Family History of Diabetes and Pancreatic Cancer as Risk Factors for Pancreatic Cancer: The PACIFIC Study

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Abstract

Genetic association studies have identified more than a dozen genes associated with risk of pancreatic cancer. Given this genetic heterogeneity, family history can be useful for identifying individuals at high-risk for this disease. The goal of this analysis was to evaluate associations of family history of diabetes and family history of pancreatic cancer with risk of pancreatic cancer. PACIFIC is a case-control study based in two large health plans. Cases were diagnosed with pancreatic ductal adenocarcinoma (PDA) and controls were selected from the health plan enrollment databases and frequency-matched to cases. Family history data were collected using an interviewer-administered questionnaire and were available on 654 cases and 697 controls. Logistic regression was used for the association analyses. First-degree relative history of diabetes was statistically significantly associated with increased risk of PDA (odds ratio (OR): 1.37, 95% confidence interval (CI): 1.10–1.71). The highest risk of PDA was observed for an offspring with diabetes (OR: 1.95, 95% CI: 1.23–3.09). In addition, history of pancreatic cancer increased risk for PDA with an OR of 2.79 (95% CI: 1.44–4.08) for any first-degree relative history of pancreatic cancer. This population-based analysis demonstrated that family history of diabetes was associated with increased risk of PDA, and confirmed previous studies showing that first-degree family history of pancreatic cancer is associated with PDA. These results support need for ongoing studies of genetic influences on pancreatic cancer in large samples and investigations of possible pleiotropic genetic effects on diabetes and pancreatic cancer.

Introduction

Pancreatic cancer is the 4th leading cause of cancer mortality in the US for both men and women (1). Most tumors are pancreatic ductal adenocarcinoma (PDA) and patients have a median survival of only 4 months (2). The estimated annual death toll in the US is 37,390 and five-year survival is only 6%. Although smoking is the best established risk factor for PDA (3), diabetes mellitus has also been consistently associated with PDA (4). An analysis from the Pancreatic Cancer Cohort (PanScan) Consortium (5) reported that 2–8 years duration of diabetes was associated with an 80% increased risk of the disease, but longer duration (>9 years) was not. The inaccessibility of the pancreas, the nonspecific symptoms

of pancreatic cancer, the advanced stages of disease at diagnosis, and a lack of effective therapy continue to make etiologic studies of pancreatic cancer challenging.

It has been estimated that 5 – 10% of pancreatic cancer is genetically influenced (6). Family-based studies and genome-wide association studies (GWAS) have reported that more than a dozen candidate genes or genomic regions are associated with risk of pancreatic cancer, including BRCA2, STK11, p16/CDKN2, PALB2, and the ABO blood group locus (7). These range from rare genetic variants conferring high risk ("high penetrance genes") to common genetic variants with relatively small risk ("low penetrance genes") (7).

Given this genetic heterogeneity, family history can be a useful disease-prediction tool, and the PancPRO model was developed to identify high-risk individuals based on their affected family members with pancreatic cancer (8). A meta-analysis of nine studies reported an 80% increased risk of pancreatic cancer associated with having an affected relative (9). More recently, Jacobs et al. (10) used data from seven PanScan studies and found an essentially identical overall odds ratio (OR) of 1.76 for the association between having a family history of pancreatic cancer in a first-degree relative and risk of pancreatic cancer. Similar results were also seen in the Cancer Prevention Study II (CPS-II), based on approximately 1.1 million men and women, in which family history of pancreatic cancer in a parent or sibling was associated with 66% increased risk of pancreatic cancer mortality (11). Few of these studies have considered whether any specificity exists across subtypes of first-degree relatives: mothers, fathers, sisters, brothers, and offspring.

Previous studies have also suggested an association between family history of diabetes and risk of pancreatic cancer, although the results have not been consistent (12, 13). Genes involved in diabetes may be associated with pancreas cancer as well. For example, the Pro12Ala variant of the PPAR- diabetes susceptibility gene was associated with risk of pancreatic cancer in a small cohort of smokers (14), although this finding was not replicated in a larger case-control study (15). Taken together, these data support the existence of genetic predisposition to pancreatic cancer and the possible role of family history in identifying high-risk individuals.

The goal of this analysis was to evaluate associations of family history of diabetes and family history of pancreatic cancer with risk of PDA using a case-control sample from two large health plans in the Western U.S.

