Original Article

Clinical and Pathologic Features of Familial Pancreatic Cancer

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BACKGROUND: Inherited predisposition to pancreatic cancer contributes significantly to its incidence and presents an opportunity for the development of early detection strategies. The genetic basis of predisposition remains unexplained in a high proportion of patients with familial PC (FPC). **METHODS:** Clinicopathologic features were assessed in a cohort of 766 patients who had been diagnosed with pancreatic ductal adenocarcinoma (PC). Patients were classified with FPC if they had ≥1 affected first-degree relatives; otherwise, they were classified with sporadic PC (SPC). **RESULTS:** The prevalence of FPC in this cohort was 8.9%. In FPC families with an affected parent-child pair, 71% in the subsequent generation were 12.3 years younger at diagnosis. Patients with FPC had more first-degree relatives who had an extrapancreatic malignancy (EPM) (42.6% vs 21.2; $P<.0001$), particularly melanoma and endometrial cancer, but not a personal history of EPM. Patients with SPC were more likely to be active smokers, have higher cumulative tobacco exposure, and have fewer multifocal precursor lesions, but these were not associated with differences in survival. Long-standing diabetes mellitus (>2 years) was associated with poor survival in both groups. **CONCLUSIONS:** FPC represents 9% of PC, and the risk of malignancy in kindred does not appear to be confined to the pancreas. Patients with FPC have more precursor lesions and include fewer active smokers, but other clinicopathologic factors and outcome are similar to those in patients with SPC. Furthermore, some FPC kindreds may exhibit anticipation. A better understanding of the clinical features of PC will facilitate efforts to uncover novel susceptibility genes and the development of early detection strategies. ***Cancer*** **2014;120:3669-75.** © *2014 American Cancer Society.*

KEYWORDS: pancreatic cancer, hereditary, epidemiology, prognosis.

INTRODUCTION

Pancreatic cancer is a lethal disease with a 5-year survival rate of less than 5%.[1] The majority of patients present with locally advanced or metastatic disease that is not amenable to surgical resection, which currently offers the only chance of cure. Of the 10% to 20% of patients who undergo resection, most (approximately 80%) still die of the disease, and the median survival is less than 2 years.[2] Long-term survivors are usually those who had small nonmetastatic tumors, clear lymph nodes, and underwent resection with negative surgical margins.[3] Pancreatic cancer evolves through noninvasive precursor lesions, and it is believed that most pancreatic cancers develop from microscopic ductal lesions known as pancreatic intraepithelial neoplasia (PanIN). A smaller percentage arises from cystic lesions (intraductal papillary mucinous neoplasms or mucinous cystic neoplasms).[4,5] Recent studies estimate that a period of 10 to 20 years is required from the time of an initiating mutation to the establishment of advanced disease, suggesting a prolonged period during which intervention may be possible.[6]

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Strategies that facilitate the early detection of pancreatic cancer or its precursors during this broad window are extremely attractive. Screening the general population is not feasible because of the low incidence of pancreatic cancer and the lack of a robust screening test. Consequently, the focus has shifted to individuals who are considered to be at high risk. Established risk factors for pancreatic cancer constitute both environmental and inherited influences and include age, ABO blood group, cigarette smoking, diabetes mellitus (DM), obesity, and a family history of pancreatic cancer.[7] An inherited predisposition to pancreatic cancer manifests in 3 different settings[8]: 1) hereditary tumor predisposition syndromes, which account for 15% to 20% of the burden of inherited diseases like hereditary breast ovarian cancer and Peutz-Jegher syndrome[9]; 2) hereditary pancreatitis; and 3) familial pancreatic cancer (FPC). FPC is defined as a kindred in which at least 2 first-degree relatives (FDRs) have pancreatic cancer that otherwise does not fulfill the diagnostic criteria for an inherited cancer syndrome.[10] The underlying genetic basis of pancreatic cancer predisposition has been identified in less than 25% of such families,[11-13] although 50% to 80% of families demonstrate an autosomal-dominant inheritance pattern.[14,15]

