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A Histomorphologic Comparison of Familial and Sporadic Pancreatic Cancers

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Abstract

Background—It is estimated that approximately 10% of pancreatic cancers have a familial component. Many inheritable genetic syndromes are associated with increased risk of pancreatic cancer, such as Peutz-Jeghers syndrome, hereditary breast-ovarian cancer and familial atypical multiple mole melanoma, but these conditions account for only a minority of familial pancreatic cancers. Previous studies have identified an increased prevalence of non-invasive precursor lesions, including pancreatic intraepithelial neoplasia, in the pancreata of patients with a strong family history of pancreatic cancer. A detailed investigation of the histopathology of invasive familial pancreatic cancer could provide insights into the mechanisms responsible for familial pancreatic cancer, as well as aid early detection and treatment strategies.

Methods—We have conducted a blinded review of the pathology of 519 familial and 651 sporadic pancreatic cancers within the National Familial Pancreas Tumor Registry. Patients with familial pancreatic cancer were defined as individuals from families in which at least a pair of first-degree relatives have been diagnosed with pancreatic cancer.

Results—Overall, there were no statistically significant differences in histologic subtypes between familial and sporadic pancreatic cancers ($p > 0.05$). In addition, among surgical resection

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specimens within the study cohort, no statistically significant differences in mean tumor size, location, perineural invasion, angiolymphatic invasion, lymph node metastasis and pathologic stage were identified ($p > 0.05$).

Conclusions—Similar to sporadic pancreatic cancer, familial pancreatic cancer is morphologically and prognostically a heterogeneous disease.

Keywords

Pancreatic cancer; familial; hereditary; pathology; morphology; histology

Introduction

Pancreatic cancer is the 4th leading cause of cancer deaths in the United States and has the highest mortality rate of all major epithelial malignancies with a 5-year survival rate of only 5%.^{1, 2} The exact causes of pancreatic cancer remain unclear, but a number of factors, such as advanced age, tobacco smoking, obesity, diabetes mellitus and long-standing chronic pancreatitis are associated with increased risk of pancreatic cancer.³⁻⁵ Additionally, nearly 10% of patients with pancreatic cancer report a family history of the disease and individuals with a family history of pancreatic cancer have an increased risk of developing pancreatic cancer themselves.⁶⁻⁹ First-degree relatives of patients with pancreatic cancer have a 2-fold increased risk of developing pancreatic cancer, individuals with two affected first-degree relatives have a 6-fold increased risk, and those with three or more affected first-degree relatives have an estimated 32-fold increased risk.^{8, 10} Many inheritable genetic syndromes are associated with an increased risk of pancreatic cancer, such as Peutz-Jeghers syndrome (PJS), familial atypical multiple mole melanoma (FAMMM), hereditary breast-ovarian cancer (HBOC), hereditary nonpolyposis colorectal carcinoma (HNPCC) and hereditary pancreatitis.^{6, 11} In addition, germline mutations in ATM and PALB2 have been identified as predisposing factors to the development of pancreatic cancer.^{12, 13} But, these conditions account for only a minor subset of familial cases, and thus, the genetic basis for much of familial pancreatic cancer remains elusive.

Clinicopathologic studies have helped define familial cancer syndromes of other organs. For example, the HNPCC and familial adenomatous polyposis syndromes were pathologically identified as distinct before the genes for these two syndromes were known.¹⁴ In contrast, studies comparing patients with sporadic versus familial pancreatic cancer have reported no major differences in pathology, apart from some reports suggesting differences in tumor location.^{8, 15, 16} Of note, Shi *et al* identified a significantly higher prevalence of non-invasive precursor lesions in patients with familial pancreatic cancer than in patients with sporadic disease.¹⁷ Although the study cohort was relatively small, the authors also found no statistically significant differences in histologic subtypes of infiltrating carcinomas arising in familial as compared to sporadic pancreatic cancer patients. However, in the familial group there was a statistically non-significant trend toward more adenosquamous carcinomas; a rare and aggressive neoplasm with a median overall survival of 11 months after resection.¹⁸ Thus, an understanding of the pathology of familial pancreatic cancer has the potential to define histologic subtypes of the disease, to guide therapy, and to inform early detection. We, therefore, analyzed invasive carcinomas from a large cohort of patients with familial

and sporadic pancreatic cancer to compare and contrast their histomorphology and other pathologic prognostic features.

