Published OnlineFirst December 8, 2009; DOI: 10.1158/1078-0432.CCR-09-0004
Published Online First on December 8, 2009 as 10.1158/1078-0432.CCR-09-0004

Susceptibility and Prevention

Increased Prevalence of Precursor Lesions in Familial Pancreatic Cancer Patients

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Abstract

Purpose: Histologic findings in 51 pancreata resected from patients with a strong family history of pancreatic cancer were compared with the findings in 40 pancreata resected from patients with sporadic pancreatic cancer. None of the patients in the familial group had a known inherited syndrome other than familial pancreatic cancer.

Experimental Design: Precursor lesions, including pancreatic intraepithelial neoplasia (PanIN), intraductal papillary mucinous neoplasm (IPMN), and incipient IPMN, were quantified. Invasive cancers were classified using established histologic criteria.

Results: The individual precursor lesions identified in both groups were histologically similar. Precursor lesions were more common in the familial cases than in the sporadic cases. The relative rate of PanINs per square centimeter was 2.75-fold higher (95% confidence interval, 2.05-3.70; adjusted for age) in familial compared with sporadic cases. PanIN-3 lesions were more common in familial versus sporadic pancreatic cancer patients (relative rate, 4.20; 95% confidence interval, 2.22-7.93; adjusted for age). High-grade incipient IPMNs were only observed in the familial cases. Nine of the 51 (18%) familial pancreatic cancers and 4 of the 40 (10%) sporadic cancers arose in association with an IPMN. No significant differences were found in the types of invasive cancers.

Conclusions: Noninvasive precursor lesions are more common in patients with a strong family history of pancreatic cancer than in patients with sporadic disease, and precursor lesions are of a higher grade in patients with a strong family history of pancreatic cancer. These findings can form a basis for the design of screening tests for the early detection of pancreatic neoplasia. (Clin Cancer Res 2009;15(24):7737–43)

Up to 10% of patients with pancreatic cancer have a family history of the disease (1, 2). Individuals with a family history of pancreatic cancer have an increased risk of developing pancreatic cancer themselves (3). It has been estimated that individuals with one first-degree relative with a pancreatic cancer have a 2-fold increased risk of developing pancreatic cancer, and the risk increases significantly with greater numbers of affected first-degree relatives (3, 4). Several genes have been identified that predispose to the familial aggregation of pancreatic cancer, and these include *BRCA2*, *CDKN2A/p16*, *STK11/LKB1*, *PALB2*, and *PRSS1* (5–11). These known genes account for only a minority of the cases of familial pancreatic cancer. The genetic basis for the majority of the familial aggregation of pancreatic cancer remains unknown.

One approach to understand the biological properties of a familial cancer gene is to carefully examine the precursor lesions that arise in the patients with the gene defect. For example, understanding of precursor lesions can help classify familial cancer genes as either "gatekeeper" or "caretaker" genes. Gatekeepers are genes that directly regulate the growth of neoplasms by inhibiting their growth or by promoting their death (12). The functions of these genes are rate-limiting for the growth of the neoplasm (12). Germline mutations in gatekeeper genes produce a dramatic increase in the number of precursor lesions, as, for example, is observed in familial adenomatous polyposis, a syndrome in which affected patients develop hundreds, or in some cases even thousands, of adenomas of the colon (13, 14). By contrast, caretaker genes do not directly promote the growth of neoplasms. Instead, the inactivation of a caretaker gene leads to a genetic instability that in turn indirectly promotes neoplastic growth by increasing the mutation rate (12). Germline mutations in caretaker genes, as seen for example in hereditary nonpolyposis colorectal cancer syndrome, are not associated with increased numbers of precursor lesions. The neoplasms that arise in patients with germline mutations in a caretaker gene rapidly progress to invasive cancer (13, 15). A careful examination of the precursor lesions could therefore

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Received 1/2/09; revised 8/27/09; accepted 9/30/09; published OnlineFirst 12/8/09.

