

Importance of Age of Onset in Pancreatic Cancer Kindreds

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Background Young-onset cancer is a hallmark of many familial cancer syndromes, yet the implications of young-onset disease in predicting risk of pancreatic cancer among familial pancreatic cancer (FPC) kindred members remain unclear.

Methods To understand the relationship between age at onset of pancreatic cancer and risk of pancreatic cancer in kindred members, we compared the observed incidence of pancreatic cancer in 9040 individuals from 1718 kindreds enrolled in the National Familial Pancreas Tumor Registry with that observed in the general US population (Surveillance, Epidemiology, and End Results). Standardized incidence ratios (SIRs) were calculated for data stratified by familial vs sporadic cancer kindred membership, number of affected relatives, youngest age of onset among relatives, and smoking status. Competing risk survival analyses were performed to examine the risk of pancreatic cancer and risk of death from other causes according to youngest age of onset of pancreatic cancer in the family and the number of affected relatives.

Results Risk of pancreatic cancer was elevated in both FPC kindred members (SIR = 6.79, 95% confidence interval [CI] = 4.54 to 9.75, $P < .001$) and sporadic pancreatic cancer (SPC) kindred members (SIR = 2.41, 95% CI = 1.04 to 4.74, $P = .04$) compared with the general population. The presence of a young-onset patient (<50 years) in the family did not alter the risk for SPC kindred members (SIR = 2.74, 95% CI = 0.05 to 15.30, $P = .59$) compared with those without a young-onset case in the kindred (SIR = 2.36, 95% CI = 0.95 to 4.88, $P = .06$). However, risk was higher among members of FPC kindreds with a young-onset case in the kindred (SIR = 9.31, 95% CI = 3.42 to 20.28, $P < .001$) than those without a young-onset case in the kindred (SIR = 6.34, 95% CI = 4.02 to 9.51, $P < .001$). Competing risk survival analyses indicated that the lifetime risk of pancreatic cancer in FPC kindreds increased with decreasing age of onset in the kindred (hazard ratio = 1.55, 95% CI = 1.19 to 2.03 per year). However, youngest age of onset for pancreatic cancer in the kindred did not affect the risk among SPC kindred members.

Conclusions Individuals with a family history of pancreatic cancer are at a statistically significantly increased risk of developing pancreatic cancer. Having a member of the family with a young-onset pancreatic cancer confers an added risk in FPC kindreds.

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This year it is estimated that 42 470 Americans will be diagnosed with pancreatic cancer and 35 240 will die from their disease (1). Both environmental and genetic factors contribute to the etiology of pancreatic cancer (2). Twenty percent of cases are attributable to cigarette smoking, the most important established risk factor (3–5). Other important risk factors include a family history of pancreatic cancer, presence of type 2 diabetes mellitus, inherited and/or long-standing chronic pancreatitis and obesity (6–12).

Numerous case reports, case-control studies, and cohort studies have demonstrated that individuals with a family history of pancreatic cancer are at increased risk of developing pancreatic cancer themselves (4,8). The National Familial Pancreas Tumor Registry (NFPTR) was created in 1994 to understand better the genetic and environmental factors that cause the familial aggregation of pancreatic cancer. As of November 5, 2009, 3491 families

had enrolled in the NFPTR. Of these, 1,146 families met the established definition of “familial pancreatic cancer (FPC)” because they had a pair of first-degree relatives with pancreatic cancer. Families that do not meet this criterion (ie, families with only one relative with pancreatic cancer or with multiple pancreatic cancers in more distant relatives and/or spouses with pancreatic cancer) are defined as sporadic pancreatic cancer (SPC) kindreds. The goal of this classification is to identify kindreds that harbor a pancreatic cancer susceptibility gene(s).

Previously, we demonstrated that members of FPC kindreds had an increased risk of developing pancreatic cancer and that this risk increased with the number of affected first-degree relatives (12,13). Germline mutations in the *CDKN2A*, *BRC2*, *PALB2*, *STK11*, and *PRSS1* genes have been shown to increase a person’s risk of developing pancreatic cancer (10,14–19); however, these known genetic

CONTEXT AND CAVEATS

Prior knowledge

It was not clear whether family members of young-onset pancreatic cancer patients are at greater risk of developing pancreatic cancer than family members of older-onset patients.

Study design

Standardized incidence ratios for members of Familial Pancreatic Cancer (FPC) and Sporadic Pancreatic Cancer (SPC) families were calculated with data from the US National Familial Pancreas Tumor Registry compared with those from the Surveillance, Epidemiology, and End Results database. A statistical model that considered death due to other causes as a competing event was used to estimate lifetime risk of pancreatic cancer among family members.

