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Prospective Risk of Pancreatic Cancer in Familial Pancreatic Cancer Kindreds

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ABSTRACT

Individuals with a family history of pancreatic cancer have an increased risk of developing pancreatic cancer. Quantification of this risk provides a rational basis for cancer risk counseling and for screening for early pancreatic cancer. In a prospective registry-based study, we estimated the risk of pancreatic cancer in individuals with a family history of pancreatic cancer. Standardized incidence ratios were calculated by comparing the number of incident pancreatic cancers observed with those expected using Surveillance, Epidemiology and End Results (SEER) rates. Familial pancreatic cancer (FPC) kindreds were defined as kindreds having at least one pair of first-degree relatives with pancreatic cancer, and sporadic pancreatic cancer (SPC) kindreds as families without such an affected pair. Nineteen incident pancreatic cancers developed among 5,179 individuals from 838 kindreds (at baseline, 370 FPC kindreds and 468 SPC kindreds). Of these 5,179 individuals, 3,957 had at least one first-degree relative with pancreatic cancer and contributed 10,538 person-years of follow-up. In this group, the observed-to-expected rate of pancreatic cancer was significantly elevated in members of FPC kindreds [9.0; 95% confidence interval (CI), 4.5–16.1], but not in the SPC kindreds (1.8; 95% CI., 0.22–6.4). This risk in FPC kindreds was elevated in individuals with three (32.0; 95% CI, 10.2–74.7), two (6.4; CI, 1.8–16.4), or one (4.6; CI, 0.5–16.4) first-degree relative(s) with pancreatic cancer. Risk was not increased among 369 spouses and other genetically unrelated relatives. Risk was higher in smokers than in nonsmokers. Individuals with a strong family history of pancreatic cancer have a significantly increased risk of developing pancreatic cancer.

INTRODUCTION

This year ~30,000 Americans will receive diagnoses of pancreatic cancer and ~30,000 will die from it (1, 2). The etiology of pancreatic cancer is heterogeneous, although a number of inherited genetic alterations have been identified that increase the risk of pancreatic cancer, including germ-line mutations in the *BRCA2*, *p16*, *PRSS1*, *STK11*, *hMLH1*, and *FANCG* genes (3, 4). These known germ-line mutations are estimated to account for only 10–20% of the clustering of pancreatic cancer in families. It is unclear whether the remainder of the clustering of pancreatic cancer in families occurs by chance, or whether members of these families have an increased risk of developing pancreatic cancer.

The National Familial Pancreas Tumor Registry (NFPTR) was established in 1994 to provide a resource for the study of familial pancreatic cancer (FPC). As of February 24, 2004, >1263 kindreds have enrolled. Kindreds are eligible to enroll if at least one family member has been diagnosed with pancreatic cancer. Kindreds are recruited through the World Wide Web[7] and through patients who are surgically treated for pancreatic cancer at The Johns Hopkins Medical Institutions. Segregation analyses performed on kindreds enrolled in the NFPTR have supported the involvement of a major gene in the etiology of pancreatic cancer (5), and genetic analyses of affected registrants in the NFPTR has demonstrated that germ-line mutations in the *BRCA2* gene cause ~16% of the familial clustering of pancreatic cancer (6). The magnitude of this estimate was recently substantiated by others (7). The identification of these germ-line mutations has helped to identify individuals at increased risk for developing pancreatic and other cancers. Mutation carriers can be counseled regarding their risk and potential options for prophylactic surgery, screening, and chemoprevention studies.

A number of new markers of pancreatic cancer and its precursors have recently been discovered using global analyses of gene expression (8, 9). Although the identification of these markers suggests that early detection should be possible, the low incidence rate of pancreatic cancer in the general population (~9 per 100,000 in the United States) limits the application of any screening test to selected groups that carry an increased risk of developing pancreatic cancer. Individuals with a strong family history of pancreatic cancer likely represent such a group, but the risk of pancreatic cancer in these individuals has not been well quantified.

To this end, we extended our previous study of NFPTR kindreds (10) by quadrupling the follow-up in our previous study. We prospectively followed members of kindreds enrolled in the NFPTR and compared the number of incident pancreatic cancers observed in spouses and genetic relatives of pancreatic cancer patients with those expected using Surveillance, Epidemiology and End Results (SEER) incidence rates.