Grant support: National Cancer Institute Specialized Program of Research Excellence in Gastrointestinal Cancer grant CA62924 and the Michael Rolfe Pancreatic Cancer Foundation.

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Translational Relevance

Individuals with a family history of pancreatic cancer have an increased risk of developing pancreatic cancer themselves. Significant effort has been placed in screening these at-risk individuals for early disease, but little is known of the precursor lesions associated with familial pancreatic cancer. In this study, we show that precursor lesions are more numerous and are of higher grade in patients with familial pancreatic cancer than they are in patients with sporadic disease. These findings have significant implications for the design of screening tests for the early detection of pancreatic cancer.

help define the biological properties of the gene(s) responsible for familial pancreatic cancer.

An understanding of the precursor lesions of familial and sporadic pancreatic cancer can also form the basis of the development of rational strategies for the early detection of pancreatic neoplasia. Early detection has been shown to save many lives that would otherwise be lost to breast, cervical, and colon cancers, and early detection is likely to improve survival of patients with pancreatic neoplasms (16). For example, Furukawa et al. reported a 4-year postoperative survival rate of 78% in patients with stage I infiltrating ductal adenocarcinomas of the pancreas (17), and Canto et al. and Brentnall et al. have reported that curable precursor lesions, including pancreatic intraepithelial neoplasia (PanIN) and intraductal papillary mucinous neoplasm (IPMN), can be detected when asymptomatic patients with a strong family history of pancreatic cancer are screened by endoscopic ultrasound (18–20).

Screening of patients with a strong family history of pancreatic cancer for early disease requires an understanding of the precursor lesions in these patients. For example, Brune et al. have shown that multifocal neoplastic precursor lesions are associated with lobulocentric atrophy of the pancreas in patients with a strong family history of pancreatic cancer, and that this multifocal lobulocentric atrophy can be detected by endoscopic ultrasound (21, 22). Furthermore, an understanding of the precursor lesions in patients with a strong family history of pancreatic cancer is needed for the development of clinical approaches to the treatment of the precursor lesions identified in these patients (23).

The purpose of this study was to define the histologic features of the noninvasive and invasive lesions in patients with familial pancreatic cancer by histologic review of a large series of pancreata resected from these patients.

Materials and Methods

Patients. The National Familial Pancreas Tumor Registry was established at The Johns Hopkins Medical Institution in 1994 (24). All procedures related to the National Familial Pancreas Tumor Registry have been approved by The Johns Hopkins Medical Institutional Review Board. As of August 10, 2009, 3,367 families have enrolled in the National Familial Pancreas Tumor Registry. Among them, 1,114 families met the established definition of familial pancreatic cancer (defined as a kindred in which at least a pair of first-degree relatives has been diagnosed with pancreatic cancer). Fifty-one familial pancreatic cancer patients and 40 sporadic pancreatic cancer patients (defined as a kindred without a pair of affected first-degree relatives) enrolled in the National Familial Pancreas Tumor Registry, who underwent surgical resection for their pancreatic cancer at The Johns Hopkins Hospital, were included in these analysis. Patients were limited to those who underwent surgery at The Johns Hopkins Hospital to ensure uniform sampling and processing of the resected specimens (25). Family history of pancreatic cancer was obtained by questionnaire and, when possible, confirmed by pathology report, review of histologic slides, medical record, and/or death certificate, the details of which have been described elsewhere (3, 26). All patients in the familial group did not have a known genetic syndrome (BRCA2, hereditary nonpolyposis colorectal cancer, or familial atypical multiple mole melanoma) other than familial pancreatic cancer.

Microscopic examination. All available histologic slides from the surgically resected pancreata were reviewed for noninvasive precursor lesions including PanINs, incipient IPMNs, and IPMNs, as well as for other histologic changes (27). The number of duct profiles containing a precursor lesion was counted, and the area with no invasive carcinoma was measured. The densities of precursor lesion were calculated (number of lesions per square centimeter). The histologic type of each invasive cancer was documented, as were the parenchymal changes associated with the precursor lesions (21).