Contribution

Members of FPC families had a more than sixfold higher incidence of pancreatic cancer than the general population, and relatives of those patients diagnosed before the age of 50 years had a more than ninefold higher incidence of pancreatic cancer; members of SPC families, regardless of the age of onset of pancreatic cancer in their relative, had more than twofold higher incidence. In contrast to its elevation of risk among FPC family members, age of onset did not alter risk among sporadic pancreatic cancer family members.

Implications

Among families with a clustering pancreatic cancer, young-onset disease is associated with particularly high cancer risk.

Limitations

Some FPC family members underwent pancreatic cancer screening, which could have increased disease detection. Also, often data were obtained from a next of kin proxy, so only 66% of prospective cancers were confirmed by medical records.

From the Editors

syndromes account for only 10%–20% of the familial clustering of pancreatic cancer. Pedigree studies support the existence of additional pancreatic cancer susceptibility genes (20), and linkage studies to localize these susceptibility genes are currently under way (21).

In addition to family history, some studies have suggested that relatives of young-onset pancreatic cancer patients may have a higher risk of developing pancreatic cancer even in the absence of multiple affected relatives (22). In other cancer syndromes, including hereditary breast and ovarian cancer syndrome and hereditary colon cancer, family members who carry the gene mutations associated with these syndromes develop cancer at a younger age than persons with sporadic cancers. For example, the Amsterdam Criteria (23), which were created to identify individuals at high risk for germline mutations associated with hereditary nonpolyposis colorectal cancer, include, as a prominent criterion, having a family member diagnosed with colon cancer before the age of 50 years. In addition, carriers of *BRCA1* and *BRCA2* gene mutations are known to develop breast or ovarian cancers at a younger age than patients with sporadic breast or ovarian cancers (24).

However, it is uncertain whether inherited pancreatic cancer is more likely than sporadic pancreatic cancer to follow a course of early-onset presentation. The average age of onset among the FPC

patients who were recruited as part of the Pancreatic Cancer Genetic Epidemiology Consortium (PacGENE) was approximately 6 years younger than the age of onset for pancreatic cancer in the general US population (around 70 years), although some of this difference may reflect ascertainment bias because many participants self-enrolled in high-risk family registries (21). Additionally, segregation analysis provided evidence of a major gene for pancreatic cancer that influences age of onset, such that the mean age of onset of pancreatic cancer was estimated to be 72 years in gene carriers compared with 110 years in noncarriers (assuming no competing causes of death). However, other studies have demonstrated that the average age of onset of pancreatic cancer is quite similar between FPC and SPC (nonfamilial) kindreds (25).

To address the question of whether the incidence of pancreatic cancer is higher among individuals with a family history of young-onset pancreatic cancer, we compared the incidence of pancreatic cancer among relatives of young- and late-onset pancreatic cancer patients enrolled in the NFPTR. Standardized incidence ratios (SIRs) were computed that compared the incidence of pancreatic cancer in these subgroups with that expected in Surveillance, Epidemiology, and End Results (SEER). Furthermore, competing risk survival analysis was conducted to estimate the risk of death due to pancreatic cancer and that due to other causes and to estimate whether age of onset of pancreatic cancer modified these risks.

Subjects and Methods

Study Subjects

This study was reviewed and approved by the Institutional Review Board of the Johns Hopkins Medical Institutions, and informed consent was obtained from all study participants. NFPTR was established at The Johns Hopkins Hospital on January 1, 1994, and to our knowledge is currently one of the largest registries of pancreatic cancer kindreds.

Family members were eligible for the study if they did not have pancreatic cancer at the time of their enrollment in the NFPTR; if they enrolled between January 1, 1994, and December 31, 2006; and if any follow-up was available. FPC kindreds were defined as families with at least a pair of first-degree relatives with ductal adenocarcinoma of the pancreas (ie, a parent–offspring or sibling pair). SPC kindreds were defined as those families which included a pancreatic cancer patient but did not include a pair of affected first-degree relatives. Follow-up was available for at least one individual from 72% of the families who had been enrolled in the NFPTR before December 31, 2006.

