

Familial Risk of Pancreatic Cancer

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Background: Pancreatic cancer is the fifth leading cause of cancer-related mortality in the United States. Although smoking and age are known risk factors for pancreatic cancer, several case reports and case-control studies have suggested that there is also a familial risk. We evaluated whether a family history of pancreatic cancer increases the risk of pancreatic cancer in first-degree relatives and whether smoking and younger age at cancer diagnosis further increase this risk. **Methods:** We conducted in-person interviews with 247 patients ("case probands") with pancreatic cancer and 420 population-based control probands to collect risk factor data and pancreatic cancer family history for 1816 first-degree relatives of the case probands and 3157 first-degree relatives of the control probands. We analyzed the data by unconditional logistic regression models, with adjustment for correlated data by use of generalized estimating equations. All statistical tests were two-sided. **Results:** A positive family history of pancreatic cancer (i.e., being related to a case proband) or ever-smoking cigarettes approximately doubled the risk of pancreatic cancer (relative risk [RR] = 2.49; 95% confidence interval [CI] = 1.32 to 4.69; RR = 2.04; 95% CI = 1.09 to 3.83, respectively). The RR increased to 8.23 (95% CI = 2.18 to 31.07) for relatives who ever smoked and were related to a case proband who was diagnosed before age 60 years. **Conclusion:** Routine questioning of patients about a family history of pancreatic cancer, the age of onset of this cancer in their relatives, and the patient's smoking status may identify individuals at high risk of pancreatic cancer. Future research exploring the genetic and environmental interactions associated with the risk of pancreatic cancer is critically important. [J Natl Cancer Inst 2001;93:640-4]

Pancreatic cancer is the fifth leading cause of cancer-related mortality in the United States and has the lowest 5-year survival rate (4.1%) of all cancers (1). In 2000, approximately 28 200 people from the United States died of pancreatic cancer (2). With limited therapeutic options available at this time to cure pancreatic cancer patients or to substantially prolong survival, understanding the risk factors and identifying people at high risk are critical to the prevention of this disease.

Although many studies have explored risk factors associated with pancreatic cancer, the only risk factors consistently reported are age and smoking status (3). The incidence of pancreatic cancer increases exponentially with age (3) and peaks in the elderly (age ≥ 80 years). Fryzek et al. (3) reviewed 17 studies linking smoking to an increased risk of pancreatic cancer and reported odds ratios ranging from 1.6 to 5.4.

An additional risk factor for pancreatic cancer may be a family history of any cancer (4-10). In addition, several genetic syndromes associated with pancreatic cancer (i.e., hereditary pancreatitis, hereditary nonpolyposis colorectal cancer [HNPCC], ataxia-telangiectasia, Peutz-Jehgers, familial breast cancer, and familial atypical multiple mole melanoma [FAMMM]) may be associated with an increased risk of pancreatic cancer (11). Case-control studies (7-10,12) that explored family history of pancreatic cancer as a risk factor have provided important clues to the underlying genetics of pancreatic cancer. However, because few studies include information about the smoking habits of relatives, it is unclear whether the smoking habits of relatives explain the familial aggregation of pancreatic cancer. Consequently, in this study, we evaluated whether a positive family history of pancreatic cancer was a risk factor for pancreatic cancer in first-degree relatives and whether smoking and younger age at cancer diagnosis increased this risk.

SUBJECTS AND METHODS

Subjects

Written informed consent was obtained from each individual participating in the study, and the study was approved by the local institutional review boards.

The first family member identified is referred to as the proband. Probands were selected from a case-control study of pancreatic cancer conducted from October 1, 1996, through March 31, 1999. Case pro-

bands were recruited by contacting eight hospital pathology departments, various oncology and surgical physician groups, and tumor registries in southeastern Michigan. Eligible case probands were between the ages of 30 and 79 years, were residents of 18 counties (Hillsdale, Lenawee, Monroe, Jackson, Washtenaw, Wayne, Ingham, Livingston, Oakland, Macomb, Shiawassee, Genesee, Lapeer, St. Clair, Bay, Gratiot, Midland, or Saginaw) at the time of diagnosis, were English speaking, and could be contacted by phone. Because the median survival time for patients with pancreatic cancer is short, we used a rapid case-finding system in the participating hospitals and physician offices. This system allowed newly diagnosed case probands to be contacted, enrolled in the study, and interviewed within a short time of diagnosis. The study pathologist (J. K. Greenson) reviewed clinical materials, including pathology reports, histology slides, and selected medical records. Only those probands who had newly diagnosed adenocarcinoma of the exocrine pancreas (topography codes C25.0-C25.3 and C25.7) (13), confirmed by pathologic criteria, were included in the study.