MATERIALS AND METHODS

Study Subjects. This study was reviewed and approved by the institutional review board of The Johns Hopkins Medical Institutions, and appropriate informed consent was obtained from all of the study participants. The NFPTR is one of the largest registries of FPC in the world. This registry recruits patients from two different populations: (*a*) patients treated for pancreatic cancer at The Johns Hopkins Hospital are invited (either by an in-person visit by the study coordinator or by mail) to participate in the NFPTR; and (*b*) individuals with a family history of pancreatic cancer are either self-referred through a study internet site[7] or referred to the registry by a non-Johns Hopkins physician, nurse, or genetic counselor. Baseline family data were obtained via a questionnaire including information on all first-degree relatives (FDRs), grandparents, aunts, and uncles, including date of birth, date of death (if deceased), cancer diagnosis (if any), and cigarette smoking. This questionnaire is completed from the perspective of pancreatic cancer case and is completed by at least one member of each family, typically the index pancreatic cancer case or their proxy. If necessary, the family member who completed the questionnaire is then contacted by the study coordinator to clarify questionnaire responses. Follow-up data are obtained when the family member who originally enrolled the family in the registry and any other family members who have made direct contact with the registry are recontacted by mail in mid-December each year to obtain updated health status on all other family members on whom data were collected in the baseline questionnaire.

Family members who did not have pancreatic cancer at enrollment, who

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enrolled in the registry between January 1, 1994, and December 29, 2002, and on whom follow-up time was available were included in this analysis. Family members were followed through December 31, 2002. Only United States kindreds were included. FPC kindreds were defined as kindreds containing at least a pair of FDRs with pancreatic cancer, and sporadic pancreatic cancer (SPC) kindreds were defined as families without an affected pair of FDRs (7). SPC kindreds included 19 kindreds with a husband and wife with pancreatic cancer. The number of FDRs with pancreatic cancer was determined individually for each study participant.

Follow-up was available on at least one individual from 84% (838 of 994) of the families that had enrolled in the NFPTR before January 1, 2003. For a family to be included in the analysis, at least one individual in that family must be alive at baseline and their date of birth must be known. Follow-up time was available on at least one individual from 94% of FPC kindreds and 78% of SPC kindreds (76% of the kindreds ascertained through Johns Hopkins and 89% of Internet referral/referral kindreds). Among the 838 kindreds included in the analysis, 280 kindreds (43 FPC at baseline) were recruited through a Johns Hopkins Hospital patient and 558 kindreds (327 FPC at baseline) were either self-referred or referred by an outside health care provider. Multiple individuals from the same family were included in the analysis. Within these 838 families included in the analysis, 92% of all FDRs of pancreatic cancer cases who were alive at baseline, contributed follow-up time in the analysis. The mean length of follow-up time was 2.74 years for individuals in FPC kindreds, 2.65 years for individuals in SPC kindreds, and 2.91 years for unrelated individuals. The mean length of follow-up for individuals who developed a pancreatic cancer during follow-up was 1.9 years, 1.8 years for individuals in FPC kindreds, and 2.2 years for individuals in SPC kindreds.

Analyses. Person-years of follow-up were calculated for each individual from time of enrollment in the registry until the date of pancreatic cancer diagnosis, date of death, the date at which the individual's health information was last updated, or the end of the follow-up period of this study (December 31, 2002). Family cancer status (SPC or FPC) and the number of affected FDRs were treated as time-dependent covariates, such that incident pancreatic cancer(s) in a family member were accounted for in the analysis. For example, an incident pancreatic cancer in one family member could change, from that point on, the other family members' family cancer status from SPC to FPC and, similarly, might increase the number of affected FDRs for a given study participant.

Individuals with prior cancer diagnoses were not excluded from the analyses because metastases to the pancreas are extremely rare; thus, virtually all reported pancreatic cancers were likely to have originated in the pancreas. Whenever possible, reported pancreatic cancers were confirmed, ideally by review of the pathology slides. When these were unavailable, the patient's medical records and pathology reports were obtained.