After written informed consent was obtained, a questionnaire was completed by either the pancreatic cancer patient (40%) or by a proxy of the patient (60%). The questionnaire included information on the cancer history and smoking exposures of patients and their family members. This information included age, sex, cancer status, age at cancer diagnosis, and ever vs never cigarette smoking status. At least one member of each family was contacted annually by mail to obtain updated health information, including vital status and cancer diagnoses for all members. Whenever possible, incident pancreatic cancers were confirmed through requisition of pathology reports, review of pathology slides, medical records, and/or death certificates.

Statistical Methods

Standardized incidence ratios were calculated by comparing the number of incident pancreatic cancers observed in kindreds enrolled in the NFPTR with those expected using SEER incidence rates for the general population (26). Person-years of follow-up were calculated from the time of enrollment in the NFPTR until the most recent contact date, date of pancreatic cancer diagnosis, date of death, or date of surgical resection of the pancreas. Total person-time in each stratum was multiplied by the age-, race-, sex-, and calendar year-specific SEER incidence rate to determine the expected incidence of pancreatic cancer. Young-onset pancreatic cancer kindreds were defined as kindreds in which a member had been diagnosed with pancreatic cancer before the age of 50 years, whereas late-onset kindreds were defined as kindreds in which all pancreatic cancers developed at age 50 years or greater. Smokers were defined as individuals reported to have smoked more than 100 cigarettes in their lifetime, and nonsmokers as individuals who never smoked or smoked fewer than 100 cigarettes. Individuals with missing smoking data were categorized independently. Confidence intervals (CIs) were determined based on the Poisson distribution and *P* values obtained using the approach of Rothman and Boice (27) as detailed in Breslow and Day (28).

Fewer than 200 individuals enrolled in the NFPTR also participate in the Cancer of the Pancreas Screening (CAPS) research protocol to screen for precancerous lesions in the pancreas. Because these individuals represented those at the highest risk of developing pancreatic cancer, exclusion of these patients would have caused an underestimation in risk. We therefore accounted for the impact of early detection (either clinical screening or screening as part of CAPS) by incorporating the effect of screening into the analysis as follows. Individuals who underwent pancreatectomy based on the results of their screening examinations were censored at their date of surgery. Individuals whose resected pancreas was found to have one or more of the following histologies (after pathological evaluation of resected tissue by R. H. Hruban) were considered to have pancreatic cancer: invasive adenocarcinoma (*n* = 0), pancreatic intraepithelial neoplasia-3 (PanIN-3) (*n* = 2, including one patient with 14 PanIN-3 lesions and a focus of microinvasive carcinoma), or intraductal papillary mucinous neoplasm with high-grade dysplasia (*n* = 2). Given that these high-grade precursor lesions are rarely observed in individuals without pancreatic cancer (29), it is very likely that these patients would have developed pancreatic cancer during follow-up if they had been left untreated. The remaining nine individuals enrolled in CAPS who underwent partial or total pancreatectomies, but were found not to have one of these high-grade lesions, were considered free of pancreatic cancer at last follow-up. In addition, there was one individual who was found to have unresectable pancreatic cancer during screening and was considered affected in all analyses.

Time-to-event analyses were conducted using competing risk methods (30–33). Briefly, although individuals are at risk for pancreatic cancer, it is probable that some individuals will die from other causes before pancreatic cancer can occur. These competing causes of death may be important, given that both known factors (ie, cigarette smoking, germline *BRCA2* mutations) and unknown genetic factors may be associated both with risk of pancreatic cancer and with mortality due to other causes (ie, other cancers, car-

diovascular disease). Because of these competing risks, the observed cumulative incidence of pancreatic cancer will be smaller. Therefore, a cause-specific proportional hazards model, in which youngest age of onset was treated as a continuous variable, was used to assess the association of the development of pancreatic cancer in study subjects with the age at onset of pancreatic cancer in a family member (34,35). The cause-specific model was essentially a standard Cox proportional hazards model that jointly modeled both the development of pancreatic cancer and all-cause mortality using the data augmentation approach that stratifies the model on event type as outlined by Lunn and McNeil (35). To estimate the cumulative incidence of pancreatic cancer in the presence of the competing risk of death, the cause-specific hazards for pancreatic cancer and the cause-specific hazards for all-cause mortality from the joint proportional hazards model were combined (36,37): $CIF(t) = \int_0^t h_1(s) \exp(-\int_0^s (h_1(u) + h_2(u) du)) ds$, where $CIF(t)$ is the cumulative incidence function, h_1 and h_2 are the cause-specific hazards for pancreatic cancer and all-cause mortality, respectively. Modeling both events in a joint cause-specific hazards model makes it possible for the cumulative incidence function of pancreatic cancer in the presence of a competing event to be estimated (31–33).