In addition to the rapid case-finding system, the population-based metropolitan Detroit Surveillance, Epidemiology, and End Results Program (SEER)¹ registry also identified newly diagnosed pancreatic cancer patients. Only three additional case probands were identified by the SEER registry, indicating that the hospital- and physician-based rapid case-finding system captured virtually all of the population-based SEER registry patients at these hospitals. The rapid case-finding system and the SEER registry identified 808 patients. Of the 358 patients who were eligible for the study, 53 died before contact could be

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made and 37 were not contacted because their physicians refused to give permission. Of the remaining 268 patients invited to participate in the study, 247 (92%) agreed to participate. The median time from diagnosis to case proband identification was 19 days, and the median time from diagnosis to interview was 48 days.

Control probands were frequency matched to case probands by age group (30–44, 45–59, 60–69, and 70–79 years), sex, ethnicity (African-American, Caucasian, and other), and county of residence (counties were grouped into nine different areas on the basis of the population size and proximity to each other). In addition, eligible control probands were English speaking and could be contacted by phone. Random-digit-dialing techniques based on the Waksberg method (14) were used to recruit control probands. This method identified 616 people. Of the 597 people who were eligible for the study, 19 were not contacted because they could not be reached by phone, one died before being contacted, and 27 were not contacted to participate because there was an overselection of control probands under 45 years of age early in the study period. Of the remaining 550 people invited to participate, 420 (76%) agreed to participate.

Data Collection

We conducted in-person interviews with the probands to collect data regarding family history of pancreatic cancer for each case and control proband. Asking questions from a structured questionnaire, the interviewer requested information about the first-degree relatives (parents, siblings, and offspring), including the age of each relative on the interview date or the age at death, sex, history of selected cancers, including pancreatic cancer, age at cancer diagnosis or age at death due to pancreatic cancer, history of diabetes, and cigarette-smoking status (ever versus never smoker). The interviewer also requested proband demographic information (age, sex, ethnicity, marital status, educational level, and annual income), cigarette smoking history, personal history of selected medical conditions, and personal-exposure history (residential and occupational) to selected chemicals. We used the double-entry method to enter data in our computer database and algorithms to detect out-of-range values, logical errors, and omissions.

Statistical Analysis

Unconditional logistic regression methods with adjustment for correlated data were performed with generalized estimating equations (15) by use of

SAS version 6.12 for the PC (16). The probands were not included in the models. The analyses treated each first-degree relative of a case or control proband as a study subject (case and control subjects, respectively). The outcome variable in the models was the pancreatic cancer status (whether the relatives had pancreatic cancer) of the relatives (17). The principal factor under study was whether each family member was related to a pancreatic cancer case proband (positive family history) or to a control proband (negative family history). For each relative, regression models were also used to examine risks associated with age, sex, ethnicity, smoking status, proband smoking status, history of diabetes, and the age of the proband. Statistical interactions between the family history of pancreatic cancer, smoking status, and age of the proband were evaluated. Individuals with missing data for any of the variables were excluded from the analyses. Relative risk (RR) estimates and 95% confidence intervals (CIs) were calculated from the coefficients in the regression models. All statistical tests were two-sided.

RESULTS

To evaluate whether family history of pancreatic cancer is a risk factor for pancreatic cancer, we conducted a case-control study. A total of 247 pancreatic cancer case probands and 420 control probands were interviewed (Table 1). The

mean ages of the case and control probands were 63.5 and 60.3 years, respectively ($P < .001$); however, the age distributions of the case and control probands were similar (Table 1). Approximately 14% of the probands were African-American, and approximately 50% were female. The characteristics of the first-degree relatives of the probands are presented in Table 2. The 247 case probands reported 1991 first-degree relatives, of whom 1816 had complete data for all variables. The case probands reported 23 (1.2%) first-degree relatives with pancreatic cancer. The 420 control probands reported 3286 first-degree relatives, of whom 3157 had complete data for all variables. The control probands reported 16 (0.5%) first-degree relatives with pancreatic cancer. No proband reported more than one first-degree relative with pancreatic cancer. The mean ages of the parents, siblings, and children of the relatives of the case and control probands were similar.