Standardized incidence ratios (SIRs) adjusted for age in 5-year intervals and for sex and ethnicity were calculated by comparing the observed number of incident pancreatic cancer cases with those expected under SEER incidence rates (11). Year-specific incidence rates were used for follow-up time accrued from 1994 to 2000. However, SEER year-specific rates were not yet available for 2001–2002; therefore, year 2000 rates were applied to person-time accrued in the years 2001–2002. Ever smokers were defined as individual who smoked at least 100 cigarettes in their lifetime. SIRs for ever smokers and never smokers were calculated with reference to the SEER population. Because smoking is not included in the SEER database, the rates that we report reflect the incidence in ever and never smokers compared with the general population (encompassing both ever and never smokers). Confidence intervals for the SIR were calculated using a Poisson distribution (12). SPLUS and SAS software were used for statistical analysis.

RESULTS

A total of 5,179 individuals from 838 kindreds (at baseline, 370 were FPC kindreds and 468 were SPC kindreds) were followed for a total of 14,128 person-years. At the start of the study 3,904 of these 5,179 individuals had a FDR with pancreatic cancer, 906 had a more distant relative with pancreatic cancer, and 369 study participants, contributing 1,072 person-years of follow-up, were not blood relatives of an individual with pancreatic cancer. Because a number of incident pancreatic cancers occurred during the period of study, 53 individuals moved, at some point during their follow-up, from the no FDR with pancreatic cancer group to the group with a FDR with pancreatic cancer. During the period of follow-up in which these 53 individuals did not have a FDR with pancreatic cancer, they contributed to the follow-up of the group of individuals without a FDR with pancreatic cancer, and during the period of follow-up in which these individuals did have a FDR with pancreatic cancer, they contributed to the follow-up of the group of individuals with a FDR with pancreatic cancer. Therefore, over the course of follow-up, a total of 3,957 study participants, who contributed 10,538 person-years of follow-up, could be classified as having at least one FDR with pancreatic cancer. Another 906 study participants did not have a FDR with pancreatic cancer, but did have a more distant relative with pancreatic cancer.

Table 1 reports age distributions of the at-risk family members by family cancer status and sex. The mean age of the members of the FPC kindreds at baseline was 52.5 and 54.3 in males and females, respectively. A similar age distribution was observed among all of the SPC kindred members and among FPC kindred members with at least one FDR with pancreatic cancer. SPC kindred members with at least a single FDR with pancreatic cancer were on average about 2 years younger (results not shown).

Twenty-five incident pancreatic cancers have developed in NFPTR kindreds after the kindred enrolled in the registry. Five of these 25 occurred after the study closed (December 31, 2002), and one occurred in a kindred from outside of the United States, such that 19 of the 25 individuals with an incident pancreatic cancer were included in our analyses. Fourteen (74%) of the 19 cases have been confirmed, 12 by examination of pathology slides or pathology reports and 2 by review of the patients' medical records. Twelve of the incident pan-

Table 1 *Mean age at baseline of at-risk family members and age at diagnosis of pancreatic cancer among incident cases in families*

	At-risk family members		Prospective cases	
	No. of individuals[a]	Age at baseline (±SD)	No. of individuals	Age at diagnosis of pancreatic cancer (±SD)[b]
FPC[c]				
Male	1141	52.5 (± 18.2)	7	69.5 (± 8.5)
Female	1330	54.3 (± 18.7)	8	68.4 (± 14.3)
SPC				
Male	1072	52.5 (± 18.7)	3	59.4 (± 9.7)
Female	1293	55.7 (± 19.2)	0	na[c]
Unrelated				
Male	135	66.8 (± 10.7)	1	>65
Female	234	63.0 (± 11.9)	0	na
Total[a]	5179	54.6 (± 18.6)	19	

[a] Because of changes in family cancer status over time, the sum of the number of individuals in each stratum is not equal to the total number of individuals in the study.
[b] To protect the confidentiality of the participants only mean ages (when >2 cases) or age group data (≤2 cases) are shown and the mean (SD) of all cases is not presented.
[c] FPC, familial pancreatic cancer; SPC, sporadic pancreatic cancer; na, not applicable.