Pancreatic intraepithelial neoplasia. PanIN is a microscopic flat or papillary, noninvasive epithelial neoplasm arising in a smaller (<0.5 cm) pancreatic duct. PanIN lesions are further classified into three grades based on their architectural and cytologic atypia (28). PanIN-1 is defined as flat or papillary lesions composed of uniform columnar mucinous cells with little, if any, nuclear atypia (Fig. 1A; ref. 28). PanIN-2 lesions have some nuclear abnormalities including loss of polarity, nuclear crowding, enlarged nuclei, pseudostratification, and hyperchromasia (Fig. 1B). PanIN-3 lesions are characterized by the presence of significant architectural and/or cytologic atypia (Fig. 1C; ref. 28).

Intraductal papillary mucinous neoplasm. IPMNs are grossly visible mucin-producing epithelial neoplasms (≥1 cm), which predominantly arise within the main pancreatic duct or one of its branches (28). IPMNs cause varying degrees of duct dilation, have a prominent papillary architecture, and produce abundant intracellular and extracellular mucin (Fig. 2). IPMNs can be further classified into IPMN with low-grade dysplasia (IPMN-adenoma), IPMN with moderate dysplasia (IPMN-borderline), and IPMN with high-grade dysplasia (*in situ* carcinoma) based on the degree of architectural and cytologic changes (28).

Incipient IPMN. "Incipient" IPMNs are histologically similar to IPMNs, but they are <1 cm and fall short of size criteria for an IPMN. In this study, a precursor lesion with a size of 0.5 to 1 cm was defined as an incipient IPMN.

Invasive carcinoma. Histologic types of invasive pancreatic carcinoma were reviewed and classified using standard nomenclature (27).

Statistics. The number of PanIN profiles and the number of incipient IPMNs in areas with no invasive carcinoma observed in the familial pancreatic cancer patients and the sporadic pancreatic cancer patients were compared using negative binomial regression, with an offset for area in square centimeter. The histologic types of the invasive pancreatic cancer and the number of IPMNs were compared using Fisher's exact tests and/or Kruskal-Wallis rank test. Data analysis was conducted using STATA v10.0.

Results

Histologic types of invasive pancreatic cancer. The majority of the invasive carcinomas in the 51 patients with familial pancreatic cancer were classic infiltrating ductal adenocarcinomas [34 of 51 (67%); Table 1]. Other types of invasive cancer identified in the familial group included 6 (12%) adenosquamous carcinomas, 9 (18%) IPMNs with an associated invasive