We used a robust grouped jackknife variance estimator to allow for correlation between family members (38). Age was used as the time scale for the survival analyses. Because there was some indication that the proportional hazards assumption did not hold with all-cause mortality, a binary interaction with age (70 years) was included for the variables in which there was an indication of non-proportionality. Nonlinear associations between covariates and events were examined using fractional polynomials (39,40) but were not found to improve the model fit, and therefore, these were not included in the final model.

Parameter estimates from the final fitted models were used to estimate the cumulative incidence pancreatic cancer in the presence of competing risks (31–33). Variability of the cumulative incidence estimates was then obtained using bootstrapping (1500 iterations) (41). Iterations (*n* = 18) in which the model had convergence problems because of small sample sizes were dropped.

All analyses were done in R version 2.7 (<http://www.r-project.org/>). All *P* values are two-sided.

Results

A total of 9040 individuals who had at least one first-degree relative with pancreatic cancer, from 1718 kindreds, were included in this study. They contributed to a total of 34 878 person-years of follow-up. A total of 41 study subjects developed prospective pancreatic cancers: 29 members of FPC kindreds, eight members of SPC kindreds, and four participants who were genetically unrelated to the probands in their families (Table 1). Twenty-seven (66%) of the 41 prospective pancreatic cancers included in this study were confirmed by review of pathology reports, microscopic slides, and/or death certificates. In addition to the 41 prospective pancreatic cancers included in the analyses, 22 prospective pancreatic cancers developed in either more distant (non-first-degree) relatives (*n* = 13) or after the follow-up period for this study (*n* = 9).

Table 1. Demographics of study population*

Subject group	Family members at risk		Incident pancreatic cancers among family members	
	No. of individuals	Mean age at baseline (±SD)	No. of individuals	Mean age at diagnosis of pancreatic cancer (±SD)
Subjects from FPC kindreds				
Men	1841	55.6 (±17.8)	10	67.7 (±8.9)
Women	2093	57.9 (±18.4)	19	68.9 (±12.4)
Subjects from SPC kindreds				
Men	1856	55.1 (±17.8)	2	73.6†
Women	2160	57.5 (±18.4)	6	73.9 (±11.5)
Genetically unrelated subjects				
Men	448	70.8 (±11.6)	2	81.1†
Women	642	67.6 (±12.1)	2	76.1†
Total	9040	58.1 (±18.0)	41	69.7 (±10.9)

* Genetically unrelated subjects are spouses and non-blood relatives associated with either FPC or SPC kindreds. Study population is from the Johns Hopkins University National Familial Pancreas Tumor Registry database. FPC = familial pancreatic cancer; SPC = sporadic pancreatic cancer.

† SDs are not presented because of small number of individuals.

We compared the incidence of pancreatic cancer in the NFPTR with that expected from SEER data (Table 2). When we controlled for age, race, sex, and calendar year, the overall observed incidence of pancreatic cancer in the FPC kindreds was higher than that expected in the general population from SEER data (FPC SIR = 6.79, 95% CI = 4.54 to 9.75, $P < .001$).

In the FPC kindreds, risk varied by the number of first-degree relatives with pancreatic cancer, such that risk was higher in individuals with three first-degree relatives who had pancreatic cancer (SIR = 17.02, 95% CI = 7.34 to 33.5, $P < .001$) but lower in individuals who had two first-degree relatives with pancreatic cancer (SIR = 3.97; 95% CI = 1.59 to 8.2, $P = .005$) or with one affected

first-degree relative (SIR = 6.86, 95% CI = 3.75 to 11.04, $P < .001$). Whereas risk was higher for FPC kindred members who had one first-degree relative with pancreatic cancer as compared with two, the confidence intervals for these two estimates largely overlap.

The observed incidence of pancreatic cancer in the SPC kindreds was also statistically significantly higher than that expected from SEER data (SPC SIR = 2.41, 95% CI 1.04 to 4.74, $P = .04$). Risk among unrelated individuals (spouses) was also elevated (unrelated SIR = 2.14, 95% CI = 0.58 to 5.49, $P = .23$), but this increase was not statistically significant. Because spouses share environmental but not genetic factors with the at-risk relatives, we included this population as an internal control group.

