Increased Risk of Incident Pancreatic Cancer Among First-degree Relatives of Patients with Familial Pancreatic Cancer[1]

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ABSTRACT

It has been estimated that familial aggregation and genetic susceptibility play a role in as many as 10% of patients with pancreatic cancer (PC). The quantified prospective risk of PC among first-degree relatives of PC patients has not been investigated. Families enrolled in the National Familial Pancreas Tumor Registry (NFPTR) prior to September 1, 1998 were followed to estimate the risk and incidence of PC among first-degree relatives of patients with PC. Analyses were performed separately on kindreds with at least two first-degree relatives with PC (familial pancreatic carcinoma (PC); $n = 150$) at the time the kindred was enrolled in the NFPTR and on kindreds without a pair of affected first-degree relatives (sporadic PC; $n = 191$). A subanalysis was performed on familial PC kindreds containing three or more affected members at the time of enrollment in the NFPTR ($n = 52$). Risk was estimated by comparing observed new cases of PC during the observation period with expected numbers based on the United States population-based Surveillance, Epidemiology and End Results program data. Incidence was estimated using person-years risk analyses. During the observational period, six incident PCs developed in the first-degree relatives: two in the sporadic PC kindreds, and four in the familial PC kindreds. The PC risk in the sporadic PC kindreds was not significantly greater than expected [observed/expected = 6.5 (95% CI = 0.78–23.3)] with an incidence rate of 24.5/10^5/year. There was a significantly increased 18-fold risk (95% CI = 4.74–44.5) of PC among first-degree relatives in familial PC kindreds, with an incidence of 76.0/10^5/year. In the subset of familial PC kindreds with three or more affected family members at the time of enrollment, there was a 57-fold (95% CI = 12.4–175) increased risk of PC and an incidence of 301.4/10^5/year compared with the Surveillance, Epidemiology and End Result age-adjusted incidence of PC in the U.S. (8.8/10^5/year). When stratified by age, the risk was largely confined to relatives over the age of 60. This study is the first analysis of incident PC occurring in familial PC kindreds. The risk and incidence of PC is exceptionally high among at-risk first-degree relatives in familial PC kindreds in which at least three first-degree relatives have already been diagnosed with PC. Familial PC kindreds are a reasonable high-risk group for PC screening and chemoprevention research.

INTRODUCTION

For years, isolated case reports have suggested that PC[3] aggregates in some families (1–4). For example, in 1973, MacDermott and Kramer (5) reported a family in which four siblings developed PC, and in 1982 Dat and Sontag (6) described a family in which three brothers developed PC. Additional families have been documented by Lynch *et al.* (7–9) in the Creighton Familial Tumor Registry, including a 1990 report of 18 families in which two or more first-degree relatives developed PC. An initial analysis of these kindreds suggested an autosomal dominant mode of inheritance, and Lynch *et al.* have estimated that between 5 and 10% of PCs are caused by inherited genetic factors (7, 9, 10).

It may be argued that the occasional aggregation of cancer in a family may be attributable to chance or to a shared environmental exposure such as cigarette smoking (11–15). However, studies that have investigated familial aggregation have consistently demonstrated that family history of PC is 2.8- to 13-fold increased among PC patients relative to controls, even after adjusting for environmental risk factors and diabetes mellitus (16–19). For example, Silverman *et al.* (19) conducted a population-based case-control study of PC in Atlanta, Detroit and New Jersey. In this study, 484 patients with PC were compared with 2099 controls. Remarkably, 5% of patients with PC reported a first-degree relative with PC, compared with only 1.5% of the controls (OR = 3.2; CI = 1.8–5.6; adjusted for age, area, and gender; Ref. 19). A family history of PC was associ-

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[3] The abbreviations used are: PC, pancreatic carcinoma; OR, odds ratio; CI, confidence interval; NFPTR, National Familial Pancreas Tumor Registry; SEER, Surveillance, Epidemiology, and End Results Registry; CI, confidence interval.

ated with a higher risk among long-term smokers than among nonsmokers or short-term and moderate-term smokers (OR = 2.2; CI 1.0–7.9), although the interaction between family history and smoking was not statistically significant (19).

To learn more about the role of genetics in the etiology of PC, the NFPTR was established at The Johns Hopkins Medical Institutions in 1994 (20–23). Between 1994 and November 1, 2000, 535 families enrolled in this registry; 244 of these kindreds had at least a pair of first-degree relatives with PC (referred to as "familial PC kindreds"), whereas 291 kindreds had at least one family member diagnosed with PC but did not have a pair of affected first-degree relatives. These latter kindreds will be referred to here as "sporadic PC kindreds" (20).