MATERIALS AND METHODS

Patient and Data Acquisition

Detailed clinicopathologic, treatment, and outcome data from a cohort of 766 patients who had a histopathologic diagnosis of pancreatic ductal adenocarcinoma (PC) was accrued from 12 hospitals associated with the Australian Pancreatic Cancer Genome Initiative between 1994 and 2012 (available at: www.pancreaticcancer.net.au; accessed February 1, 2014). Recruitment was focused on biospecimen acquisition for genomic studies and, thus, biased the cohort toward resected cases. Patients were classified with FPC if they had $\geq$1 FDR with a confirmed diagnosis of pancreatic cancer, and the remaining patients were classified with sporadic PC (SPC). No patient had a known genetic predisposition or hereditary cancer syndrome at enrolment. Ethical approval was obtained from the human research ethics committee at each participating institution. All cases underwent central pathology review by at least 1 specialist pancreatic histopathologist (A.J.G., A.C., J.G.K.) who was blinded to the diagnosis and clinical outcome to verify the diagnosis of PC and to define histopathologic features in a standardized manner using a synoptic report developed for the purpose.[16] Tumors were staged according to the *AJCC Cancer Staging Manual* (7th edition, 2009).[17]

Clinicopathologic information initially was acquired retrospectively but became prospective in 2006. Prospectively recruited participants underwent a structured interview by a trained interviewer using a validated questionnaire.[18] Detailed baseline information included demography; cigarette smoking and alcohol consumption; personal and family history of malignancy; and medical comorbidities, including DM and pancreatitis. Cigarette smoking was stratified into 3 groups: active smokers, prior smokers, and nonsmokers. Active smoking was defined as ongoing use or cessation within 6 months of diagnosis. Prior smokers were defined as those who had smoked >100 cigarettes but had ceased >6 months previously, and they were stratified further based on duration of abstinence (from 6 months to 10 years vs >10 years). Nonsmokers were defined as those who had smoked <100 cigarettes in their lifetime. Cigarette smoking was quantified using pack-years with 1 pack-year representing smoking 20 cigarettes per day for 1 year. Alcohol consumption was classified on the basis of average consumption of all alcohol types for 12 months before PC diagnosis using the number of standard drinks (10 g ethanol) per day, where mild alcohol consumption represents 0 to 2 standard drinks per day, moderate consumption represents 3 or 4 standard drinks, and heavy consumption represents $\geq$5 standard drinks per day. DM was based on physician diagnosis or treatment with insulin or oral hypoglycemics. The duration of diabetes before diagnosis was stratified into 2 groups: $\leq$2 years and >2 years. In both prospective and retrospective cases, additional clinical data were obtained from hospital notes, physician records, and family members. The date and cause of death were obtained from cancer registries and treating clinicians.

Statistical Analysis

Disease-specific survival was used as the primary endpoint and was calculated from the date of histopathologic diagnosis to the date of death or last clinical follow-up. Nonresected patients and those who underwent R2 resection (macroscopically positive resection margins) were excluded from survival analyses. Patients who were alive at the census date (June 1, 2013) were censored. Univariate Kaplan-Meier analyses of patient, tumor, and treatment variables were used to compare median survival using the log-rank test. Chi-square and Fisher exact tests were used to compare categorical variables, and the Student *t* test was used to compare continuous variables. Reported *P* values are 2-sided, and variables with *P* values <.05 were considered statistically significant. Statistical analyses

TABLE 1. Distribution of Relatives With Pancreatic Ductal Adenocarcinoma and Extrapancreatic Malignancy