Table 2. Standardized incidence ratios (SIRs) of pancreatic cancer among family members at risk: overall and stratified by family history and smoking status*

Family history	No. of individuals	Person-years of follow-up	Observed cases	Expected cases	SIR* (95% CI)	P
Familial						
Overall	3934	16760	29	4.27	6.79 (4.54 to 9.75)	<.001
Three or more first-degree relatives	176	797	8	0.47	17.02 (7.34 to 33.5)	<.001
Two first-degree relatives	1043	4477	7	1.76	3.97 (1.59 to 8.2)	.005
One first-degree relatives	2715	11486	14	2.04	6.86 (3.75 to 11.04)	<.001
Young-onset kindred	705	3093	6	0.64	9.31 (3.42 to 20.28)	<.001
Late-onset kindred	3229	13666	23	3.63	6.34 (4.02 to 9.51)	<.001
Smokers	1399	6125	14	1.54	9.09 (4.97 to 15.25)	<.001
Nonsmokers	2009	8553	12	1.88	6.38 (3.02 to 11.15)	<.001
Unknown smoking history	526	2083	3	0.85	3.53 (0.73 to 10.32)	.112
Sporadic						
Overall	4015	13876	8	3.32	2.41 (1.04 to 4.74)	.04
Young-onset kindred	472	1695	1	0.36	2.74 (0.05 to 15.30)	.59
Late-onset kindred	3544	12181	7	2.96	2.36 (0.95 to 4.88)	.06
Smokers	1377	4681	4	1.31	3.04 (0.83 to 7.79)	.09
Nonsmokers	2096	7215	3	1.39	2.15 (0.45 to 8.98)	.32
Unknown smoking history	542	1979	1	0.62	1.61 (0.04 to 8.93)	.91
Unrelated						
Overall	1091	4240	4	1.86	2.14 (0.58 to 5.49)	.23
Smokers	434	1407	2	0.67	2.98 (0.37 to 10.77)	.28
Nonsmokers	434	1619	2	0.65	3.07 (0.37 to 11.11)	.27
Unknown smoking history	223	1213	0	0.55	0 (0 to 6.71)	.94

* Age-, sex-, race-, and calendar year-specific standardized incidence ratios were computed compared with data from the Surveillance, Epidemiology, and End Results database.

To understand the effect of having a young-onset pancreatic cancer in the family on an individual's risk of developing pancreatic cancer, families were stratified into young- and late-onset kindreds (Table 2). We defined young-onset pancreatic cancer families as those in which there was at least one family member who was diagnosed with pancreatic cancer before the age of 50 years. Our data suggest that individuals from familial pancreatic kindreds in which at least one family member was diagnosed younger than 50 years are at higher risk of developing pancreatic cancer than individuals from FPC kindreds without a young-onset pancreatic cancer (FPC young-onset SIR = 9.31, 95% CI = 3.42 to 20.28, $P < .001$; FPC late-onset SIR = 6.34, 95% CI = 4.20 to 9.51, $P < .001$). A similar difference in pancreatic cancer risk between families with and without a young-onset cancer patient was not seen among the SPC kindreds (SPC young-onset SIR = 2.74, 95% CI = 0.05 to 15.30, $P = .59$; SPC late-onset SIR = 2.36, 95% CI = 0.95 to 4.88, $P = .06$).

To estimate the lifetime risk of pancreatic cancer in the FPC and SPC kindreds, we conducted time-to-event (pancreatic cancer) analyses using Cox proportional hazards modeling that considered deaths due to other causes as competing events (Table 3). It is important to note that the hazard ratio (HR) estimates obtained in these models do not directly estimate the cumulative incidence because the cause-specific hazard ratio only assesses the instantaneous risk of that event without considering the cumulative effect of the competing event (36,37). Therefore, in Figure 1, we provide the cumulative risk estimates for pancreatic cancer as well as risk of death due to other causes derived from the proportional hazards modeling.

In the FPC kindreds, the hazard of pancreatic cancer increased as the age of the youngest proband decreased (HR = 1.55 per year of decreased age of the proband, 95% CI = 1.19 to 2.03). Risk was also statistically significantly higher among FPC kindred members with three first-degree relatives with pancreatic cancer compared with those with a single first-degree relative with pancreatic cancer (HR = 2.95, 95% CI = 1.24 to 7.04).

Whereas data for time to pancreatic cancer were not substantially different for men compared with women and for cigarette smokers compared with nonsmokers, men (HR = 1.36, 95% CI = 0.97 to 1.92, $P = .07$), and ever-smokers (HR = 1.47, 95% CI = 0.96 to 2.25, $P = .07$), the FPC kindreds had an increased hazard of death due to causes other than pancreatic cancer, although these differences were not statistically significant.

