2	945	54.6

Table includes all participants with diabetes information, including those diagnosed with diabetes less than 2 years before pancreatic cancer diagnosis or selection as a control ($n = 36$) and also any participants diagnosed with diabetes after cancer/selection ($n = 4$)

these studies have included small numbers of cases with limited follow-up information.

In contrast to our results, an increased risk of pancreatic cancer for those with the greatest duration of diabetes was observed in the two meta-analyses discussed above. For example, Huxley et al. [15] reported a slight attenuation of risk with duration > 5 years, compared to 1–4 years, yet saw elevated risk with diabetes regardless of duration (RR: 2.05 for duration 1–4 years, RR: 1.54 for duration 5–9 years and RR: 1.51 duration for duration > 10 years). One might expect a longer exposure to diabetes to be associated with higher cancer risk; however, type 2 diabetes begins with insulin resistance and relative hyperinsulinemia. Later in the natural history, there is further loss of the islet β-cells, resulting in hypoinsulinemia [34]. If insulin levels contribute to diabetes and act as an independent risk factor for pancreatic cancer, then it follows that patients with a longer duration of diabetes, who are more likely to be hypoinsulinemic, would be at lower risk compared to those who are earlier in their diabetes natural history and have higher serum insulin levels. In fact, biomarker studies have demonstrated greater risk of pancreatic cancer with prediagnostic elevations in post-load plasma glucose [35, 36], C-peptide in nonfasting blood specimens [37], serum and plasma glucose [38, 39], HbA1c [40], and insulin [41]. Furthermore, the diabetes drug metformin, an insulin sensitizer which tends to lower insulin levels, has been associated with decreased pancreatic risk, whereas insulin and insulin secretagogues have been associated with increased pancreatic cancer risk, [42, 43] offering additional support to the hypothesis that insulin is the agent affecting risk. However, it should be recognized that many diabetics receive insulin injections, and it is possible that the insulin levels resulting from the administered insulin would also contribute to risk of pancreatic cancer. Studies of type 1 diabetics who receive routine insulin treatment have not demonstrated an excess risk of pancreatic cancer, albeit these studies are limited by very low numbers [42, 43]. It is possible that many of the type 1 diabetics were relatively hypoinsulinemic even after the insulin injections, since type 1 diabetes patients are generally less insulin-resistant and relatively hypoinsulinemic compared to type 2 diabetes patients. The lack of an effect of administered insulin may also be the result of differences in the sites of action due to differences in the site of production as compared with routes of administration. Alternatively, there may be additional biological abnormalities beyond insulin and the IGF pathway involved in diabetes (e.g., C-peptide or elevated circulating free fatty acids) that influence pancreatic cancer risk.

The relationship between diabetes and pancreatic cancer risk is further complicated by the potential for pancreatic cancer to cause diabetes [34]. Thus, it is vital in studies of risk to exclude any patient in whom diabetes has been caused by pancreatic cancer. Although there are no clinical features to distinguish diabetes due to pancreatic cancer from other diabetes, a short duration between diabetes diagnosis and pancreatic cancer diagnosis suggests that diabetes may result from pancreatic cancer [13, 44]. A recent case–control study

Table 3 Pancreatic cancer risk with gender and the duration of diabetes

Population	Diabetes status	Case	Control	Total	Unadjusted OR (95 % CI)	OR[a] (95 % CI)
All participants						
	Never	1,480	1,607	3,087	Ref	Ref
	2–8 Years	91	56	147	1.76 (1.26, 2.48)	1.79 (1.25, 2.55)
	9+ Years	50	56	106	0.97 (0.66, 1.43)	1.02 (0.68, 1.52)
Males						
	Never	719	763	1,482	Ref	Ref
	2–8 Years	32	21	53	1.62 (0.92–2.83)	1.79 (1.00–3.21)
	9+ Years	30	32	62	1.00 (0.60–1.65)	1.14 (0.67–1.93)
Females						
	Never	761	844	1,605	Ref	Ref
	2–8 Years	59	35	94	1.87 (1.22–2.87)	1.81 (1.15–2.87)
	9+ Years	20	24	44	0.92 (0.51–1.69)	0.88 (0.47–1.65)

[a] Adjusted by age, race, gender, study, smoking, alcohol use, body mass index, and family history of pancreatic cancer