Variable	No. (%)		*P*
	FPC, N = 68	SPC, N = 698	
FDR with PC			
2 FDR	6 (8.8)	—	
1 FDR	53 (77.9)	—	
1 FDR and 1 SDR	8 (11.8)	—	
1 FDR and 2 SDR	1 (1.5)	—	
FDR with EPM			
No. of FDRs with an EPM			
1	20/68 (29.4)	115/698 (16.5)	
2	4/68 (5.9)	27/698 (3.9)	
3	4/68 (5.9)	6/698 (0.9)	
4	1/68 (1.5)	0	
Mean no.	1.52	1.26	.0372
Total no. of FDRs with an EPM	44	187	
EPM site			
Breast	7/68 (10.3)	34/698 (4.9)	.0579
Colorectal	7/68 (10.3)	44/698 (6.3)	.2077
Prostate	3/68 (4.4)	16/698 (2.3)	.2834
Endometrial	2/68 (2.9)	4/698 (0.6)	.0345
Ovarian	1/68 (1.5)	6/698 (0.9)	.6133
Melanoma	6/68 (8.8)	4/698 (0.6)	<.0001
Gastric	3/68 (4.4)	12/698 (1.7)	.1261
Lung	4/68 (5.9)	26/698 (3.7)	.3813
Total with an EPM in ≥1 FDR	29/68 (42.6)	148/698 (21.2)	<.0001

Abbreviations: EPM, extrapancreatic malignancy; FDR, first-degree relative; FPC, familial pancreatic cancer; PC, pancreatic ductal adenocarcinoma; SDR, second-degree relative; SPC, sporadic pancreatic cancer.

were performed using Statview 5.0 software (Abacus Systems, Berkeley, Calif).

RESULTS

Patient Cohort

The cohort consisted of 766 consecutive patients who had a histopathologic diagnosis of PC, including 698 who had SPC and 68 who satisfied the criteria for FPC. The clinicopathologic characteristics of these patients are summarized in Supporting Tables 1 and 2 (see online supporting information). The majority of patients (77.9%) underwent pancreatic resection with curative intent. In the FPC subset, 57 patients (83.8%) underwent pancreatic resection, and 11 underwent a diagnostic biopsy only. The majority of FPC families (77.9%) had 2 affected FDRs, and 8.8% had 3 affected FDRs. The remaining FPC families had combinations of affected FDRs and second-degree relatives, as described in Table 1.

Clinicopathologic Variables and Outcome

Patients from families with FPC represented 8.9% of all cases. There was no difference in overall outcome between the SPC and FPC cohorts (Fig. 1A,B), and the median survival of resected patients was 19.8 months and 17.4 months, respectively (P=.1468). In addition, resected FPC and SPC patients did not differ according to the distribution of any prognostic clinicopathologic variables (Table 2 and Supporting Table 1; see online supporting information). In both cohorts, patients who had tumors located in the head of the pancreas and/or who received adjuvant chemotherapy had a better survival. The limited numbers in the FPC cohort likely influenced the statistical significance of other clinicopathologic variables, such as size and lymph node status.

Distribution according to sex in FPC patients and SPC patients was similar, as was the mean age at diagnosis (65.8 years vs 66.0 years, respectively; P=.8952). Furthermore, there was no difference in the proportion of patients diagnosed at an early age (<50 years) (Table 2). Of the 68 patients who had FPC, 40 were members of an affected parent-child pair. In 28 of those 40 patients, the age at diagnosis was confirmed in both the affected parent and the child; and, in 20 of these (71.4%), the age of the child at diagnosis was >5 years younger than that of the affected parent. For parent-child pairs, the mean age at diagnosis in was 72.9 years in parents and 60.6 years in affected offspring (P<.0001). The parent of origin did not appear to affect the age at diagnosis in the successive generation: children were diagnosed 12.3 years earlier if the father was affected and 12.2 years earlier if the mother was affected (P=.9675).

Patients with resected FPC had more precursor lesions (specifically, PanIN 2 and PanIN 3) distinct from the carcinoma in the resected specimen than patients with resected SPC (36.8% vs 23.9%, respectively; P=.0320) (Table 2). The presence of PanIN 2 and PanIN 3 was not associated with a difference in survival among patients with FPC or SPC (Fig. 1C,D).