Using these models adjusted for effects smoking and gender on all-cause mortality, we estimated the lifetime risk of pancreatic cancer and the risk of death due to other causes (Figure 1). The cause-specific proportional hazards model suggested that the cumulative incidence of pancreatic cancer by age 80 years was 15.7% (95% bootstrap CI = 8.5% to 23.7%) among FPC kindred members who had either one or two first-degree relatives with pancreatic cancer and at least one relative whose disease onset was at 40 years of age. In this family history group, the cumulative incidence of pancreatic cancer decreased to 7.1% (95% CI = 3.6% to 10.7%) when the youngest age of onset of pancreatic cancer was at 60 years and to 3.1% (95% CI = 0.9% to 6.9%) when the youngest age was at 80 years.

The cumulative incidence of pancreatic cancer by age 80 years was 38.5% (95% bootstrap CI = 13.1% to 64.3%) among FPC kindred members with three first-degree relatives with pancreatic cancer and at least one relative whose disease onset was at 40 years of age. The cumulative incidence of pancreatic cancer decreased to 19.2% (95% CI = 6.1% to 34.3%) for FPC kindred members when the youngest age of onset of pancreatic cancer was at 60 years and to 8.7% (95% CI = 1.9% to 21.4%) when the youngest age was at 80 years.

In SPC kindreds, time to pancreatic cancer did not vary by proband age of onset (HR = 0.99, 95% CI = 0.59 to 1.66, $P = .99$) (Table 3). Additionally, there was an interaction between age and smoking such that smokers older than 70 years had a hazard ratio for death of 1.05 (95% CI = 0.66 to 1.68, $P = .83$) compared with nonsmokers, whereas smokers younger than 70 years had a hazard ratio for death of 3.22 (95% CI = 1.22 to 8.54, $P = .019$) compared

Table 3. Cause-specific hazard ratio (HR) models*

Characteristics of individuals	Pancreatic cancer, HR† (95% CI)	P	Death from other causes, HR (95% CI)	P
Familial				
Youngest age of onset in relative (per year younger)	1.55 (1.19 to 2.03)	.001	1.09 (0.90 to 1.32)	.38
Three or more first-degree relatives	2.95 (1.24 to 7.04)	.015	—	
Ever-smoker	—		1.47 (0.96 to 2.25)	.075
Unknown smoking history	—		1.09 (0.64 to 1.87)	.076
Male	—		1.36 (0.97 to 1.92)	.079
Sporadic				
Youngest age of onset	0.99 (0.59 to 1.66)	.99	0.95 (0.80 to 1.14)	.61
Ever-smoker, age <70 y	—		3.22 (1.22 to 8.54)	.019
Ever-smoker, age >70 y	—		1.05 (0.66 to 1.68)	.83
Unknown smoking history, age <70 y	—		6.32 (1.30 to 30.70)	.02
Unknown smoking history, age >70 y	—		1.54 (0.91 to 2.61)	.11
Male, age <70 y	—		0.93 (0.46 to 1.88)	.83
Male, age >70 y	—		1.69 (1.14 to 2.50)	.01

* The HRs were estimated from a Cox proportional hazards model in which the competing event is treated as censored. These models cannot be interpreted in the same manner as a standard proportional hazards model without a competing event (see text). CI = confidence interval.

† The inferences regarding youngest age of onset were not changed by including smoking status and sex. Therefore, the reduced model is presented as the bootstrap estimates for cumulative incidence are based on these models.