We next assessed whether there was a familial risk of pancreatic cancer. A positive family history of pancreatic cancer

Table 1. Characteristics of the pancreatic cancer case probands and the control probands

Characteristic	Pancreatic cancer case probands (n = 247)		Control probands (n = 420)	
	No.	%	No.	%
Age at interview/diagnosis, y				
30–39	7	2.8	30	7.1
40–49	20	8.1	50	11.9
50–59	57	23.1	103	24.5
60–69	75	30.4	134	31.9
70–79	88	35.6	103	24.5
Sex				
Male	127	51.4	197	46.9
Female	120	48.6	223	53.1
Ethnicity				
Caucasian	212	85.8	350	83.3
African-American	34	13.8	62	14.8
Other*	1	0.4	8	1.9

*Other refers to the Asian/Pacific Islander or unknown ethnicity.

Table 2. Characteristics of the first-degree relatives of the case and control probands

Characteristic	Relatives of case probands				Relatives of control probands			
	No.	Mean age, y	No. with pancreatic cancer	Mean age at diagnosis, y*	No.	Mean age, y	No. with pancreatic cancer	Mean age at diagnosis, y*
All family members	1991		23		3286		16	
First-degree relatives								
Parents	518	72.7	12	74.6	840	70.8	9	63.6
Sibling	760	57.6	11	56.6	1263	55.4	7	59.4
Offspring	713	35.5	0	†	1183	34.4	0	†

*Mean age at diagnosis or death was only calculated for those observed with pancreatic cancer.

†No mean age at diagnosis calculated because there was no observed pancreatic cancer.

(being related to a case proband) was associated with an increased risk of pancreatic cancer (RR = 2.49; 95% CI = 1.32 to 4.69) (Table 3). Although smoking was associated with an increased risk of pancreatic cancer (RR = 2.04; 95% CI = 1.09 to 3.83), we detected only a marginal increased risk with increasing age (RR = 1.03 per year; 95% CI = 1.02 to 1.04). There was no statistically significant association between the risk of pancreatic cancer and the sex, ethnicity, diabetes history of the relative, or age of the proband (Table 3).

We next assessed the statistical interaction between family history of pancreatic cancer and the smoking status of first-degree relatives. We found that those relatives who smoked and who had a positive family history of pancreatic cancer (i.e., those related to a case proband) had a 6.02-fold increased risk (95% CI = 1.98 to 18.29) compared with that of relatives who did not smoke and who had no family history of pancreatic cancer (i.e., those related to a control proband). First-degree relatives who did not smoke and who had a positive family history of pan-

creatic cancer were at intermediate risk (RR = 3.64; 95% CI = 1.12 to 11.80), as were those who smoked and who had a negative family history of pancreatic cancer (RR = 2.88; 95% CI = 0.94 to 8.84).

We also evaluated the statistical interactions among the age of the proband at diagnosis/interview, family history of pancreatic cancer, and smoking status. Table 4 shows that first-degree relatives who never smoked but who had a positive family history of pancreatic cancer (i.e., those related to a case proband) had an approximately twofold increase in the risk of pancreatic cancer, regardless of the proband's age at diagnosis. If case probands were diagnosed with pancreatic cancer before the age of 60 years, then their first-degree relatives who smoked had an 8.23-fold increased risk of pancreatic cancer (95% CI = 2.18 to 31.07). The two-way interaction between the age of the case proband and smoking status was statistically significant ($P = .048$). However, the interactions between the age of the proband and a positive family history of pancreatic cancer ($P = .64$)

and between smoking status and a positive family history of pancreatic cancer ($P = .44$) were not statistically significant. These results suggest a statistical interaction between smoking status and a positive family history with younger age at the onset of pancreatic cancer in a first-degree relative. By contrast, no statistical interaction was observed between the age of the case proband at diagnosis and the risk of pancreatic cancer in first-degree relatives who did not smoke.

Among the first-degree relatives of control probands (i.e., negative family history of pancreatic cancer), there was no statistical interaction between smoking status and the age of the proband (Table 4). Similarly, among first-degree relatives with a negative family history, the age of the control proband had no appreciable effect on the risk of pancreatic cancer.

DISCUSSION

In evaluating whether there is a familial risk of pancreatic cancer, we found that almost 10% of the 247 pancreatic cancer case probands interviewed reported a first-degree relative with pancreatic cancer compared with 5% of the 420 population-based control probands. Furthermore, we found that a positive family history of pancreatic cancer and smoking are both important risk factors for pancreatic cancer. In addition, our results suggest that there is an important interaction between a family history of younger age at onset of pancreatic cancer (<60 years) in a first-degree relative and smoking. However, among nonsmoking first-degree relatives, the RRs are about equal for early- and late-onset pancreatic cancer. To our knowledge, this study is the first to suggest that the age of onset of pancreatic cancer in first-degree relatives is an important contributing risk factor of pancreatic cancer in people who smoke.