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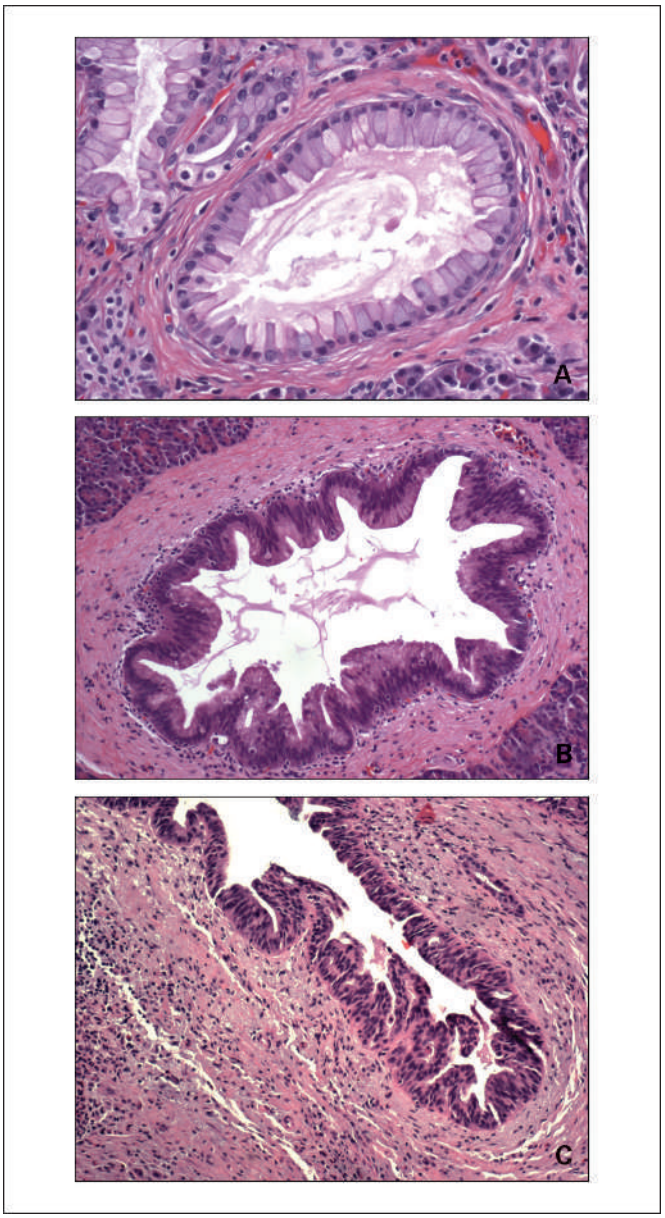

Fig. 1. Representative H&E-stained PanIN lesions from case 51 of the familial group. *A,* a PanIN-1 lesion showing mucinous columnar epithelial proliferation with little nuclear atypia (×200). *B,* a PanIN-2 lesion showing proliferated ductal epithelium with some nuclear atypia and pseudostratification (×100). *C,* a PanIN-3 lesion showing marked architectural and nuclear atypia (×100).

adenocarcinoma (IPMN + CA), 1 (2%) undifferentiated carcinoma, and 1 (2%) signet ring cell carcinoma. Classic infiltrating ductal adenocarcinoma also accounted for the majority of the infiltrating cancers in the sporadic group [34 of the 40 cases (85%)]. The other histologic types of invasive cancer identified in the sporadic pancreatic cancer group included 1 (2%) adenosquamous carcinoma, 4 (10%) IPMN + CA, and 1 (2%) undifferentiated carcinoma. These observed differences in the histologic types of invasive carcinoma between the patients with familial and the patients with sporadic pancreatic cancers were not statistically significant ($P = 0.214$). There was a trend toward more adenosquamous carcinomas in the familial group (12% versus 2%, $P = 0.12$).

Precursor lesions. Pancreatic parenchyma not involved by the patient's invasive carcinoma was available for review from 49 of the 51 familial pancreatic cancer cases and all 40 of the sporadic cases. The number of noninvasive precursor lesions, including PanINs and incipient IPMNs, was counted in these tissues (Table 2). Precursor lesions were seen in 48 of 49 familial cases, and multiple precursor lesions were present in 46 of the 49 (94%; Fig. 1); in contrast, only 35 of the 40 sporadic case had precursor lesions and 34 of the 40 (85%) had multiple lesions. The relative rate of PanIN lesions per square centimeter was 2.75-fold higher [95% confidence interval (95% CI), 2.05-3.70; adjusted for age] in familial compared with sporadic cases. This corresponds to a rate of 1.51 PanIN lesions/cm^2 for a familial case and 0.55 PanIN lesion/cm^2 for a sporadic case at the observed mean age of 66 years. In the familial cases, the number of the PanIN lesions ranged from 0 to up to 3.8/cm^2. Of the 5 sporadic cases without precursor lesions, all had a classic infiltrating ductal adenocarcinoma. The number of PanIN lesions in the sporadic cases ranged from 0.0/cm^2 to 2.01/cm^2.