The present study was conducted to quantify the prospective PC risk among first-degree relatives of PC index cases in the NFPTR. A prospective analysis should help overcome many of the biases inherent in retrospective studies of cancer families. In addition, if there were an increased prospective risk of PC in first-degree relatives in familial PC kindreds, it would support the concept that genetic predisposition plays a role in the development of some forms of PC (24).

MATERIALS AND METHODS

Subjects. The NFPTR was established at The Johns Hopkins Medical Institutions in 1994 to study the potential role of genetic factors in the development of PC (20, 23). All procedures related to the NFPTR have been approved by The Johns Hopkins Institutional Review Board. Patients may enter the Registry by one of three processes: (*a*) patients treated surgically for PC at The Johns Hopkins Hospital are sent a letter inviting them to join the Registry; (*b*) patients may request enrollment information via The Johns Hopkins Pancreatic Cancer Internet site;[4] or (*c*) patients can be referred to the Registry by a physician from another institution. Once the index patient has agreed to participate in the Registry and informed consent has been obtained, the index patient is asked to complete an extensive questionnaire that asks about medical and family history and exposure to possible PC-related risk factors such as smoking and industrial chemicals. This questionnaire is derived from one developed for hereditary colon cancer, which has undergone extensive verification testing (25). Data are entered into a computer database, and whenever possible all cancers are confirmed by review of pathology reports, death certificates, medical records, and/or diagnostic microscopic slides. Family members, particularly those with PC, or next of kin to such relatives, are also invited to complete questionnaires. Informed consent is also obtained from these family members and next-of-kin who wish to participate. Once registered, families are contacted regularly (approximately once a year) by the NFPTR and asked about the health status of family members. Whenever possible, reported new cancers are confirmed by obtaining the patient's medical records, death certificate, diagnostic pathology reports and/or microscopic slides. All patients with cancer are also asked for blood samples for current and future research studies, such as analysis of *BRCA2*, *p16*, and/or *DPC4* genes.

[4] Internet address: http://pathology.jhu.edu/pancreas.

Analysis. For the present study, we examined the prospective risk of PC among first-degree relatives who were alive and clinically free of cancer at the time the kindred enrolled in the Registry. All 341 families enrolled in the registry prior to September 1, 1998, were included in this analysis. As previously defined, kindreds with at least a pair of first-degree relatives with PC at the time the family enrolled in the NFPTR were considered familial ("Familial PC kindreds"; $n = 150$), whereas those without a pair of first-degree relatives were considered sporadic ("Sporadic PC kindreds"; $n = 191$; Ref. 20). Follow-up data obtained during the observation period of January 1, 1994, to December 31, 1998, were collected from the 150 Familial PC kindreds and 191 Sporadic PC kindreds. First-degree relatives of the index case of PC contributed person-years of observation from date of enrollment in the NFPTR until the closing date of the study, the date of their death, the date they were lost to follow-up, or the date they developed PC, whichever came first. Subjects were censored at their 85th birthday because the reliability of data concerning the incidence of PC was considered inadequate above that age.

Using a Fortran computer program for cohort analysis (26), person-years at risk were calculated according to gender, race, and 5-year age categories during each year of observation for the first-degree relatives from the Familial PC and Sporadic PC kindreds separately. Expected numbers of incident PC cases were calculated by multiplying the number of person-years for each 5-year age group and gender by the corresponding age-, race-, and gender-specific incidence rates for PC from the United States population-based SEER registry for the year 1994 (27). The "relative risk", and 95% confidence limits of PC among first-degree relatives in the Familial PC and Sporadic PC kindreds were estimated using the ratio of observed PCs to the number of expected PCs (28). "Absolute risks" for the Familial PC and Sporadic PC kindreds were separately calculated by dividing the total number of observed new cases of PC by the number of person-years accumulated by the at-risk first-degree relatives.

Subanalysis. Two subanalyses were performed, as follows. (*a*) The above calculations were repeated on a subset of the Familial PC kindreds, defining the group as those Familial PC kindreds in which there were three or more family members diagnosed with PC at the time the kindred enrolled in the NFPTR; and (*b*) because smoking is a known risk factor for PC (11–15), questionnaire data on smoking behavior were analyzed. At-risk first-degree relatives were subdivided into three groups: non- smokers, ever-smokers, and smoking-behavior-unknown. Differences between smoking behaviors among the at-risk first-degree relatives in the Familial PC and Sporadic PC kindreds were evaluated by χ^2 analyses.