Table 4 Pancreatic cancer risk by duration of diabetes

Population	Case	Control	Total	OR[a] (95 % CI)
All participants				
Never	1,480	1,607	3,087	Ref
<2 Years	29	11	40	3.02 (1.47, 6.21)
2–3 Years	11	11	22	1.10 (0.46, 2.62)
3–4 Years	27	10	37	2.97 (1.41, 6.26)
5 Years	15	11	26	1.42 (0.64, 3.16)
6 Years	17	11	28	1.66 (0.76, 3.63)
7–8 Years	21	13	34	1.95 (0.96, 3.96)
9–11 Years	23	17	40	1.44 (0.76, 2.74)
12–15 Years	11	17	28	0.74 (0.34, 1.61)
16+ Years	16	22	38	0.89 (0.46, 1.74)

[a] Adjusted by age, race, gender, study, smoking, alcohol use, body mass index, and family history of pancreatic cancer

of pancreatic cancer cases ($n = 736$) and age- and sex-matched controls ($n = 1{,}875$) evaluated the temporality of the relationship using clinical information of fasting glucose levels collected up to 5 years before diagnosis of pancreatic cancer [13]. The proportion of cases with diabetes and controls with diabetes was similar in the time period 3–5 years before pancreatic cancer diagnosis, with a small increase in the proportion of diabetic cases reported 3 years before diagnosis, and a large increase in the proportion of diabetic cases within 2 years of a pancreatic cancer diagnosis. These results suggest that diabetes discovered during the 2 years prior to pancreatic cancer diagnosis is likely the result of the cancer. In an effort to minimize the effect of possible reverse causality on our results, we excluded individuals diagnosed with diabetes within 2 years of their pancreatic cancer diagnosis. This type of reverse causality is less of a concern among those with a longer duration because pancreatic cancer is a highly fatal disease and it is unlikely that someone with undetected pancreatic cancer would remain healthy for a period of many years. A recent study on the natural history of pancreatic cancer found that almost 20 years span from the initiating mutation until cancer death; with 11.7 years from mutation to the rise of a parental clone, another 6.8 years until the development of metastatic subclones, and 2.7 years until death, on average [45]. Interpreting our findings that diabetes is a risk factor for those with diabetes for 2–8 years, but not longer than 9 years, before pancreatic cancer diagnosis, in light of this analysis suggests that the effect of diabetes occurs during the phase where the parental clone leads to the development of metastatic subclones and their escape from the pancreas.

Obesity is the leading cause of type 2 diabetes. Both obesity and diabetes appear to be risk factors of pancreatic cancer but it is difficult to fully tease apart their independent effects. Many of the hypothesized biologic pathways are the same for diabetes and obesity including insulin resistance, inflammation, and oxidative stress [12, 35]. Although the results have been mixed, most studies have found that higher BMI is correlated with an increased risk of pancreatic cancer [12, 46], as well as younger age at onset and poorer survival [47]. A recent study of the same pooled data used here found elevated risk for those in the highest quartile of BMI (OR = 1.33, 95 % CI:1.12, 1.58) [9], as did a similar study of 14 cohorts with >2,000 pancreatic cancer cases which found the obese to be at 54 % higher risk [48]. Our associations with diabetes remained after adjustment for BMI, as did the BMI associations when adjusted for diabetes, suggesting that they may have separate effects on risk.

This study had a number of strengths including a large number of cases with considerable follow-up. The prospective nature of the cohorts allowed diabetes status to be

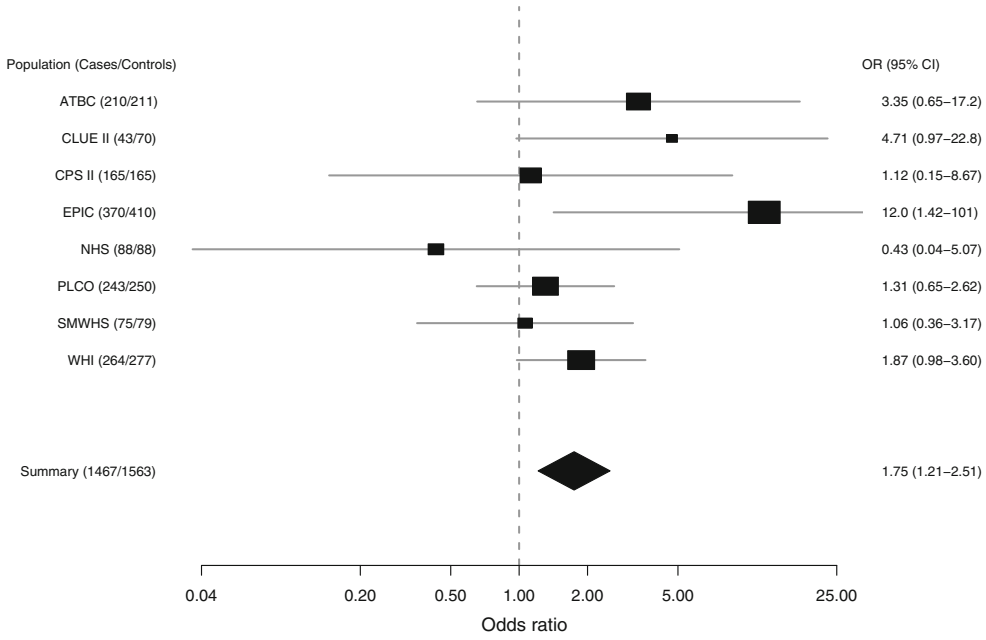

Fig. 1 Risk estimates for pancreatic cancer associated with diabetes by study for 2–8 years