Our findings are consistent with those of two case-control studies (7,9). In a case-control study in the Francophone community of Montreal, ON, Canada, Ghadirian et al. (7) compared the familial history of pancreatic cancer in first- and second-degree relatives of 179 pancreatic cancer patients. They found that 7.8% of the pancreatic cancer patients, but only 0.6% of the population-based control subjects, had a positive family history of pancreatic cancer. Fernandez et al. (8) reported individuals who had a positive family history of pancreatic cancer had a threefold increased risk (RR = 3.0; 95% CI = 1.4 to

Table 3. Factors associated with pancreatic cancer risk in first-degree relatives of case and control probands in a multivariate regression analysis*

Factor	No. of case relatives (n = 1816)†	No. of control relatives (n = 3157)†	RR‡	95% CI‡
Family history of pancreatic cancer	23	16	2.49	1.32 to 4.69
Smoking, ever	849	1571	2.04	1.09 to 3.83
Proband smoking, ever	1126	1984	1.26	0.65 to 2.43
History of diabetes	144	267	1.76	0.76 to 4.11
Ethnicity (Caucasian/other)	1513	2539	0.82	0.39 to 1.72
Female sex	873	1533	0.96	0.49 to 1.88
Age, per y	1816	3157	1.03	1.02 to 1.04
Age of proband, per y	1816	3157	0.99	0.96 to 1.02

*Multivariate model with adjustment for age, sex, ethnicity, ever smoking, proband ever smoking, history of diabetes, and age of the proband.

†Relatives with missing values in any variable are excluded from the analysis.

‡RR = relative risk of the factor among relatives of case probands; CI = confidence interval.

Table 4. Interaction between smoking status of each relative and age of diagnosis or death from pancreatic cancer of the proband

Smoking*	Age of proband, y	Relatives of control probands (n = 1357)†			Relatives of case probands (n = 1816)†		
		No.	RR‡,§	95% CI‡	No.	RR‡,§	95% CI‡
No	>60	985	1.0		679	2.02	1.02 to 4.01
No	30–59	601	0.94	0.40 to 2.21	288	2.15	0.63 to 7.27
Yes	>60	934	1.79	0.90 to 3.56	564	3.61	1.35 to 9.64
Yes	30–59	637	1.90	0.53 to 6.82	285	8.23	2.18 to 31.07

*Smoking status of the first-degree relatives.

†Relatives with missing values in any variable are excluded from the analysis.

‡RR = relative risk; CI = confidence interval. Statistical tests were two-sided.

§Multivariate model with adjustment for age, sex, ethnicity, age of the proband, proband ever smoking, and history of diabetes.

6.6) of pancreatic cancer compared with individuals who had a negative family history. This risk was not confounded by tobacco use, alcohol consumption, dietary factors, and medical history of pancreatitis and diabetes.

More recently, Silverman et al. (10) reported the results of a population-based, case-control study of malignancies, including pancreatic cancer, that occur in excess in African-Americans. Their results were based on direct interviews with pancreatic cancer patients and population-based control subjects. Of the 1153 patients initially identified for this study, 471 died before the interview could be conducted. Of the remaining 682 case patients, 525 (77%) were interviewed (10). Case patients with a family history of pancreatic cancer had a statistically significant increased risk of pancreatic cancer (RR = 3.2; 95% CI = 1.8 to 5.6). Case patients with a family history of pancreatic cancer and a long-term history of smoking had an even higher risk (RR = 5.3; 95% CI = 2.1 to 13.4) (10). Although these reported risks are similar to those in our study, Silverman et al. (10) reported no difference in pancreatic cancer risk associated with a positive family history of pancreatic cancer by age of diagnosis/interview and no statistically significant two-way interaction between a positive family history and proband smoking status. It should be noted that the study by Silverman et al. (10) did not evaluate the contribution of smoking habits of the relatives when determining the risk of pancreatic cancer associated with family history of pancreatic cancer.