Table 2 *Risk of pancreatic cancer among unrelated family members and among individuals with a first-degree relative with pancreatic cancer in the familial (FPC) kindreds and sporadic (SPC) kindreds*

Family status[a]	No. of individuals	Person-years of follow-up	Observed cases	Expected cases[b]	SIR[c] (95% CI)
FPC Kindreds	1993	5273	11	1.22	9.0 (4.5–16.1)
SPC Kindreds	1964	5265	2	1.12	1.8 (0.22–6.42)
Unrelated	369	1073	1	0.41	2.4 (0.06–13.5)

[a] FPC kindreds were defined as kindreds having at least one pair of first-degree relatives with pancreatic cancer, and SPC kindreds as families without such an affected pair.
[b] Adjusted for age, sex, and race.
[c] SIR, standardized incidence ratio; CI, confidence interval.

Table 3 *Risk of pancreatic cancer (PC) among members of familial pancreatic cancer (FPC) kindreds stratified by their number of first-degree relatives (FDRs) with pancreatic cancer*

No. of FDRs with PC[a]	No. of individuals	Person-years of follow-up	Observed cases	Expected cases[b]	SIR[c] (95% CI)
3 or more	106	287.2	5	0.156	32.0 (10.4–74.7)
2	634	1597.9	4	0.623	6.4 (1.8–16.4)
1	1253	3388.0	2	0.442	4.5 (0.54–16.3)

[a] Denotes each individual's number of FDRs with pancreatic cancer (*i.e.*, the number of their parents, siblings, and children with pancreatic cancer).
[b] Adjusted for age, sex, and race.
[c] SIR, standardized incidence ratio; CI, confidence interval.

creatic cancers developed in males and seven in females. The mean age at diagnosis for the patients with an incident pancreatic cancer was 67.8 years (Table 1). Fifteen cases occurred in FPC kindreds, three in SPC kindreds, and 1 in the spouse of a pancreatic cancer patient. Three prospective pancreatic cancers occurred in a single FPC kindred. These cancers occurred in two brothers and a cousin, all of whom were cousins of one of the baseline pancreatic cancer cases.

The observed incidence of pancreatic cancer among the familial kindreds is significantly higher than expected (Table 2). Members of FPC kindreds having at least one FDR affected with pancreatic cancer had a 9.0-fold increased risk [95% confidence interval (CI), 4.5–16.1] of developing pancreatic cancer. Members of SPC kindreds having a FDR with pancreatic cancer did not have an increased risk (SIR, 1.8; 95% CI, 0.22–6.4). In addition, study participants not genetically related to a patient with pancreatic cancer (*i.e.*, spouses and others who married into the kindreds) did not have a significantly increased risk of pancreatic cancer (SIR 2.4; 95% CI, 0.06–13.5). Eleven of 14 (79%) of the incident cancers described in this Table have been confirmed.

Among the FPC kindred members, the risk of pancreatic cancer increased as their number of FDRs with pancreatic cancer increased (Table 3). FPC kindred study participants having three or more affected FDRs had a 32.0-fold increased risk of developing pancreatic cancer (95% CI, 10.4–74.7). Those with two affected FDRs with pancreatic cancer had a 6.4-fold increased risk (95% CI, 1.8–16.4), whereas those with a single affected FDR had a 4.5-fold increased risk (95% CI, 0.54 –16.3).

Five of the 19 incident pancreatic cancer cases included in this study occurred in study participants more distantly related to a patient with pancreatic cancer (greater than first-degree). Four of 5 developed in FPC kindreds, whereas the fifth occurred in a SPC kindred. Unbiased estimates of risk could not be obtained for this subgroup because we do not uniformly collect information on relatives more distant than first-degree.

Smoking data (ever *versus* never smokers) were available for 83.7% of study participants. Overall, 40% of the study population were ever smokers. Among study participants with least a single affected FDR, the proportion of ever smokers was not significantly different between members of FPC kindreds (42%) and members of SPC kindreds (39%). Of the 17 prospective pancreatic cancer cases that developed in individuals with known smoking data, 11 (65%) occurred in ever smokers. The observed incidence of pancreatic cancer among ever smoking members of FPC kindreds with at least one FDR with pancreatic cancer was significantly higher than expected (SIR, 19.2; 95% CI, 7.7–39.5; Table 4). This risk was lower but remained significantly elevated among the never smoking members of FPC kindreds with a least one FDR with pancreatic cancer (SIR, 6.3; 95% CI, 1.7–16.0). It should be noted that the SEER standard population used to compute the expected rates is based on a standard population that contains both ever smokers and never smokers.