The *BRCA2* tumor suppressor gene was sequenced in germline DNA obtained from family members with PC from 30 Familial PC kindreds, as has been described previously (29). In 27 of the cases, the entire gene was sequenced, and in three cases, only the region around the 6174delT hotspot of mutation was sequenced. Germline DNA from 11 of the Familial PC kindreds had been screened previously for *DPC4* gene mutations, and 21 kindreds had been screened previously for *p16* gene mutations (30, 31).

Table 1 Description of NFPTR kindreds as of September 1, 1998

	Total no. of family members diagnosed with PC at time the kindred enrolled in the NFPTR[a]	No. of kindreds	No. of first-degree relatives at risk for PC	No. of incident PC cases during observation period
Familial PC kindreds[b]	2	98	392	1
	3	35	143	1
	4	13	49	1
	≥5	4	14	1
	Total	150	598	4
Sporadic PC kindreds	1	188	631	2
	>1[c]	3	11	0
	Total	191	642	2

[a] Excludes unrelated family members (*i.e.,* spouses).
[b] Familial PC kindreds contained at least a pair of first-degree relatives with PC at entry.
[c] Some Sporadic PC kindreds contained second-degree or higher relatives affected with PC.

RESULTS

As of September 1, 1998, 341 families had enrolled in the NFPTR. These included 150 Familial PC kindreds and 191 Sporadic PC kindreds. Fifty-two of the 150 Familial PC kindreds contained three or more members with PC at the time of enrollment (Table 1). Three of the Sporadic PC kindreds contained a second- or third-degree relative of the index case with PC. One of these three kindreds contained three other affected, though distantly related, members. Eighty-three of the 150 Familial PC kindreds were self-referrals from the Internet, 38 were referrals from a physician at another institution, and in 29 of the 150 Familial PC kindreds, the index patient was a patient who was treated surgically for PC at The Johns Hopkins Hospital. In 164 of the 191 Sporadic PC kindreds, the index patient was treated surgically for PC at The Johns Hopkins Hospital, 18 were self-referrals from the Internet, and 9 were referred from physicians at another institution. Fifty-five percent of the questionnaires from the 341 kindreds enrolled in this study were completed by the index patient and 45% by a next-of-kin informant. The diagnosis of PC in the index patient was confirmed in 292 (86%) of the 341 kindreds.

With the exception of family history, the PC patients in the Sporadic PC and Familial PC kindreds were clinically and pathologically indistinct. The average age at diagnosis in the Familial PC kindreds was 65.9 years, and in the Sporadic PC kindreds it was 64.2 years. None of the kindreds had recognized familial pancreatitis or a familial cancer syndrome, and the light microscopic appearance of the PCs in the two groups was reviewed by one of the authors (R. H. H.), and there were no differences in the types of carcinomas (32) seen.

By the close of the observational period (December 1, 1999), six incident primary PCs had developed in PC patients' at-risk first-degree relatives. The incident PCs were distributed equally between males and females. Four of these developed in the Familial PC kindreds, and two developed in the Sporadic PC kindreds (Table 2). Three of the four incident PCs that developed in Familial PC kindreds developed in kindreds which had three or more family members with PC at the time the family enrolled in the NFPTR. The pedigrees of all six kindreds with an incident PC can be found on the Internet.[5] As can be seen in Table 2, 5 of the 6 incident PCs and 29 of the 31 other cancers in these six kindreds were independently confirmed by review of either pathology reports or slides, from medical records, and/or from death certificates.