In the pancreata from the patients with familial pancreatic cancer, the PanIN lesions identified were mostly PanIN-1 (0.84/cm^2) and PanIN-2 (0.51/cm^2). However, 32 of the 49 (65%) pancreata also harbored at least one PanIN-3 lesion. Similar to the familial cases, the PanIN lesions in the sporadic cases were mostly PanIN-1 lesions (0.35/cm^2). PanIN-2 (0.14/cm^2) and PanIN-3 lesions were significantly less common. Only 14 of the 40 (35%) sporadic cases had one or more PanIN-3 lesions. Overall, the rate of PanIN-3 lesions per square centimeter was greater (relative rate, 4.20; 95% CI, 2.23-7.93) for familial compared with sporadic pancreatic cancer patients. This corresponds to a rate of 0.19 PanIN-3 lesion/cm^2 in familial cases and a rate of 0.04 PanIN-3 lesion/cm^2 in sporadic cases at the observed mean age of 66 years. Cigarette smoking was not significantly associated with the number of PanIN lesions.

Incipient IPMNs were identified in 16 of the 49 (33%) familial cases and in 3 of the 40 (6%) sporadic cases. Ten of these 16 (63%) familial patients had incipient IPMNs with high-grade dysplasia. Two of the three sporadic cases had only low-grade

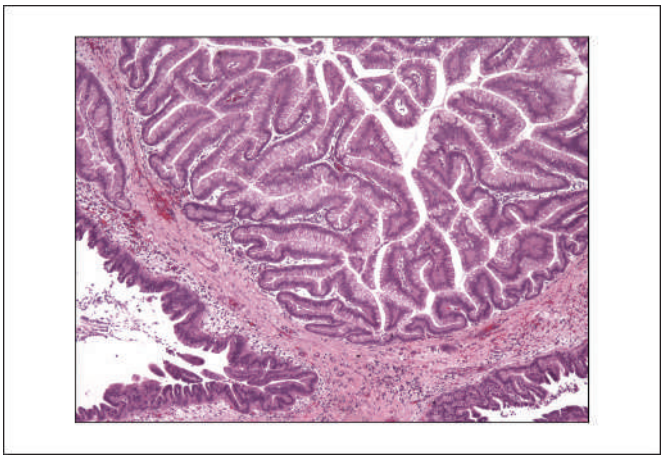

Fig. 2. Representative H&E section (×40) containing an IPMN lesion from case 21 of the familial group. The lesion had a prominent papillary structure associated with moderate to marked nuclear atypia.

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Table 1. Demographics and histologic findings

	Familial cases (n = 51)	Sporadic cases (n = 40)
Age	66.98 ± 11.47	65.25 ± 10.62 (P = 0.43)
Race		
White	48	37
Black	0	1
Other	3	2 (P = 0.80)
Gender		
Male	29	21
Female	22	19 (P = 0.84)
Stage		
T_1N_0	1	3
T_2N_0	5	2
T_2N_1	2	4
T_3N_0	8	6
T_3N_1	35	25 (P = 0.49)
Histologic types		
Ductal CA	34	34
IPMN + CA	9	4
Adenosquamous CA	6	1
Signet ring cell CA	1	0
Undifferentiated CA	1	1 (P = 0.21)
Tumor location		
Head	43	33
Body	3	2
Tail	2	2
others	3	3 (P = 1.0)
Margin		
Positive	8	10
Negative	43	30 (P = 0.299)

dysplasia, and one had both low-grade and moderate dysplasia. No incipient IPMN with high-grade dysplasia was seen in the sporadic cases. The rate of incipient IPMNs per square centimeter was 11.82-fold (95% CI, 1.88-74.08) higher in familial compared with sporadic pancreatic cancer patients after controlling for age. Cigarette smoking was not significantly associated with the rate of incipient IPMN lesions.