Two of the three prospective cancers in SPC kindreds developed in smokers, and one arose in a never smoker. The observed-to-expected incidence of pancreatic cancer among individuals from SPC kindreds with at least one FDR with pancreatic cancer was 3.6 (95% CI, 0.1–19.8) for ever smokers and 1.7 (95% CI, 0.1–9.7) for never smokers. The single prospective pancreatic cancer case that occurred in a study participant genetically unrelated to a pancreatic cancer case developed in a smoker.

The greatest elevation of pancreatic cancer risk relative to the SEER rates was observed in study participants ages 45 to 64.9 (Table 4). Individuals, ages 45 to 64.9, who were members of FPC kindreds and had at least one FDR with pancreatic cancer had a 15.8-fold (95% CI, 4.3–40.4) increased risk of developing pancreatic cancer. Individuals ages 65 and older with the same family history had a 7.4-fold (95% CI, 2.9–15.2) increased risk. No incident pancreatic cancer cases developed in individuals less than 45 years of age. The youngest observed incident pancreatic cancer case was diagnosed at about 45 years of age.

If we assume the incidence of pancreatic cancer among individuals without a family history is approximately equivalent to the population incidence rate of 9 per 100,000, we can estimate that the incidence of pancreatic cancer in individuals who are members of an FPC kindred and have at least one FDR with pancreatic cancer would be 81 per 100,000 person-years (Table 5). Among FPC kindred members with three or more FDRs with pancreatic cancer, this estimated incidence would rise to 288 per 100,000 person-years.

All of the families included in this analysis, regardless of their

Table 4 *Standardized incidence ratios (SIRs) for pancreatic cancer in members of kindreds with at least one first-degree relative with pancreatic cancer by smoking status and age*

	No. of individuals[a]	Person-years of follow-up	Observed cases	Expected cases	SIR (95% CI)[b]
Smoking status					
Ever smoker	546	1761	7	0.365	19.2 (7.7–39.5)
Never smoker	1214	2941	4	0.640	6.25 (1.70–16.0)
Unknown	233	572	0	0.214	0 (0–17.3)
Age					
<45	738	1739	0	0.020	0 (0–615)
45–64.9	833	2033	4	0.253	15.8 (4.31–40.4)
≥65	620	1502	7	0.947	7.4 (2.97–15.2)

[a] Because of changes in age strata during follow-up, numbers do not equal total number of individuals in study.
[b] CI, confidence interval.

Table 5 *Estimated incidence of pancreatic cancer in the general United States (U.S.) population among familial pancreatic cancer kindred members with at least one first-degree relative (FDR) with pancreatic cancer*

No. of FDRs with pancreatic cancer	Incidence (per 100,000) in the general U.S. population[a]
3 or more	288
2	58
1	41
1 or more	81
General U.S. (reference)	9

[a] SIR × incidence of pancreatic cancer in the general U.S. population.

learning about the registry through their treatment at Johns Hopkins, through an outside health care provider, or through the internet, have self-selected to participate in the registry, presumably because of their personal family history of pancreatic cancer at the time of enrollment. Given that the analysis is stratified by family history, we feel that any potential bias due to this self-selection on the risk of *new* family members developing pancreatic cancer is minimal. On average, 16% of families were lost to follow-up, 22% in SPC kindreds and 6% in FPC kindreds. It is possible that families in which an incident pancreatic cancer occurred were less likely to be lost to follow-up, and, thus, our risk estimates may be slightly overestimated. However, given that follow-up was available on 94% of all FPC kindreds, we believe this bias to be minimal within this group.

DISCUSSION

We demonstrate that the risk of pancreatic cancer is significantly increased in FPC kindreds and that this risk increases with increasing numbers of affected FDRs.