The first-degree relatives in the 341 kindreds enrolled in the NFPTR prior to September 1, 1998, were analyzed further for incident PC risk. These included 1145 (1107 white, 38 nonwhite) first-degree relatives from the 150 Familial PC kindreds and 1282 (1213 white, 69 nonwhite) first-degree relatives from the 191 Sporadic PC kindreds. Two hundred and forty-six of the 1145 first-degree relatives in the Familial PC kindreds came from families with three or more affected family members at the time the kindred enrolled in the NFPTR. Five hundred thirty-two of the 1145 first-degree relatives in the Familial PC kindreds were excluded from the analysis either because they had reached the age of 85 ($n = 34$) or because they had died before the kindred had enrolled in the NFPTR ($n = 498$). The excluded cases included 141 of the 246 first-degree relatives from families with three or more affected family members. Four hundred and fifty of the 1282 first-degree relatives from the Sporadic PC kindreds were excluded because they had reached the age of 85 ($n = 29$) or because they had died prior to the family enrolling in the NFPTR ($n = 421$). Follow-up on most kindreds was performed at least once and was available on 598 (97.5%) of the 613 at-risk first-degree relatives in the Familial PC kindreds and on 642 (77%) of the 832 at-risk first-degree relatives from the Sporadic PC kindreds. Our inability to obtain follow-up on some of the Sporadic PC Kindreds largely reflects the extremely high mortality rate of this disease. The majority (62%) of the probands (the person through whom contact with the family was initiated) in the Sporadic PC kindreds were patients with PC, and 70% of the 191 probands in the Sporadic PC kindreds were deceased at last follow-up. By contrast, only twenty-one (14%) of the 150 probands in the Familial PC kindreds were deceased at last follow-up.

As seen in Table 3, the ratio of observed:expected incident PCs was 6.5 (95% CI = 0.78–23.3) for the Sporadic PC

[5] Internet address: http://pathology.jhu.edu/pancreas_pedigrees.

Table 2 Incident cancers in the Familial and Sporadic PC kindreds enrolled in the NFPTR as of September 1, 1998

	At time of enrollment in NFPTR			Incident cancers during observation period		
Kindred no.	Family member	Type of cancer[a]	Age at diagnosis (yr)	Family member	Type of cancer[a]	Age at diagnosis (yr)
2005	Index (female)	Pancreas*	47	Son 1	Pancreas*	68
	Daughter 1	Pancreas*	34	Son 2	Lung*	65
	Daughter 2	Pancreas*	73			
	Grandson	Pancreas*	39			
	Husband	Prostate*	73			
	Daughter 3	Esophageal*	56			
2001	Index (female)	Pancreas*	78	Sister	Pancreas*	75
	Mother	Pancreas*	70			
	Father	Pancreas*	63			
	Brother 1	Pancreas*	61			
	Brother 2	Pancreas*	67			
2031	Index (male)	Pancreas*	71	Sister 2	Pancreas*	59
	Father	Pancreas*	93	Son	Bladder*	52
	Sister 1	Breast*	38			
	Brother	Prostate*	54			
	Sister 2	Breast*	54			
	Mother	Breast*	50			
2053	Index (female)	Pancreas*	78	Sister 3	Pancreas*	74
	Father	Pancreas*	53			
	Brother 1	Pancreas*	58			
	Brother 2	Mesothelioma*	64			
	Sister 1	Breast, Melanoma	59, 66			
	Sister 2	Breast*	63			
2043	Index (male)	Pancreas*	70	Brother	Pancreas	69
	Mother	Gall Bladder*	55			
1141	Index (male)	Pancreas*	47	Brother	Pancreas*	56
	Sister	Ovarian*	Unknown	Sister	Unknown Primary*	48

[a] * Indicates diagnosis of cancer confirmed.

Table 3 Risk and incidence of PC among at-risk first-degree relatives in the NFPTR

No. of PC in kindred at time of registry in NFPTR	No. of at-risk first-degree relatives in kindred	Age group (yr)	Person-years at risk	Number of incident PC				Incidence (per 10^5/year)
				Observed	Expected	O:E[a]	95% CI	
Sporadic PC kindreds[b]		0–29	167	0	0	1.00		0
		30–59	971	1	0.04	25.2	0.63–139	20.6
		60–84	493	1	0.27	3.8	0.09–20.6	40.6
	642	Total	1631	2	0.31	6.5	0.78–23.3	24.5
Familial PC kindreds with 2 or more[c]		0–29	81	0	0	1.00		0
		30–59	612	1	0.03	39.3	0.84–186	32.7
		60–84	359	3	0.19	15.5	3.3–46.1	167.0
	598	Total	1052	4	0.23	18.3	4.74–44.50	76.0
Familial PC kindreds with 3 or more[c]		0–29	16	0	0	1.00		0
		30–59	93	0	0	1.00		0
		60–84	91	3	0.05	61.09	12.4–175.0	660.8
	105	Total	199	3	0.05	56.6	12.4–175.0	301.4

[a] O:E, ratio of observed:expected incident PCs.
[b] These kindreds may have contained family members with PC who were more distantly related to the index case.
[c] Kindreds containing at least a pair of first-degree relatives with PC. Kindreds with three or more are a subset of kindreds with two or more first-degree relatives.

kindreds, 18.3 (95% CI = 4.74–44.5) for the Familial PC kindreds, and 56.6 (95% CI = 12.4–175) for the subset of Familial PC kindreds with three or more family members with PC at the time of enrollment. Although there is an increasing trend in relative risk comparing the Sporadic PC, the Familial PC, and the subset of Familial PC kindreds with more than three affected family members, the CIs overlap so that the apparent differences are not statistically significant.