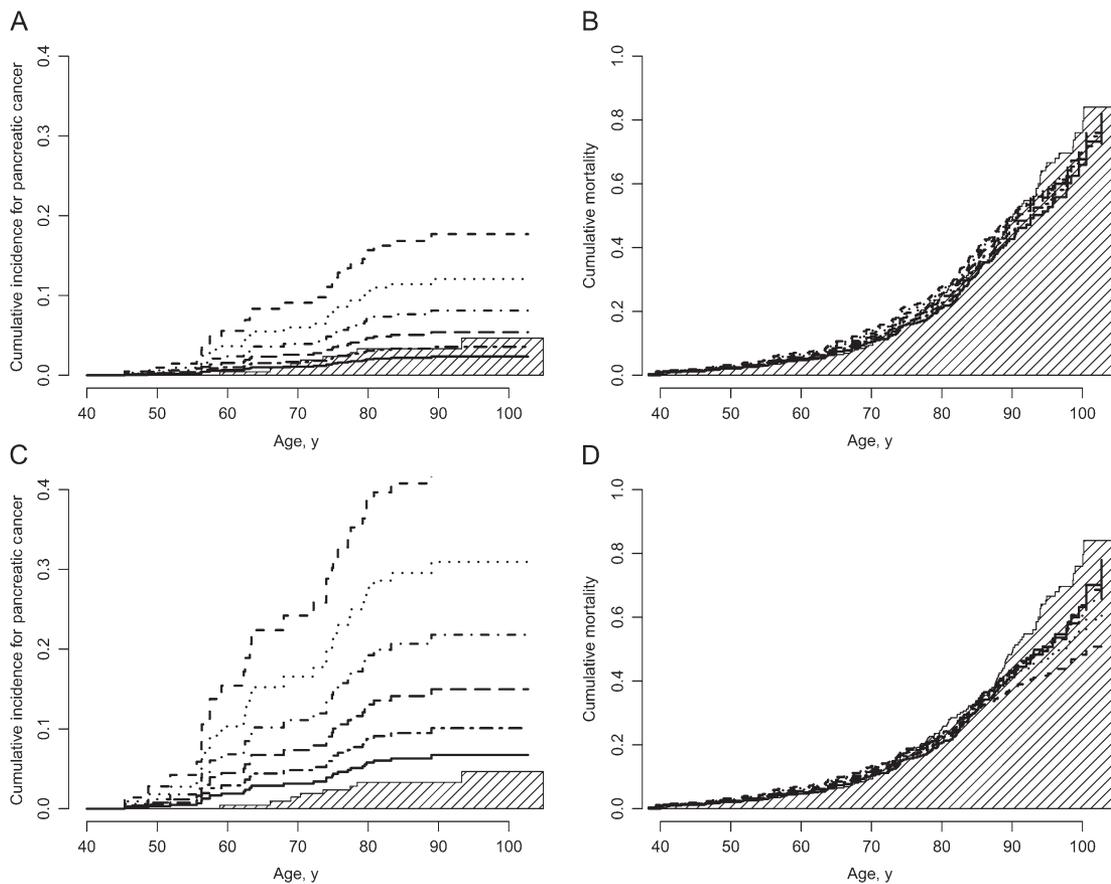


Figure 1. Cumulative risk of pancreatic cancer among members of pancreatic cancer families compared with cumulative risk of death from other causes. **A)** Cumulative risk of pancreatic cancer among members of familial pancreatic cancer (FPC) kindreds who have one or two first-degree relatives with pancreatic cancer. **B)** Cumulative risk of death due to other causes in FPC kindred members as in **(A)**. **C)** Cumulative risk of

pancreatic cancer in FPC kindred members with three or more first-degree relatives with pancreatic cancer. **D)** Cumulative risk of death due to other causes in FPC kindred members as in **(C)**. In all panels, **solid and dashed lines** reflect cumulative risk in FPC kindreds by youngest age of onset of pancreatic cancer: age 40, 50, 60, 70, 80, and 90 years from top to bottom. **Shaded area** reflects risk in sporadic kindred members.

with nonsmokers (Table 3). In the sporadic kindreds, men older than 70 years had an increased hazard of death due to causes other than pancreatic cancer compared with women (HR = 1.69, 95% CI = 1.14 to 2.50, $P = .01$), whereas risk of death due to other causes was similar in men and women younger than 70 years (HR = 0.927, 95% CI = 0.46 to 1.88, $P = .83$) (Table 3). The cumulative incidence of pancreatic cancer by age 80 years was 3.3% (95% CI = <0.1% to 5.9%) among sporadic kindred members at the median youngest age of onset in the kindred of 62 years (Figure 1). Given the limited number of incident pancreatic cancers that developed in individuals not genetically related to the proband ($n = 4$), accurate estimation of the cumulative risk of pancreatic cancer in the unrelated individuals was not possible.

Discussion

A family history of pancreatic cancer is one of the strongest risk factors for the development of pancreatic cancer. Our results indicate that individuals from familial pancreatic kindreds in which at least one member of the family had been diagnosed with pancreatic cancer at a young age had a statistically significantly increased risk of developing pancreatic cancer themselves. The lifetime risk of

pancreatic cancer was higher when there was an early-onset pancreatic cancer in the family, and this risk decreased as the youngest age of onset in the family increased. The lifetime (by age 80 years) risk of pancreatic cancer was 15.7% for individuals with one or two first-degree relatives with pancreatic cancer who came from a family in which one of the members of the family was diagnosed at age 40 years. This lifetime risk rose to 38.9% (Figure 1) for individuals with three first-degree relatives with pancreatic cancer who came from a family in which one of the members of the family was diagnosed at age 40 years. By contrast, individuals from families who had either one or two first-degree relatives with late-onset pancreatic cancer (at age 80 years) had a cumulative incidence risk of pancreatic cancer that was the same as the risk in individuals from SPC kindreds (2.9 and 3.3 by age 80 years, respectively). This trend is similar to that which is observed in other cancers, such as breast, ovarian, and colon cancers (23–25).