Nine of the 51 (18%) familial pancreatic cancers arose associated with an IPMN (Table 1). These invasive carcinomas included eight classic ductal adenocarcinomas and one colloid (mucinous noncystic) adenocarcinoma. Pancreatic parenchyma with no invasive carcinoma was available for review from seven of the nine IPMN + CA cases. Each harbored a single IPMN lesion with high-grade dysplasia (*in situ* carcinoma). IPMNs were observed in 4 of the 40 (10%) sporadic cases (Table 1); all were associated with an invasive carcinoma. This difference in prevalence was not statistically significant (P = 0.37). The invasive carcinomas arising in association with these IPMNs included three classic infiltrating ductal carcinomas and one colloid adenocarcinoma. One of the four sporadic cases with IPMN harbored two IPMNs: one IPMN with moderate dysplasia and the other with high-grade dysplasia associated with invasive carcinoma. The other three sporadic IPMN cases had a single IPMN with high-grade dysplasia.

Histologic subtypes of IPMNs in both familial and sporadic group were also analyzed. Three of four IPMNs in the sporadic group were of pancreatobiliary subtype; the remaining one was of intestinal subtype. Histologic subtypes of IPMNs in the familial group included pancreatobiliary subtypes in five cases, intestinal subtype in two cases, gastric subtype in one case, and oncocytic subtype in one case.

High-grade precursor lesions. Thirty-five of the 49 (71%) familial cases harbored high-grade precursor lesions (including PanIN-3 and incipient IPMNs). Twenty-two of these 35 had multiple high-grade lesions. By contrast, 14 of the 40 (35%) sporadic cases had high-grade lesions, and 10 of these 14 contained more than one high-grade lesion. The total number of PanIN and incipient IPMN lesions per square centimeter was 2.78-fold higher (95% CI, 2.07-3.74) in familial compared with sporadic pancreatic cancer patients.

Table 2. Precursor lesions in the familial (n = 49) and sporadic cases (n = 40)

Precursor	Familial (per cm^2)	Sporadic (per cm^2)
Total PanIN	1.51*	0.55
PanIN-1	0.84*	0.35
PanIN-2	0.51*	0.14
PanIN-3	0.19*	0.04
Total incipient IPMN	0.04*	0.01
HG incipient IPMN	0.03	0
Total precursor	1.55*	0.56
Total HG precursor	0.22*	0.04

NOTE: Total precursor = PanIN-1 + PanIN-2 + PanIN-3 + incipient IPMN. Total high-grade precursor = PanIN-3 + high-grade incipient IPMN.
Abbreviation: HG, high grade.
*P < 0.05.
P values comparing the rate in familial vs sporadic obtained through negative binomial regression models adjusted for age; see text for details.

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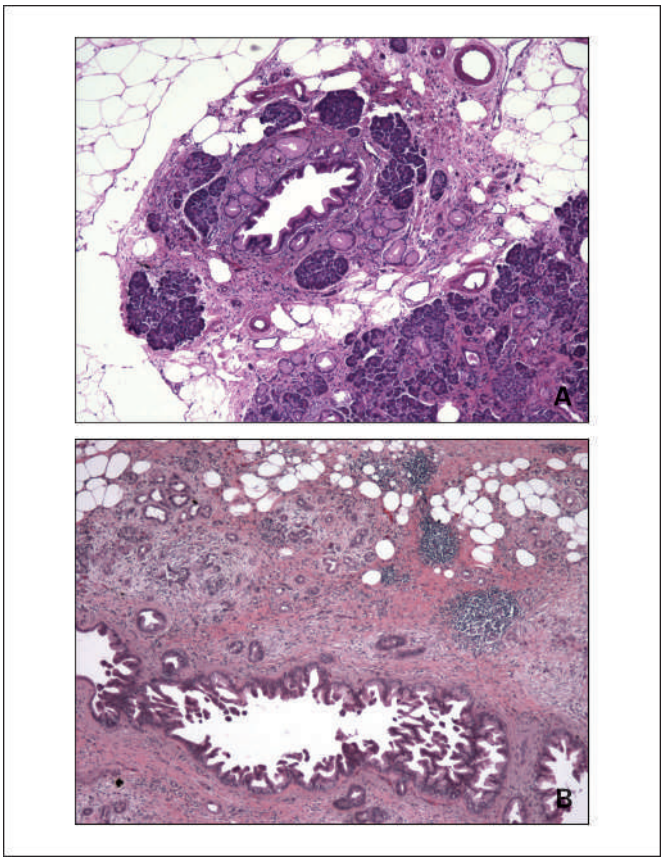