Methods

Patients

Study approval was obtained by the Johns Hopkins Hospital Institutional Review Board. All biopsies and surgical resection materials were obtained through the National Familial Pancreas Tumor Registry (NFPTR) at Johns Hopkins (www.nfptr.org).¹⁹ The NFPTR is an ongoing research study that enrolls patients with a personal or family history of pancreatic cancer. Between 1994 and the end of 2011, the NFPTR enrolled 1384 patients with familial pancreatic cancer (defined as a kindred with at least two first degree relatives with confirmed exocrine pancreatic cancer)²⁰ and 2912 kindreds with sporadic pancreatic cancer (defined as a kindred with at least one member with pancreatic cancer but without a pair of first-degree relatives affected with the disease). Of these, 1170 had histopathology available for review. Although no germline testing was performed within this study, patients with family or personal history of PJS, FAMMM, HBOC or HNPCC were specifically excluded from this study. Of the 1170 patients, 519 satisfied criteria as familial pancreatic cancer, while 651 met criteria for sporadic pancreatic cancer. Demographic data including patient age, gender, race and family history were also recorded. Without knowledge of the patient group, hematoxylin-and-eosin stained slides for each patient including immunohistochemical stains, when available, were reviewed. Histologic subtypes of pancreatic cancer were classified based on standardized nomenclature.²¹ Among the surgical resections, perineural and angiolymphatic invasion were scored for each specimen. However, in cases where only 1 slide was available for histologic review, the absence of each of these parameters was scored as unknown (Table 2). The presence of lymph node metastases was also scored, but if no lymph nodes were submitted for pathologic review, this parameter was scored as unknown. Gross reports were reviewed for each resection to record tumor location and size. Tumors were staged using the seventh edition of the American Joint Committee on Cancer (AJCC) Staging Manual.²²

Statistical analysis

Statistical analyses to assess differences between familial and sporadic pancreatic cancers were compared using Fisher's exact test for dichotomous variables and Kruskal-Wallis test for continuous variables. All tests were two-sided and statistical significance was defined as a p value < 0.05 . Data analysis was conducted using STATA, version 12 (Statacorp, College Station, TX) and SPSS Statistical software, version 20 (IBM, Armonk, NY).

Results

The clinical demographics and histopathology of the 519 familial and 651 sporadic pancreatic cancers are summarized in Table 1.

Familial pancreatic cancers

Among the familial cohort, patients at clinical presentation ranged in age from 29 to 95 years (mean, 65.3 years) and there was a slight female predominance ($n = 276$, 53%). Racial data were available for all (100%) patients, the vast majority of which were Caucasian ($n = 490$, 94%). Microscopically, the vast majority of the invasive carcinomas in the familial group were classic infiltrating ductal adenocarcinoma (499 of 519, 96%). Other types of invasive carcinoma identified in the familial group included 6 (1%) adenosquamous carcinomas, 4 (1%) colloid carcinomas, 5 (1%) undifferentiated carcinomas, one undifferentiated carcinoma with osteoclast-like giant cells, one medullary carcinoma, one large-duct type adenocarcinoma, one mixed ductal-neuroendocrine carcinoma and one mixed ductal-acinar-neuroendocrine carcinoma. When compared to the sporadic pancreatic cancer cohort, no statistically significant differences in mean patient age ($p = 0.80$), gender ($p = 0.06$), race ($p = 0.63$) and histologic subtype ($p = 0.38$) were identified by univariate analysis.