Previous Extrapancreatic Malignancy

There were 11 previously diagnosed extrapancreatic malignancies (EPMs) in 10 patients from the FPC cohort and 76 EPMs in 72 patients from the SPC cohort. The proportion of patients with FPC or SPC with a previously diagnosed malignancy was similar (14.7% vs 10.3%, respectively; P=.2636). The types of prior EPMs were similar in both cohorts, and the most common were breast cancer, colorectal cancer, prostate cancer, and melanoma (Supporting Table 3; see online supporting information). A history of prior EPM was not related to survival in resected FPC patients (16.7 months vs 19.8 months;

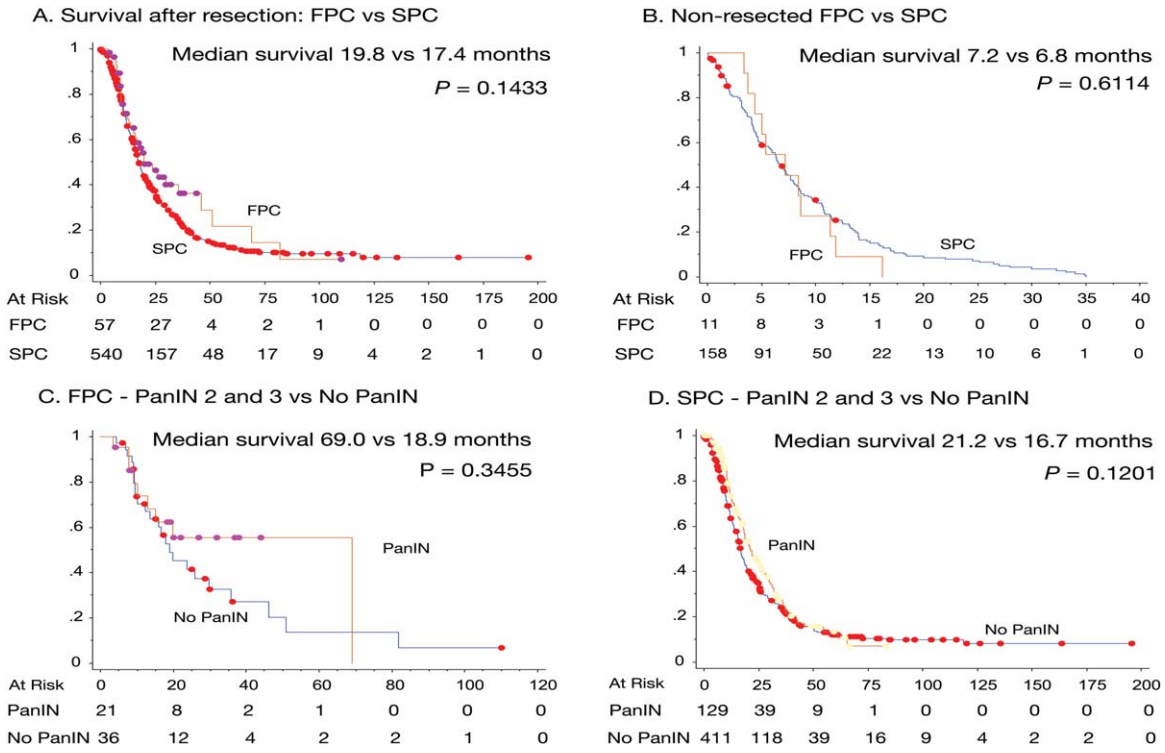

Figure 1. Kaplan-Meier survival curves illustrate (A) survival post-resection in patients with familial pancreatic cancer (FPC) and sporadic pancreatic cancer (SPC); (B) survival in patients with nonresected FPC and SPC; (C) survival in patients with FPC who underwent localized resection with and without pancreatic intraepithelial neoplasia 2 (PanIN 2) and/or PanIN 3; and (D) survival in patients with SPC who underwent localized resection with and without PanIN 2 and/or PanIN 3.

P=.5699) or resected SPC patients (16.1 months vs 17.8 months, respectively; P=.9408).