Materials and Methods

Data Collection

The Pancreatic Cancer: Investigation into Finding Causes (PACIFIC) Study is a case-control study of pancreatic cancer based in the defined populations of two large health plans (Group Health Cooperative (GHC) in Seattle, WA and Kaiser Permanente Northern California, (KPNC)). Case subjects were newly diagnosed pancreatic cancer cases recruited from either July 2005 (GHC) or August 2005 (KPNC) through December 2009, using an ultra-rapid identification procedure with physician consent. A total of 1,209 eligible cases (1,031 at KPNC and 178 at GHC) were identified during the study period, all of whom were at least 21 years of age and enrolled in their health plan at the time of diagnosis. Controls were randomly sampled from enrollment files at each health plan and frequency-matched to cases on age (5 year intervals) and sex. A total of 1,670 controls were identified as eligible. They were recruited using identical methods to that of cases, except no physician consent was obtained. Sex and age data were available from administrative records, whereas race, ethnicity, diabetes and smoking histories up to one year prior to diagnosis for cases and reference date for controls were obtained at interview.

Family history data were collected using an interviewer-administered questionnaire that queried history of cancer, diabetes, and other chronic diseases among parents, siblings, and offspring of study subjects, as well as vital status and age (or age at death) of each relative. Interviewers recorded the type of cancer verbatim; subsequently, ICD-9 codes were applied. Specific information on type 1 versus type 2 diabetes was not obtained.

Of the 1,209 eligible cases, 531 (44%) died prior to the interview. Of the remaining 678 cases, and after excluding 3 adopted cases, family history data were available on 654 (96%) cases. Of the 1,620 eligible controls, 874 (54%) were successfully enrolled in the study. After excluding 18 adopted controls, family history data were available on 697 of the enrolled controls (80%).

Statistical Methods

All analyses were conducted using SPSS 19.0. Logistic regression was used to evaluate the associations between family history of diabetes and family history of pancreatic cancer with case/control status (16), with adjustment for sex, age (continuous), race, and ethnicity. Odds ratios (OR) and 95% confidence intervals (CI) were calculated for the following subsets of family history: maternal, paternal, parental, brother, sister, sibling, parent and/or sibling, offspring, and all first-degree relatives. For family history of diabetes, we also calculated risk of PDA for two or more first-degree relatives with diabetes. This estimate was not possible for family history of pancreatic cancer because only one case had two relatives with pancreatic cancer, a brother and a sister.

Results

As shown in Table 1, distributions of age, sex, and Caucasian race were similar for cases and controls. The proportion of ever smokers was higher among cases than controls (54% vs. 49%), with smoking among controls similar to the prevalence of ever smoking among whites in this age group based on National Health Interview Survey data (17) (Prevalence of current smokers was 15.9% and 8.9% among cases and controls, respectively). The proportion of individuals with a personal history of diabetes diagnosed at least one year prior to reference date was also higher in cases than in controls (21% vs. 15%).

We observed a statistically significant association between history of diabetes in parents, sisters, and siblings and risk of PDA, with ORs of 1.32, 1.60, 1.39, respectively (Table 2). The highest risk was observed for having an offspring with diabetes (OR: 1.95, 95% CI: 1.23–3.09). As expected from these results, history of diabetes in any first-degree relative was also statistically significantly associated with risk of PDA (OR: 1.37, 95% CI: 1.10–1.71). The risk of PDA associated with having two or more relatives with diabetes was slightly higher (OR: 1.41, 95% CI: 1.06–1.88).

We observed a more than two-fold increase in risk of PDA associated with a paternal or maternal history of pancreatic cancer, although these associations were not statistically significant (Table 3). However, for mothers and fathers combined, the observed elevation in risk was statistically significant (OR: 2.57, 95% CI: 1.29–5.12). We observed only a modest increase in risk with having a brother with pancreatic cancer (OR: 1.49), but a more than two-fold increase in risk associated with a sister with a similar history (OR: 2.47). As with parental history, the combined sibling association was statistically significant (OR: 2.28, 95% CI: 1.01–5.13). As expected from the age distribution of study participants, the number of offspring with pancreatic cancer was small, limiting the precision of our estimates for this association (OR: 0.55, 95% CI: 0.05–6.20). Combining all first-degree relatives resulted in the largest magnitude of risk in this analysis (OR: 2.79, 95% CI: 1.44–4.0).