Surgically resected cases

Of the 1170 specimens with histopathology within the registry, 563 (48%) were surgical resections that corresponded to 166 familial and 397 sporadic pancreatic cancers (Table 2). The 166 surgically resected pancreatic cancers in the familial cohort ranged in size from 0.1 to 6.5 cm (mean, 3.24 cm) and were predominantly centered within the head of the pancreas ($n = 136$, 82%). Perineural invasion ($n = 151$, 91%), angiolymphatic invasion ($n = 83$, 50%) and lymph node metastasis ($n = 119$, 72%) were frequent findings. Based on the seventh edition of the AJCC pathologic prognostic staging system, the familial pancreatic cancers were classified as follows: 4 (2%) stage IA, 12 (7%) stage IB, 26 (16%) stage IIA, 116 (70%) stage IIB, 2 (1%) stage III and 1 (1%) stage IV. No significant differences between resected familial and sporadic pancreatic cancers were identified with regards to mean tumor size ($p = 0.82$), location ($p = 0.40$), perineural invasion ($p = 0.10$), angiolymphatic invasion ($p = 0.05$), lymph node metastasis ($p = 0.77$) and pathologic stage ($p = 0.98$).

Discussion

Overall, there were no statistically significant differences in histologic subtypes between familial and sporadic invasive pancreatic cancers. Furthermore, among surgical resections, no differences in mean tumor size, location, perineural invasion, angiolymphatic invasion, lymph node metastasis and pathologic stage were identified. Similar to sporadic pancreatic cancer, familial pancreatic cancer is morphologically and prognostically a heterogeneous disease.

A number of genetic syndromes have been linked to specific histologic subtypes of pancreatic cancer. For example, pancreatic cancer has been described in kindreds with HNPCC. Patients with HNPCC harbor germline mutations in one of the DNA mismatch repair genes including *MLH1*, *PMS2*, *MSH2* and *MSH6*. Inactivation of one of these proteins results in microsatellite instability and a distinctive medullary histologic appearance.²³⁻²⁵ Recognition of the medullary morphology can be used to suggest the possibility of HNPCC in a patient with pancreatic cancer and initiate microsatellite instability testing.⁶ In addition,

PJS is associated with germline mutations in the *STK11/LKB1* gene and characterized by mucocutaneous melanocytic macules and hamartomatous polyps of the gastrointestinal tract. Individuals with PJS have a 132-fold increased risk of developing pancreatic cancer.^{26, 27} A number of studies have observed the presence of IPMN precursor lesions in patients with PJS.²⁸ More importantly, the association between PJS and IPMNs has significant ramifications in pancreatic cancer screening as most clinically significant IPMNs are large enough that they can be detected by radiographic imaging.^{29, 30} In contrast, germline mutations in the *CDKN2A* gene, which have been linked to FAMMM, have not been reported to be associated with unique histopathologic findings. Similarly, patients with *PRSSI* hereditary pancreatitis, who are predisposed to developing pancreatic ductal adenocarcinoma, do not demonstrate any defining morphologic features. Considering the presence of multiple gene-specific pathologic findings, the lack of detectable differences between familial and sporadic pancreatic cancers may indicate that many susceptibility genes instead of just one remain to be identified. Further, correlation with other predisposing genes (e.g. *BRCA2*, *PALB2*, *ATM*, etc.) rather than a heterogeneous group of familial pancreatic cancer patients may reveal distinct morphologic and prognostic features.

Despite the lack of detectable differences in the histopathology between familial and sporadic pancreatic cancers, several studies have reported a higher frequency of precursor lesions in familial pancreatic cancer patients.²⁹⁻³⁴ In fact, both PanINs and incipient IPMNs can be quite extensive with a 2.78-fold higher prevalence per square centimeter in familial compared to sporadic cases.^{17, 35} Furthermore, these precursor lesions in familial pancreatic cancer patients tend to be of a higher-grade.¹⁷ Thus, although the histomorphology of familial pancreatic cancer may have limited potential in identifying kindreds with this disease, the presence of numerous precursor lesions may be more informative.