In all, there were sixteen incident non-PCs in the Familial PC kindreds and six incident non-PCs in the Sporadic PC kindreds. In the Familial PC kindreds, these included three colon cancers, two bladder cancers, two lung cancers, two basal cell skin cancers, a leukemia, a breast cancer, a larynx cancer, a liver cancer, a prostate cancer, a ureter cancer, and a uterine cancer. The lung cancer and bladder cancer developed in a kindred which also had an incident PC (Table 2). In addition, a

first-degree relative in one of the Familial PC kindreds developed chronic pancreatitis. In this kindred, the index case, two of her siblings, her mother, and a maternal uncle all died of PC. The six incident non-PCs in the Sporadic PC kindreds included an adenocarcinoma of an unknown origin, a breast cancer, a lung cancer, a lymphoma, a bladder cancer, and a melanoma.

The incidence of PC was $24.5/10^5$/year in the Sporadic PC kindreds, $76.0/10^5$/year in the Familial PC kindreds, and $301.4/10^5$/year in the Familial PC kindreds, with three or more affected persons at the time the family enrolled in the NFPTR (Table 3). For reference, the expected incidence of PC is $8.8/10^5$/year (SEER data). When stratified by age, all incident PC developed in first-degree relatives 30 years of age and older (Table 3), and in the Familial PC kindreds, the increased risk appeared to be largely confined to relatives 60 years of age and older (Table 3).

Cigarette smoking has been reported as a risk factor for PC (11–15). Because the SEER database does not include a smoking history variable, we were not able to analyze the risk by smoking behavior using SEER data. However, we did compare smoking behavior between the first-degree relatives in the Familial PC and Sporadic PC kindreds. In most cases (79%) these smoking histories were obtained from a next-of-kin informant. In general, smoking histories obtained from next-of-kin have been reported to be reasonably accurate, particularly when reporting ever-smoker *versus* never-smoker (33–35). Analysis of smoking showed that significantly more of the first-degree relatives in the Familial PC kindreds were smokers (44.8% *versus* 31.8%; $P = 0.003$ for males; 46.1% *versus* 28.1%, $P \leq 0.0005$ for females). Three of the six (50%) first-degree relatives who prospectively developed PC smoked at some time in their lives, whereas 37% of the first-degree relatives who did not prospectively develop PC smoked. Similarly, 50% of the first-degree relatives who prospectively developed a cancer other than PC were ever smokers.

Results of genetic analyses for germline mutations in the *p16* and *DPC4* genes of selected Familial PC kindreds in the NFPTR have been reported previously (30, 31). No *DPC4* or *p16* gene mutations were identified. In addition, in the present analysis, no mutations were found when germline DNA from 30 patients with PC from 30 of the Familial PC kindreds were screened for mutations in the *BRCA2* gene. This included three of the patients with an incident PC.

Remarkably, two additional incident PCs have developed in first-degree relatives in NFPTR kindreds since the close of this study, and two have developed in more distantly related relatives. These four additional incident PCs were not included in our analyses, but they do illustrate that the high rate of incident PCs observed during the study period has continued. The seventh incident PC to develop in an NFPTR kindred developed in one of the 94 Familial PC kindreds that registered after the last date of enrollment for this study (September 1, 1998). At the time this kindred enrolled in the NFPTR, the kindred contained six cases of PC: the index, a brother, a sister, the mother, and two paternal uncles. The 45-year-old daughter of the index patient prospectively developed PC.

The eighth incident PC to develop in a NFPTR kindred developed in a Familial PC kindred that successfully enrolled in this study, but the incident PC developed after the close of the study, and this incident PC was therefore also not included in the statistical analyses performed. At the time of enrollment, two family members in this kindred had been diagnosed with PC (the index patient and her son). In October 2000, the 52-year-old daughter of the index patient was diagnosed with PC.