Familial clustering of pancreatic cancer has been recognized for decades (13–17), and numerous case–control studies have shown that patients with pancreatic cancer are more likely to have a family history of pancreatic cancer than are controls (18–23). Most case–control studies of pancreatic cancer have found a 2- to 5-fold excess of pancreatic cancer in FDRs of patients with pancreatic cancer, and several studies have suggested that this risk is particularly high among smoking relatives of patients with pancreatic cancer (20, 24).

The aggregation of a cancer in a family could be due to chance, or caused by a shared environmental exposure, or have a genetic basis, or it could be attributable to a combination of these factors. Our findings add to the growing body of evidence that the familial aggregation of pancreatic cancer is often not due to chance.

Environmental exposures may contribute to this aggregation. Cigarette smoking is the largest known risk factor for pancreatic cancer, accounting for 25% of all pancreatic cancers; and Rulyak *et al.* (25) found that smoking is an independent risk factor for FPC (odds ratio, 3.7; 95% CI, 1.8–7.6). Our results support the conclusion that smoking adds to the increased risk associated with a family history of pancreatic cancer (26).

Inherited genetic factors also contribute to the familial aggregation of pancreatic cancer. The risk among individuals from a FPC kindred with at least one FDR with pancreatic cancer was 9.0 (95% CI, 4.5–16.1), whereas the risk was only 2.4 (95% CI, 0.06–13.5) among individuals genetically unrelated to a pancreatic cancer case. This contrasts with the findings of the National Familial Brain Tumor Registry, in which the clustering of brain tumors by calendar year rather than age, and the development of brain tumors in spouses suggest that environmental, not genetic, factors contribute to the etiology of familial brain tumors (26).

Previous segregation analyses also support a genetic etiology to some of the familial aggregation of pancreatic cancer (5). In the current study, 29% of the tested kindreds with an incident pancreatic cancer had a germ-line *BRCA2* gene mutation. These families were tested as part of a previous study by Murphy *et al.* (6), which targeted families with at least three cases of pancreatic cancer. This finding adds support to the growing body of evidence that germ-line *BRCA2* gene mutations cause a significant fraction of the familial clustering of pancreatic cancer (6, 7).

The classification of families in the FPC category is based on observed family history, and is done without knowledge of the family's gene status. The risk estimates that we present for FPC kindred members may, in fact, underestimate the risk of pancreatic cancer among families in which a gene is responsible for the clustering of pancreatic cancer.

The finding that the risk of pancreatic cancer increases with the number of FDRs with pancreatic cancer suggests that a highly penetrant gene or genes may be responsible for the familial aggregation of pancreatic cancer in kindreds in which multiple family members have pancreatic cancer, whereas a less penetrant gene or genes may be present in the families with fewer pancreatic cancers. Alternatively, a single gene whose penetrance is modified by the presence of an environmental factor or second gene may explain the difference in risk between the densely aggregated and less densely aggregated families.

As screening tests for early pancreatic cancer and chemoprevention protocols are considered (27–29), it is important to have accurate estimates of pancreatic cancer risk. Our study not only quantifies pancreatic cancer risk in families, but it also demonstrates that the increased risk begins as early as age 45 years. Future screening and chemopreventive trials should consider these age data in trial design.

The applicability of these screening tests and chemoprevention protocols will be limited by the relatively low annual incidence rate of pancreatic cancer in the general population (1). It is unlikely that any screening test will have the sensitivity and specificity needed to detect nine patients in 100,000. We estimate the incidence rate of pancreatic cancer among individuals with three or more affected FDRs is 2.88 per 1,000 per year, which may be high enough to warrant screening for early pancreatic cancer and/or chemoprevention when such programs become available (27–30).

The need for early detection and effective chemoprevention protocols is appreciated in the 25 patients who have developed an incident pancreatic cancer in the NFPTR. Twenty-two of these 25 patients presented with metastases. This statistic is particularly remarkable because these individuals were aware of the signs and symptoms of pancreatic cancer through the experiences of their family members who died of pancreatic cancer. The single incident pancreatic cancer that was detected early was detected serendipitously during abdominal imaging for a renal calculus.

In summary, this prospective, registry-based study demonstrates that a strong family history of pancreatic cancer significantly increases the risk of developing pancreatic cancer, and this study helps quantify the risk of pancreatic cancer in kindreds in which a family member has received a diagnosis of pancreatic cancer.

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