Family History of EPM

Patients with FPC were significantly more likely to have at least 1 FDR with an EPM (44.1% vs 21.2%; P<.0001). Furthermore, they were more likely to have multiple FDRs with an EPM (mean, 1.52 vs 1.26 FDRs; P=.0372) (Table 1). The most common malignancies in both FPC and SPC were breast cancer, colorectal cancer, melanoma, lung cancer, and prostate cancer. The distribution of malignancies in FDRs was similar in both cohorts, except that FPC kindreds were more likely to develop melanoma (8.8% vs 0.6%; P<.0001) and endometrial cancer (2.9% vs 0.6%; P=.0345). There was a trend toward higher rates of breast cancer in FPC kindreds (10.3% vs 4.9%; P=.0579) (Table 1 and Supporting Table 4; see online supporting information).

Other PC Risk Factors

The prevalence of DM in patients with FPC and SPC was 27.9% and 28.9%, respectively (P=.8623). All diabetics in this study had type 2 or 3c DM. There was no statistically significant difference between the FPC and SPC cohorts with regard to the mean duration of DM before PC diagnosis (6.1 years vs 5.0 years, respectively; P=.6112) or the proportion diagnosed within 2 years of PC (58.3% vs 53%, respectively; P=.7346) (Table 3). There was no association between the presence or duration of DM and the age at PC diagnosis in resected FPC and SPC patients. (Supporting Table 6; see online supporting information). A DM duration >2 years was associated with poor post-resection survival in both the FPC cohort and the SPC cohort (Supporting Fig. 1B-D; see online supporting information). Multivariate analysis demonstrated that positive lymph nodes, involved margins, tumor size $\geq$ 20 mm, adjuvant chemotherapy, a postresection CA 19.9 level >120 U/mL, and a DM duration >2 years were independent prognostic factors (Supporting Tables 5, 6, and 7; see online supporting information). Multivariate analyses were not performed in the FPC and SPC cohorts individually because of the limited number of patients with FPC.

TABLE 2. Comparison of Clinicopathologic Variables in Patients with Resected Pancreatic Ductal Adenocarcinoma

Variable	No. (%) FPC	No. (%) SPC	*P*
Mean age at diagnosis, y	65.8	66.0	.8952
Age <50 y	4/57 (7)	44/540 (8.1)	.7653
Location: Pancreatic body/tail	10/57 (17.5)	97/540 (18)	.9326
Lymph nodes involved	38/57 (66.7)	356/540 (65.9)	.9106
Differentiation poor	19/56 (33.9)	146/537 (27.2)	.2841
Tumor size >20 mm	50/57 (87.7)	427/540 (79.1)	.6547
Margins involved	18/57 (31.6)	199/540 (36.9)	.4312
Perineural invasion	43/53 (81.1)	397/522 (76)	.4059
Vascular invasion	26/47 (55.3)	265/506 (52.4)	.6987
Multifocal disease: PanIN2 or PanIN3	21/57 (36.8)	129/540 (23.9)	.0320
Before 2004[a]			
Any adjuvant chemotherapy	7/15 (46.7)	68/290 (23.4)	.0417
Adjuvant chemotherapy ≥3 cycles	5/15 (33.3)	34/290 (11.7)	.0145
After 2004			
Any adjuvant chemotherapy	31/42 (73.8)	155/246 (63)	.1761
Adjuvant chemotherapy ≥3 cycles	29/42 (69)	136/246 (55.3)	.0956

Abbreviations: FPC, familial pancreatic cancer; PC, pancreatic ductal adenocarcinoma; PanIN 2, pancreatic intraepithelial neoplasia 2; PanIN 3, pancreatic intraepithelial neoplasia 3; SPC, sporadic pancreatic cancer.
[a] Prior to 2004 adjuvant chemotherapy was not the standard of care in Australia.