Fig. 3. PanIN lesions associated with parenchymal abnormalities (H&E, ×40). *A,* a PanIN-1B lesion with associated lobular parenchyma showing partial acinar atrophy, acinar to ductal metaplasia. Note the residual normal acinar cells. *B,* a PanIN-3 lesion with associated parenchyma showing lobulocentric atrophy with loss of acinar parenchyma in a lobular pattern, fibrosis, and acinar-ductal metaplasia, and clusters of islets of Langerhans.

Parenchymal changes associated with the precursors. With the exception of a few cases with marked chronic pancreatitis in the background pancreatic parenchyma, the pancreatic parenchyma not associated with noninvasive precursor lesions or with invasive cancer was histologically unremarkable. As expected, the pancreatic parenchyma adjacent to the infiltrating carcinomas in both the familial and the sporadic cases uniformly showed marked fibrosis, parenchymal atrophy, and a mixed inflammatory response.

The pancreatic parenchyma adjacent to the noninvasive precursor lesions often showed various degrees of lobulocentric atrophy and/or fibrosis (21, 29). This lobulocentric atrophy was characterized by loss of acinar parenchyma in the lobule surrounding the precursor lesion, fibrosis, acinar to ductal metaplasia, and aggregation of the islets of Langerhans. The degree of the parenchymal changes associated with the precursor lesions was variable, ranging from partial acinar atrophy with mainly focal acinar to ductal metaplasia (Fig. 3A) to a complete loss of acinar cells and replacement of the lobular unit by acinar to ductal metaplasia, fibrotic stroma, and aggregates of islets of Langerhans (Fig. 3B). Lobulocentric atrophy of varying degrees was seen in 42 of the 49 (86%) pancreata from the patients with familial pancreatic cancer. Similar changes were also seen in the pancreata from the patients with sporadic pancreatic cancer, but at a lower frequency [21 of 40 (53%); $P = 0.001$]. This can be explained by the smaller numbers of precursor lesions in the pancreata of the sporadic group.

Discussion

Familial pancreatic cancers seem to arise from both PanINs and IPMNs, the same types of precursor lesions as for sporadic pancreatic cancers. We found that PanINs and incipient IPMNs are more numerous and of higher grade in the pancreata from the patients with familial pancreatic cancer than they are in the pancreata from patients with sporadic pancreatic cancer. In both the familial and sporadic cases, the precursor lesions were associated with lobulocentric atrophy with fibrosis as well as acinar to ductal metaplasia. Because the precursor lesions were more common in the familial cases, these foci of lobulocentric atrophy were also more common in the familial cases. No significant differences were found in the histologic types of infiltrating carcinoma seen in the two groups, although there was a trend toward more adenosquamous carcinoma in the familial group. These findings have a number of significant implications.

First, because familial and sporadic pancreatic cancers seem to arise from the same types of precursors (PanINs and IPMNs), it is likely that tests designed to screen for sporadic precursor lesions should be able to detect familial precursor lesions and vice versa. In particular, approximately 10% to 18% of sporadic and familial cancers arise in association with an IPMN, and imaging modalities shown to be sensitive and specific for precursor lesions such as IPMNs will be effective in both populations.