In summary, we report the pathology of the largest familial pancreatic cancer cohort described to date. While certain subtypes of pancreatic cancer have historically been linked with genetic syndromes, the current study illustrates no statistically significant differences between the morphologies of familial versus sporadic pancreatic cancers. Despite the increased prevalence of precursor lesions, familial pancreatic cancer is a heterogeneous disease. However, correlation with specific, predisposing germline mutations may yield distinct and clinically significant pathologic findings.

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Figure 1.

Histopathology of familial pancreatic cancer. In addition to conventional ductal adenocarcinoma (A, well-differentiated; B, moderately-differentiated; and C, poorly-differentiated), multiple histologic subtypes of invasive pancreatic cancer were identified within the familial pancreatic cancer cohort. These include (D) adenosquamous carcinoma, (E) colloid carcinoma, (F) undifferentiated carcinoma (G) undifferentiated carcinoma with osteoclast-like giant cells, (H) medullary carcinoma, acinar cell carcinoma (not shown) and mixed variants (not shown).

Table 1

Clinicopathologic comparison between familial and sporadic pancreatic cancers.

Patient or tumor features	Total, n = 1170	Familial, n = 519	Sporadic, n = 651	p
Mean age (range), y	64.7 (21 - 105)	65.3 (29 - 95)	64.2 (21 - 105)	0.802
Gender				
Male	587 (50%)	243 (47%)	344 (53%)	0.060
Female	583 (50%)	276 (53%)	307 (47%)	
Race	n = 386	n = 76	n = 310	
Caucasian	360 (93%)	71 (93%)	289 (93%)	0.191
Black	10 (3%)	0 (0%)	10 (3%)	
Other	16 (4%)	5 (7%)	11 (4%)	
Histologic subtype				
Adenocarcinoma, NOS	1122 (96%)	499 (96%)	623 (96%)	0.383
Adenosquamous carcinoma	14 (1%)	6 (1%)	8 (1%)	
Colloid carcinoma	14 (1%)	4 (1%)	10 (2%)	
Undifferentiated carcinoma	9 (1%)	5 (1%)	4 (1%)	
Undifferentiated carcinoma with osteoclast like giant cells	2	1	1	
Medullary carcinoma	1	1	0	
Large-duct type adenocarcinoma	5	1	4 (1%)	
Acinar cell carcinoma	1	0	1	
Mixed ductal-neuroendocrine	1	1	0	
Mixed ductal-acinar-neuroendocrine	1	1	0	

Table 2

Clinicopathologic comparison of surgically resected familial and sporadic pancreatic cancers.

Patient or tumor features	Total, n = 563	Familial, n = 166	Sporadic, n = 397	<i>p</i>
Mean age (range), y	64.6 (21 - 87)	65.0 (39 - 86)	64.5 (21 - 87)	0.802
Mean tumor size, cm	3.33 (0.1 - 10)	3.24 (0.1 - 6.5)	3.36 (0.1 - 10)	0.120
Location				
Head	438 (78%)	136 (82%)	302 (76%)	0.402
Body	67 (12%)	13 (8%)	54 (14%)	
Tail	44 (8%)	13 (8%)	31 (8%)	
Uncinate	7 (1%)	2 (1%)	5 (1%)	
Diffuse	7 (1%)	2 (1%)	5 (1%)	
Perineural invasion	521 (93%)	157 (95%)	364 (92%)	0.159
Angiolymphatic invasion	301 (53%)	83 (50%)	218 (55%)	0.309
Lymph node metastasis	407 (72%)	119 (72%)	288 (73%)	0.837
AJCC TNM staging				
Stage IA	20 (3%)	4 (2%)	16 (3%)	0.891
Stage IB	52 (9%)	16 (10%)	36 (9%)	
Stage IIA	82 (14%)	27 (16%)	55 (13%)	
Stage IIB				
T1N1M0	9 (2%)	3 (2%)	6 (2%)	
T2N1M0	71 (13%)	21 (13%)	50 (13%)	
T3N1M0	313 (56%)	92 (55%)	221 (56%)	
Stage III	9 (2%)	2 (1%)	7 (2%)	
Stage IV	7 (1%)	1 (1%)	6 (2%)	