TABLE 3. Risk Factors for Pancreatic Ductal Adenocarcinoma

Variable	No. (%) FPC	No. (%) SPC	P
Diabetes mellitus (DM)	19/68 (27.9)	202/698 (28.9)	
Missing date of diagnosis	6/19 (31.6)	98/202 (48.5)	.8623
DM ≤2 y	7/19 (36.8)	47/202 (23.3)	.5551
DM >2 y	6/19 (31.6)	57/202 (28.2)	.9327
Chronic pancreatitis	6/68 (8.8)	37/698 (5.3)	.2283
Alcohol			
Missing alcohol data	0 (0)	18/698 (2.6)	
Nil or low alcohol intake: ≤2 SD	58/68 (85.3)	541/698 (77.5)	.3000
Moderate alcohol intake: 3-4 SD	5/68 (7.4)	68/698 (9.7)	.4831
Heavy alcohol intake: ≥5 SD	5/68 (7.4)	71/698 (10.2)	.4216
Cigarette smoking			
Missing date ceased	2/21 (9.5)	31/165 (18.8)	
Never smoked	41/68 (60.3)	318/698 (45.6)	.0315
Prior smoker	21/68 (30.9)	165/698 (23.6)	.3314
Prior ≤10 y	5/21 (23.8)	50/165 (30.3)	.9702
Prior >10 y	14/21 (66.7)	84/165 (50.9)	.0627
Active smoker	6/68 (8.8)	197/698 (28.2)	.0003
Mean smoke exposure, pack-years	25.7	34.9	.0479

Abbreviations: FPC, familial pancreatic cancer; PC, pancreatic ductal adenocarcinoma; SD, standard drinks per day (10 g ethanol).

A history of chronic pancreatitis was present at similar rates in both FPC and SPC (8.8% vs 5.3%, respectively; *P*=.2283) and was not associated with an earlier age of diagnosis. There was no difference in postresection survival between those with and without a history of pancreatitis (median survival, 18.1 months vs 17.9 months, respectively; *P*=.3481).

Patients with SPC were significantly more likely than those with FPC to be active smokers at the time of diagnosis (28.2% vs 8.8%; *P*=.0003). Furthermore, patients in the SPC cohort who were active and prior smokers had higher levels of smoke exposure, with a mean of 34.9 pack-years of smoking versus 25.7 pack-years for patients in the FPC cohort who were active and prior smokers (*P*=.0479) (Table 3). On average, active smokers were 9.8 years younger at diagnosis in the resected FPC cohort (57.3 years vs 67.1 years; *P*=.0144) and 5.2 years younger at diagnosis in the resected SPC cohort (62.4 years vs 67.6 years; *P*<.0001) compared with never smokers and prior smokers who had an abstinence duration >10 years. In the resected SPC cohort, prior smokers with an abstinence duration ≤10 years were 3.7 years younger at diagnosis than never smokers and prior smokers who had an abstinence duration >10 years (63.9 years vs 67.6 years; *P*=.0237), but this was not significant in the FPC cohort. There was no statistically significant difference in age at diagnosis between FPC and SPC active smokers (57.3 years vs 63.0 years, respectively; *P*=.2342) or never smokers and prior smokers who had an abstinence duration >10 years (67.1 years vs 67.6, respectively; *P*=.7536). There was no difference in survival after resection between the 3 smoking classes (Supporting Figs. 1E, 2A,B; see online supporting information).

The majority of patients with both FPC and SPC had a low alcohol intake (nil or <2 standard drinks per day) in the 12 months before diagnosis (85.3% vs 77.5%, respectively; *P*=.3000), and only 7.4% and 10.2%, respectively, were heavy drinkers (*P*=.4216). There was no correlation between alcohol intake and age at diagnosis in the FPC cohort (Supporting Fig. 2C-E; see online supporting information).

DISCUSSION

The prevalence of familial PC in this cohort was 8.9%. There was no difference in age at diagnosis between FPC patients and SPC patients, but 71% of FPC families exhibited probable anticipation. FPC patients were more likely to have multifocal precursor lesions but fewer active smokers and lower smoke exposure. Patients with FPC were more likely to have 1 or more kindreds with an EPM

but were not more likely to have a personal history of an EPM.