Second, the multifocality of the noninvasive precursor lesions seen in the patients with familial pancreatic cancer suggests that some familial pancreatic cancers are caused by a mutation in a "gatekeeper" gene rather than a "caretaker" gene. Indeed, Brune et al. (21) reported that in some patients, as many as 20% of the pancreatic ducts in patients with a strong family history of pancreatic cancer harbor a precursor lesion. The classification of the familial pancreatic cancer gene as a gatekeeper gene, in turn, suggests that examining multiple precursor lesions for shared loci of loss of heterozygosity should help localize the genetic locus of the familial pancreatic cancer gene (30). The multifocality of the precursor lesions in patients with a family history of pancreatic cancer also suggests that these patients remain at risk for multifocal synchronous or metachronous disease following partial pancreatectomy. This risk of synchronous and metachronous disease has already been observed in patients with apparently sporadic IPMNs (31, 32).

Third, the association of multifocal precursor lesions with multifocal lobulocentric atrophy in patients with a strong family history of pancreatic cancer has significant implications for screening for early disease. Several screening tactics are already being evaluated using technologies such as endoscopic ultrasound, computed tomography, and magnetic resonance cholangiopancreatography (18–22). In these studies, endoscopic ultrasound imaging has shown chronic pancreatitis-like abnormalities in the pancreata that harbored multifocal precursor lesions, a pattern produced by the multiple foci of lobulocentric atrophy caused by multifocal PanINs (18, 19, 21, 22, 33). Thus, an individual PanIN lesion may not be detectable using currently available imaging modalities, but the parenchymal changes

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induced by multifocal PanINs can be appreciated using endoscopic ultrasound (18, 19, 21, 22).

Finally, some inherited cancer syndromes are associated with neoplasms with a specific histology. For example, a medullary phenotype is seen in patients with a familial history of hereditary nonpolyposis colorectal cancer (34–36), and individuals with Peutz-Jeghers syndrome may be predisposed to develop IPMNs (37–39). Similarly, Koorstra et al. (40) have recently reported an undifferentiated carcinoma with osteoclast-like giant cells of the pancreas in a patient with familial atypical multiple mole melanoma syndrome. Here we were able to characterize the histologic subtypes of invasive pancreatic cancer in familial pancreatic cancer patients without a known genetic defect. We found no significant differences in the type of infiltrating carcinomas observed in patients with familial and sporadic pancreatic cancers; however, there was a trend toward more adenosquamous carcinomas in the familial group (12% versus 2%). Of interest, Whelan et al. (41) reported a patient with familial atypical multiple mole melanoma syndrome who developed a squamous (presumably an adenosquamous) carcinoma of the pancreas. Should follow-up studies confirm a greater proportion of adenosquamous carcinomas in patients with familial pancreatic cancer, this would be clinically significant because adenosquamous carcinomas are very aggressive neoplasms with a median survival of only 6 months after resection (27).

A limitation of the current study is that we looked at precursor lesions at a single point in time (the moment of surgical resection). We are therefore not able to define the frequency and speed at which noninvasive precursor lesions progress to infiltrating cancer. These two characteristics of precursor lesions are critical because they will define the optimal frequency at which at-risk patients should be screened, and they will guide the clinical management of precursor lesions once they are identified.

In summary, we showed that precursor lesions are more common in patients with familial pancreatic cancer than in patients with sporadic disease. These precursor lesions in patients with familial pancreatic cancer also tend to be of a higher grade. The multifocality of the precursor lesions suggests that the gene responsible for the some cases of familial pancreatic cancer has "gatekeeper" properties. The lobulocentric atrophy and the resultant heterogeneity of the pancreatic parenchyma produced by these multifocal precursor lesions provide a basis for the design of screening tests for the early detection of pancreatic neoplasia (21).

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Published OnlineFirst December 8, 2009; DOI: 10.1158/1078-0432.CCR-09-0004

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Clinical Cancer Research

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Clin Cancer Res Published OnlineFirst December 8, 2009.