Discussion

In this study, history of diabetes in any first-degree relative was statistically significantly associated with risk of PDA (OR=1.37, 95% CI 1.10–1.71). Statistically significant associations between history of diabetes in parents, siblings and offspring and risk of PDA were also observed. The risk of PDA associated with having two or more relatives with diabetes was slightly higher (OR=1.41), and was also statistically significant. We also confirmed results from previous studies showing that family history of pancreatic cancer in first-degree relatives was associated with increased risk of PDA.

To our knowledge, this study is the first to examine risk of pancreatic cancer associated with family history of diabetes among subsets of first-degree relatives. An early population-based case-control study did not find any association with diabetes in first-degree relatives, whereas a clinic-based study found a moderate association (12, 13). We found that the strongest relationship was for history of diabetes in offspring (OR=1.95) with lower, but still statistically significant associations for history of diabetes among parents (OR=1.32), and siblings (OR=1.39). This difference could be due to recall bias if cases have poorer knowledge of the health status of their siblings and parents than of their offspring. Family history of diabetes did not distinguish between type 1 and type 2 diabetes, also potentially biasing the results.

Despite these limitations, these results, if confirmed, imply that there could be common, underlying genetic susceptibility to both diabetes and pancreatic cancer, diseases that involve the same organ. Based on case-control data from the Cancer Genetic Markers of Susceptibility (CGMES) PanScan-I GWAS, we recently examined 37 common type 2 diabetes susceptibility variants for association with risk of pancreatic cancer (18). Although the results did not provide strong evidence for association of these variants with risk of PDA, nominally significant associations were found for two genes, FTO and MTNR1B. In addition, familial aggregation of lifestyle factors such as obesity and cigarette smoking, both established risk factors for diabetes, could explain the familial associations reported here.

These results confirm previous studies demonstrating familial aggregation of pancreatic cancer. The largest study to date, the CPS-II study, based on approximately than 1.1 million men and women and 7,306 pancreatic cancer deaths, reported a relative risk (RR) of 1.66 (95% CI 1.43–1.94) for the association between pancreatic cancer in a parent or sibling and pancreatic cancer mortality (11). Similarly, recent findings from the PanScan Consortium that included 1,183 cases and 1,205 controls found a nearly 80% increase in risk associated with a family history of pancreatic cancer in a first-degree relative (OR: 1.76, 95% CI: 1.19–2.61) (10). Data from the nationwide Swedish Family-Cancer Database, created by linking the Swedish Cancer Registry with an administrative register of all Swedish families, calculated standardized incidence rations (SIRs) for offspring of parents with pancreatic tumors. The resulting SIR for pancreatic cancer in offspring was 1.73 (95% CI 1.13–2.54) for pancreatic adenocarcinoma in a parent (19). The magnitude of the association for a first-degree family history of pancreatic cancer in the present study was higher (OR=2.79) than estimates from these previous studies. This may be due to potential biases in the present study, including differential interview rates among eligible cases and controls. That is, only 80% of the study controls completed the family history questionnaire, due primarily to failure to complete the study interview, compared to 97% of the living cases. Despite the ultra-rapid case ascertainment, 44% of cases died before interview, also possibly introducing bias in the estimation of familial risk. Finally, due to the modest size of this study, the confidence interval is relatively wide (1.44–4.08), and includes the point estimates from the previous studies. Nonetheless, the accumulating evidence demonstrates that history of

pancreatic cancer in a first-degree relative confers an approximately 2-fold increased risk of pancreatic cancer.

An important next step in this research will be to determine the extent to which recently discovered genetic susceptibility variants contribute to the familial risk of pancreatic cancer. GWAS and candidate gene studies have implicated several genetic susceptibility variants, including the ABO locus on chromosome 9 (20,21) and chromosomal regions 1q32.1 and 13q22.1 (22). Most recently, The SET binding factor 2 (SBF2) on chromosome 11p15.4 has been associated with pancreatic cancer survival (23). Currently available methods can be applied to determine the genetic variance in pancreatic cancer risk attributable to associated single nucleotide polymorphisms based on GWAS data (24).