Understanding the influence of family history and age of onset of pancreatic cancer on the lifetime risk of pancreatic cancer will help to inform the clinical counseling and screening of high-risk families. Current screening strategies for pancreatic cancer are directed at those who are most at risk. For example, the inclusion criteria for the ongoing CAPS trial (42,43) include family history

of pancreatic cancer and gene mutation status (*BRCA2*, *STK11*, *CDKN2A*), but they do not include age at which the pancreatic cancers were diagnosed in the family. The results of the current analyses should help guide this and other screening trials by suggesting that the age of onset of the pancreatic cancers in a kindred be included among the eligibility criteria.

Moreover, the findings we present will help to guide future cancer risk counseling to individuals even in the absence of an identified gene or genes. Better quantification of risk can help alleviate the psychological stress of the unknown for individuals who have lost one or more loved ones to pancreatic cancer. For example, if the earliest age at which a member of a kindred developed onset of pancreatic cancer was older than 80 years, our data suggest that individuals in that kindred are at low risk. Our aggregate risk estimates, based on the observed incidence of pancreatic cancer in our family cohort, can help to direct at-risk individuals to counseling and early detection trials, especially when used in connection with our recently developed and validated risk prediction model PancPRO, which provides individual-level risk assessment (44). By using full pedigree data (age, pancreatic cancer status, age of onset, and relationship for all biological relatives), PancPRO estimates an individual's probability of carrying a pancreatic cancer susceptibility gene and their lifetime risk of developing pancreatic cancer (44).

This study is the first to our knowledge to examine the influence of age of onset on the prospective risk of pancreatic cancer in high-risk families. Strengths of our study include the large sample of FPC and SPC patients, extensive follow-up, and the use of only prospective data. Our large sample of both FPC and SPC kindreds allows us to compare directly the influence of age at onset in these two groups. Furthermore, our use of prospective data limits recall bias.

One potential limitation to our study is that some patients underwent early detection screening for pancreatic cancer, including 13 individuals who had a surgical resection of their pancreas based on the results of screening. However, because screening of high-risk individuals is becoming more common, this limitation is common to many prospective studies of pancreatic cancer kindreds. We accounted for the screened individuals in the risk-set. Only screened individuals who underwent surgical resection and were found to have high-grade precursor lesions ($n = 4$), that is, precursors rarely found in individuals without invasive pancreatic cancer (29), were considered as "affected," given the very high probability these lesions would develop into invasive cancer within a few years if not removed surgically. Aside from the single patient who developed pancreatic cancer while under screening, all other screened individuals, including nine patients who underwent surgical resection and were found to have lower grade precursor lesions, were considered as free of pancreatic cancer at the end of follow-up. We conducted sensitivity analysis to examine the impact of this assumption by conducting analysis treating these four individuals with high-grade precursor lesions as "unaffected," and while the point estimates were lower, the tests of hypothesis and inferences were consistent.

We were able to verify 66% of our prospective cancers. In most of the unconfirmed cases, we were not able to confirm the diagnosis because we were not able to obtain permission from the patient or their next of kin because of the high mortality rate of this disease. When we examined data for the entire registry, in the

cases where permission and records were obtained, more than 92% of the pancreatic cancers were confirmed. Furthermore, because at-risk individuals do not typically have medical record confirmation of their relatives' cancer when presenting to clinicians seeking screening, our results should be generalizable to those seeking screening for their risk of pancreatic cancer. Another potential limitation to our study is that 60% of our questionnaire data were obtained from a next of kin proxy, not the patient themselves. However, given that our data suggest that NFPTR reported family history of pancreatic cancer is highly accurate (~92% sensitivity), and that lifetime smoking patterns have previously been shown to be highly accurate when reported by proxy (45), we believe that any bias because of the use of proxy data is minimal.

In summary, in this study, we expanded upon our previous study of the prospective risk of developing pancreatic cancer by examining whether being related to an individual who developed pancreatic cancer at a young age is predictive of an increased risk of disease. These data should help to further inform risk assessment and subsequent early detection screening of individuals at high risk of developing pancreatic cancer.

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