The ninth incident PC occurred in the 80-year-old nephew of the index patient in a Familial PC kindred. At the time of enrollment, this kindred contained three family members with PC, two with breast cancer, and one with leukemia. The tenth incident PC occurred in the 74-year-old first cousin of the index patient in a Familial PC kindred. At the time of enrollment, two family members in this kindred had been diagnosed with PC and one had been diagnosed with colon cancer.

No incident PCs have developed in the 100 Sporadic PC kindreds that have enrolled in the NFPTR between the close of the enrollment in this study (September 1, 1998) and November 1, 2000.

DISCUSSION

It has long been suggested that there is a familial form of PC (3, 36, 37). Several large familial PC registries have been established to explore this possibility (20, 38). These registries are invaluable resources for genetic testing for germline mutations in candidate familial cancer genes, and they have been used to study the patterns of aggregation of pancreatic and non-PCs in families (20). For example, an initial analysis of the first 212 kindreds enrolled in the NFPTR revealed an increased risk of pancreatic and non-pancreatic cancer (including breast, colon, and lung cancer) in second-degree relatives of index patients in Familial PC kindreds compared with second-degree relatives in Sporadic PC kindreds (20). Similarly, Crowley *et al.* (39) found an increased risk of breast, colon, male genital, and stomach cancer among 65 kindreds in the Familial Pancreatic Registry at the University of Pittsburgh (38).

To our knowledge, the present analysis is the first in which relatives of PC patients were followed prospectively. Importantly, an analysis of prospective cancer risk reduces the potential for selection bias inherent in self-referred registries such as the NFPTR. To date (November 1, 2000), ten incident PCs have prospectively developed in NFPTR kindreds. Six of these developed during the observation period of this study. Our analyses of these kindreds indicate that first-degree relatives in Familial PC kindreds develop PC at a much higher rate than would be expected in the general population. When limited to Familial PC kindreds in which the index case plus at least two other relatives are affected, the risk of PC in previously unaffected first-degree relatives is 57-fold greater than expected.

It is unlikely that this increased risk is attributable to shared environmental exposure. The PCs occurred in relatives who were usually living in different communities during their adult lives, and the cancers occurred in the sixth or greater decade of life. Nonetheless, more of the at-risk first-degree relatives from the Familial PC kindreds were smokers than were those from the Sporadic PC kindreds. Smoking is associated with a 2- to 3-fold increased the risk of PC (11–13, 15). These observations therefore suggest that smoking may contribute to, although not fully explain, the observed incidence of PC in the Familial PC kindreds. However, in a large, population-based case-control study,

Silverman *et al.* (19) did not find a statistically significant interaction between smoking and family history.

Our results suggest that the aggregation of PC in some families has a genetic basis (24). Indeed, some of the genes that play a role in the familial aggregation of PC have already been identified. To date, at least five genetic syndromes associated with familial aggregation of PC have been characterized, including familial breast cancer with germline mutations in the *BRCA2* gene (29, 40–43), familial atypical multiple-mole melanoma with germline mutations in the *p16* tumor suppressor gene (44–47), the Peutz-Jeghers Syndrome with germline mutations in the *STK11/LKB1* gene (48–53), hereditary nonpolyposis colorectal cancer with germline mutations in one of the DNA mismatch repair genes (54–56), and hereditary pancreatitis with germline mutations in the *cationic trypsinogen* gene (57–60). These syndromes and genes, however, do not explain our findings. None of the incident PCs occurred in families with clinical evidence of one of these syndromes, and no mutations were identified in the subsets of kindreds examined for germline mutations in the *BRCA2*, *p16*, and *DPC4* genes (30, 31). Therefore, our findings suggest that there is a distinct syndrome of isolated familial PC. (19)

Although the gene or genes responsible for familial PC have not yet been identified, we found that first-degree relatives of patients with familial PC form a high-risk group of individuals. Interventions might be targeted to such persons, and they provide a reasonable model for PC screening, cancer prevention, and chemoprevention research (61). For example, the higher smoking rate seen in the familial kindreds suggests that efforts to promote smoking cessation may be particularly useful in the familial PC kindreds. Furthermore, Brentnall *et al.* (61) have recently reported a surveillance program to identify and treat patients who have precancerous conditions of the pancreas and a family history of PC (62). It is anticipated that as new PC chemoprevention and screening modalities become available, this group of individuals may be among the first to benefit from such applications.

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