Our study has a number of methodologic strengths that support the reliability of the observations. First, we used data from in-person interviews with newly reported diagnosed incident case probands. In-person interviews provide more reliable information than self-administered questionnaires or telephone interviews. This design aspect is unusual in studies of pancreatic cancer because of the short time between diagnosis and the onset of severe debility and death. Second, we assessed the thoroughness of our case-finding mechanisms for Wayne, Oakland, and Macomb counties by also searching the regional SEER registry to identify eligible case probands at participating hospitals who had been missed. We found only three such case probands, indicating that substantial selection bias in case as-

certainment was unlikely. Third, we had high participation among case and control probands, also indicating that substantial selection bias was unlikely. Fourth, we included only those case probands with histologically confirmed adenocarcinoma of the exocrine pancreas. This decision increased the reliability of our findings because the results are for a single type of pancreatic cancer that has been verified in the case probands.

The greatest strength of our study was the collection of risk information for each first-degree relative. Pancreatic cancer has been shown to aggregate in families. Our family-based study design allowed a more comprehensive assessment of familial aggregation of cancer than is possible in a simple case-control study. The reliability of the surrogate information about the first-degree relatives' smoking habits, age, and sex by the probands is believed to be high because other studies have shown that such data are reliably ascertained by proxy interviews (18). Recall bias regarding family history of pancreatic cancer may have contributed to an overestimate of risk because the case probands may have been more attuned than the control probands to their families' pancreatic cancer experience. The accuracy of reporting cancers in first-degree relatives has been found to be generally high but may vary by cancer site (19). For pancreatic cancer, Love et al. (19) found that family history of pancreas was reported accurately 71% of the time. Although we did not verify the diagnoses in the relatives, we did collect information on several types of cancers among the first-degree relatives of the probands. The proportion and ranking of reported cancers in relatives by the pancreatic cancer case probands are similar to the proportion and ranking of reported cancers in relatives by the control probands. For example, approximately 30% of the cancers reported in first-degree relatives of the case probands were breast cancer compared with 29% in the control probands, 20% of the cancers reported by the case probands were prostate cancer compared with 22% in the control probands, 15% of the cancers reported by the case probands were colon cancer compared with 14% in the control probands, and 16% of the cancers reported by the case probands were lung cancer compared with 23% in the control probands. Thus, potential recall bias by the case probands is unlikely to have played a major role. In addition,

seven pancreatic cancers were reported for siblings and offspring of control relatives in our study, which was close to the expected 3.55 calculated with the use of data from the SEER Program from 1973 to 1996, suggesting that the number of pancreatic cancers among relatives was not likely underestimated by the control probands.

Although we identified a familial association of pancreatic cancer, this disease does not often occur in association with an easily recognized clinical syndrome. However, the occurrence of an excess of pancreatic cancers in conditions known to result from germline mutations, such as mutations in the MSH2 gene located on chromosome 2p (in HNPCC) (20), in the p16-positive subset gene on chromosome 9p (in FAMMM) (21), or in the cyclin-dependent kinase inhibitor-2A gene (in melanoma) (21,22), is estimated to represent up to 10% of all pancreatic cancers. Because we found that a younger age at onset of pancreatic cancer in a first-degree relative is an important risk factor for individuals who smoke, we believe that this is evidence of a potential interaction between the genetic and environmental exposure components associated with the etiology of pancreatic cancer. However, whether these components are linked with a particular genetic syndrome is unclear.

Identification of high-risk individuals is clinically relevant and widely practiced when there are screening modalities that can diagnose early-onset disease and subsequent treatments that positively impact the health status of the individual. Clinicians should routinely use information about the increased risk of pancreatic cancer associated with a family history of pancreatic cancer and individual smoking habits to strongly encourage individuals to quit smoking and to target smoking-cessation programs appropriately and aggressively to high-risk populations. In addition, medical-care options will broaden for high-risk individuals as screening methods and surveillance and subsequent treatments of early-onset pancreatic cancer are developed. Evolving clinical research evaluating screening methods to detect pancreatic dysplasia in patients with a strong family history of pancreatic cancer and subsequent curative surgical treatments are yielding early promising results (23). Future research exploring the genetic and environmental interactions associated with pancreatic cancer is criti-

cally important and may identify additional risk factors that will likely assist in the further interpretation of the risk factors that we have identified.

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NOTES

¹*Editor's note:* SEER is a set of geographically defined, population-based, central cancer registries in the United States, operated by local nonprofit organizations under contract to the National Cancer Institute (NCI). Registry data are submitted electronically without personal identifiers to the NCI on a biannual basis, and the NCI makes the data available to the public for scientific research.

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