In conclusion, this population-based analysis of pancreatic cancer cases and controls demonstrated that family history of diabetes was statistically significantly associated with an approximately 30% increased risk of PDA with the highest risk of PDA seen for an offspring with diabetes (OR: 1.95). In addition, history of pancreatic cancer was a risk factor for PDA for any first-degree relative history of pancreatic cancer. These results support a need for further studies of genetic influences on pancreatic cancer in large samples, and investigations of possible pleiotropic genetic effects on diabetes and pancreatic cancer. Such research would advance our understanding of the etiology of pancreatic cancer, and contribute to strategies for the early detection and, perhaps, prevention of this devastating disease.

Acknowledgments

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Table 1

Characteristics of Pancreatic Cancer Cases and Controls

	Cases		Controls	
	N=654	%	N=697	%
Sex				
Female	331	50.6	358	51.4
Male	323	49.4	339	48.6
Age (years, mean ±SD)	68.1 ± 11.2		67.8 ± 11.1	
Race				
White/Caucasian	488	74.6	545	78.2
Black	57	8.7	36	5.2
Asian/Pacific Islander	57	8.7	53	7.6
Other	52	8.0	63	9.0
Hispanic Ethnicity[*]				
Hispanic	57	8.9	65	9.4
Not Hispanic	582	91.1	625	90.6
Smoking[*]				
Ever	354	54.3	343	49.4
Never	298	45.7	352	50.6
Personal History of Diabetes[*]				
Yes	134	20.6	105	15.1
No	518	79.4	592	84.9

[*]Samples sizes vary due to missing data

Table 2

Association between family history of diabetes in first degree relatives and risk of pancreatic cancer

Family History of Diabetes[*]	Cases (%)	Controls (%)	Adjusted[**] Odds Ratio	95% Confidence Interval
Father	77/579 (13.3)	76/640 (11.9)	1.30	(0.97–1.74)
Mother	123/614 (20.0)	109/665 (16.4)	1.15	(0.91–1.64)
Parents	187/578 (32.4)	167/634 (26.3)	1.32	(1.03–1.69)
Brothers	81/400 (20.3)	81/444 (18.2)	1.18	(0.85–1.66)
Sisters	89/417 (21.3)	67/446 (15.0)	1.60	(1.14–2.26)
Siblings	141/332 (42.5)	126/354 (35.6)	1.39	(1.05–1.82)
Offspring	53/319 (16.6)	32/340 (9.4)	1.95	(1.23–3.09)
Parents and/or siblings	256/392 (65.3)	236/413 (57.1)	1.34	(1.07–1.68)
Any first degree relative	278/341 (81.5)	255/340 (75.0)	1.37	(1.10–1.71)
Two or more first degree relatives	140/341 (41.1)	111/340 (32.6)	1.41	(1.06–1.88)

[*] Sample sizes vary due to missing data and exclusion of cases and controls with no brothers, sisters, siblings or offspring as appropriate

[**] Adjusted for sex (male/female), age (continuous), race (Black, Asian/Pacific Islander, White, Other), Hispanic Ethnicity (Hispanic/non-Hispanic)

Table 3

Association between family history of pancreatic cancer in first degree relatives and risk of pancreatic cancer

Family History of Pancreatic Cancer[*]	Cases (%)	Controls (%)	Adjusted[**] Odds Ratio	95% Confidence Interval
Father	15/577 (2.6)	7/650 (1.1)	2.25	(0.90–5.62)
Mother	13/609 (2.1)	6/678 (0.9)	2.45	(0.92–6.52)
Parent	28/562 (5.0)	12/637 (1.9)	2.57	(1.29–5.12)
Brother	8/434 (1.8)	6/460 (1.3)	1.49	(0.52–4.36)
Sister	11/431 (2.6)	5/453 (1.1)	2.47	(0.85–7.19)
Sibling(s)[†]	18/532 (3.4)	9/562 (1.6)	2.28	(1.01–5.13)
Offspring	1/541 (0.2)	2/588 (0.3)	0.55	(0.05–6.20)
Parent and/or Sibling	46/550 (8.4)	20/597 (3.4)	2.63	(1.54–4.52)
Any First Degree Relative	47/538 (8.7)	22/580 (3.8)	2.79	(1.44–4.08)

[*] Sample sizes vary due to missing data and exclusion of cases and controls with no brothers, sisters, siblings or offspring as appropriate

[**] Adjusted for sex (male/female), age (continuous), race (Black, Asian/Pacific Islander, White, Other), Hispanic Ethnicity (Hispanic/non-Hispanic)

[†] One case had both a brother and sister with pancreatic cancer