An 8.9% prevalence of FPC is consistent with previous case-control and cohort studies,[19-21] although the requirement of histologic confirmation in relatives lowers the rate of familial aggregation.[22,23] Previous reports of a younger age at diagnosis in patients with FPC are inconclusive,[14,24] and some suggest an earlier onset by 5 years and a higher proportion (approximately 16%) of young-onset disease.[25,26] We observed no difference in age at diagnosis between the FPC and SPC cohorts overall (mean age, 65.8 years vs 66.0 years, respectively) or in the proportion of patients with young-onset (age <50 years) disease (9.6% vs 8.6%, respectively). However, active smokers were 9.8 years (FPC) and 5.2 years (SPC) younger at diagnosis compared with never smokers and those who had ceased smoking >10 years previously. In 71% of affected parent-child pairs, on average, the child was 12.3 years younger at diagnosis. It is unlikely that this was related to environmental risk factors, because most of these patients were nonsmokers. Anticipation has been reported in 32% to 85% of FPC families, with successive generations developing PC 10 to 20 years earlier.[15,25,27] Age at diagnosis, anticipation, and smoking have important implications for risk management, screening program development, and the identification of novel susceptibility genes.[28]

Patients with FPC were twice as likely as those with SPC to have at least 1 FDR with an EPM (42% vs 21%). In the majority of inherited cancer syndromes, the risk of malignancy is not confined to a single organ. In addition to pancreatic, breast, and ovarian cancers, breast cancer susceptibility gene (*BRCA2*) mutation carriers are at increased risk of prostate cancer, gallbladder cancer, bile duct cancer, gastric cancer, and melanoma.[29] A personal history of EPM was present in nearly 15% of patients with FPC, which was not significantly greater than that in patients with SPC at 10%. This is consistent with previous reports of a 13% to 16% incidence of previous EPM in SPC. [30] Approximately 8% of cancer patients in the United States and Australia are expected to develop a second invasive malignancy; and an estimated 6% will develop a second malignancy in a different organ.[30-32] The occurrence of multiple primary malignancies in FPC kindreds is suggestive of an underlying genetic predisposition, with variable penetrance, interaction with other modifier alleles, and gene-environment factors.[33] Understanding these complex phenotypes is important for the discovery of novel susceptibility loci, particularly at a time when advances in genomic sequencing have enabled the generation of large numbers of cancer genomes.

Patients with SPC were more likely to be active smokers at the time of PC diagnosis and had higher exposure to cigarette smoke than patients with FPC. There was no difference in other risk factors, such as alcohol consumption, DM, and chronic pancreatitis. Recent data also support the notion that patients who smoke and have a family history of malignancy in an FDR require a reduced dose of tobacco exposure for the development of PC.[34] A higher proportion of multifocal precursor lesions in patients with FPC is consistent with previous findings.[35] It is noteworthy that this did not affect outcomes after localized resection.

Consistent with previous studies, we observed no difference in survival between patients with resected FPC and those with resected SPC.[24,36] We identified longstanding DM (>2 years) as an independent prognostic variable in all patients who underwent resection. However, the role of DM as a prognostic marker is less well established,[37,38] and previous studies have yielded conflicting results.[39,40]

Our current study has several potential limitations. First, because of the nature of the data, we were not able to adjust rates of EPM in close relatives for family size. Second, we used patients with PC as proxy respondents to gain information about cancer diagnoses in FDRs. Although it has been demonstrated that proxy reporting is particularly accurate for cancer diagnoses in FDRs, there remains potential for recall bias.[41] Furthermore, histologic confirmation of PC in family members was not possible in all patients, because they often had advanced disease at presentation without a tissue diagnosis, which was common practice at that time. Approximately 40% of the patients in this study were acquired retrospectively and, as such, our results are subject to the bias associated with retrospective data. Finally, our study was weighted toward resected patients because of minimum tissue requirements for additional studies.

In conclusion, in this cohort, FPC represented nearly 9% all patients with PC. FPC is likely to be a heterogeneous syndrome with phenotype determined by the underlying genetic variants and modified by environmental risk factors. Some familial clustering is likely to occur because of phenocopies from common environmental exposures. Robust clinical characterization of FPC is indispensable for ongoing efforts to identify susceptibility genes, particularly in the age of massively parallel genomic sequencing.

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CONFLICT OF INTEREST DISCLOSURES

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