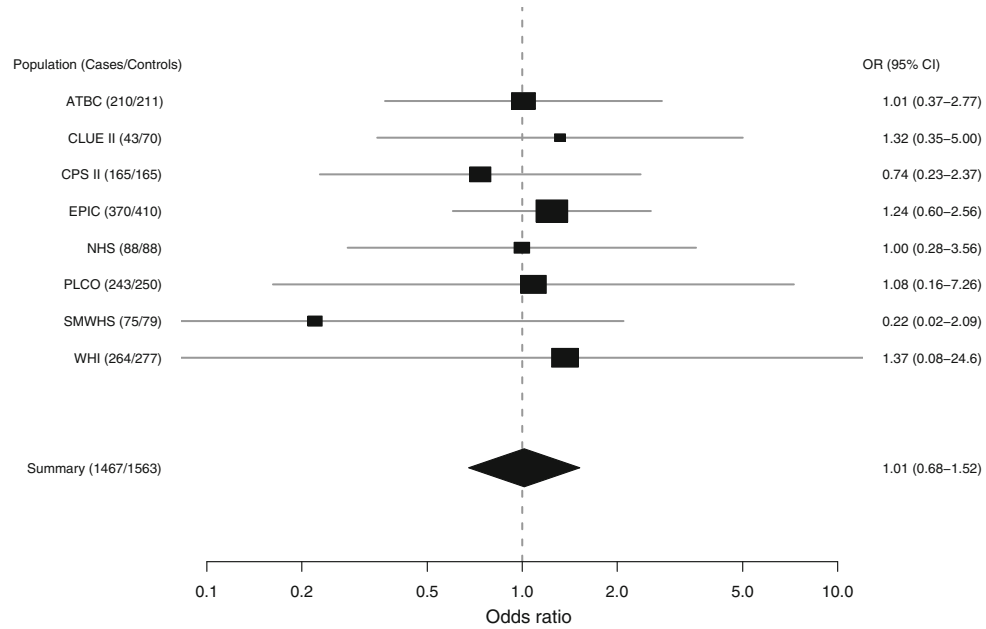

Fig. 2 Risk estimates for pancreatic cancer associated with diabetes by study for 9+ years

assessed before the diagnosis of cancer, eliminating recall bias. By excluding patients diagnosed with diabetes within 2 years of a pancreatic cancer diagnosis, we minimized the possibility that associations seen here are due to reverse causality. The major limitation is that we measured diabetes from self-report in cohorts of people who were enrolled before the recent rise in diabetes. Recent estimates of the prevalence of diabetes in the United States among those over 20 years of age are approximately 11 % [49]. Most of the cohorts included in this analysis had much lower prevalence, with the exception of CLUE II, in large part because they occurred decades earlier. Further, approximately one-third of diabetics are estimated to be undiagnosed [50]. The resulting misclassification would be expected to be non-differential across cases and controls and would tend to bias our results toward the null. In addition, self-reported estimations of duration may not be accurate and we were unable to include glucose or insulin measures in the models. There is also the possibility of misclassification of pancreatic cancer cases; however, cases were rigorously confirmed and it is unlikely that subjects would remain healthy with asymptomatic

pancreatic cancer for years. Due to very low numbers of people reporting type 1 diabetes in our sample ($n = 4$ among cases), we did not analyze type 1 and type 2 diabetes separately and thus cannot assess whether the association with pancreatic cancer is different. We did not have available medication data and therefore were unable to measure the effect of diabetes-related treatments, which have been shown to affect pancreatic cancer risk [31]. It is possible that this may account for some of the attenuation in risk seen by duration, as those with the longest duration of diabetes would likely have received the treatments associated with decreased risk for the longest period of time.

In summary, our results support a growing literature that suggests diabetes is an independent risk factor for pancreatic cancer. With the rise of the obesity epidemic, the number of diabetics in the United States and globally is increasing rapidly. There are few identified risk factors for pancreatic cancer and even fewer that can be modified. Reducing diabetes by controlling obesity could benefit pancreatic cancer rates, in addition to the many other known health benefits.

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