Prior History of Pancreatitis Accelerates the Development of Pancreatic Adenocarcinoma

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Objectives: Presentation of pancreatic adenocarcinoma (PC) as acute pancreatitis (AP), association of chronic pancreatitis (CP) with PC, and role of inflammation in PC carcinogenesis are well recognized. We hypothesized that inflammatory changes associated with remote history of AP (≥2 years before PC diagnosis) would result in earlier age of PC diagnosis.

Methods: We evaluated PC patients prospectively enrolled in the Pancreatic Adenocarcinoma Gene Environment Risk (PAGER) study at the University of Pittsburgh for history of pancreatitis and reviewed relevant medical records and imaging studies. Univariate and multivariable linear regression analyses evaluated the relationship between PC and remote history of AP.

Results: Among 790 patients with histologically confirmed PC, 114 (14.4%) had a history of pancreatitis (AP within 2 years of PC diagnosis in 69 [8.7%], remote history of AP in 28 [3.5%], CP in 4 [0.5%], and unknown duration of pancreatitis in 13 [1.6%]). After controlling for age, sex, body mass index, smoking, alcohol history, and diabetic status at diagnosis, patients with a remote history of AP were diagnosed on average 4.7 years earlier with PC when compared with PC patients without history of AP ($P < 0.035$).

Conclusions: Remote history of AP may accelerate carcinogenesis in PC.

Key Words: acute pancreatitis, pancreatic adenocarcinoma, age of presentation, carcinogenesis

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Pancreatic adenocarcinoma (PC) is associated with a 5-year survival rate of approximately 6%, ranking it among the top 5 most lethal malignancies in the United States.[1] Screening for PC remains impractical given its low incidence. Chronic pancreatitis (CP) is a well-established risk factor for the development of PC,[2,3] with the risk highest in patients with hereditary or tropical etiologies.[4] Pancreatic adenocarcinoma in the setting of CP typically occurs years, often decades, after the initial presentation or diagnosis of CP, suggesting that persistent inflammation is likely related to this risk.

Chronic inflammation in other gastroenterological conditions such as inflammatory bowel disease has been linked with malignancy through both extrinsic pathways stemming from chronic inflammatory conditions, which increase the risk of malignancy, and intrinsic pathways through activated oncogenes that promote inflammatory conditions.[5] Progression from inflammation to malignancy likely occurs as preneoplastic lesions proliferate,[6] with neoplastic development accompanied by early epithelial-to-mesenchymal transition and entry of malignant cells into the circulation before detection of tumor formation.[7,8] The molecular pathology of sporadic PC is dominated by activating mutations in the *KRAS* gene, estimated to be present in greater than 90% of tumors, with additional common mutations in the *TP53*, *CDKN2A*, and *SMAD4* genes.[9] *KRAS* mutations promote pancreatic tissue destruction and tumorigenesis by downstream activation of nuclear factor–like 2 (Nrf2).[10,11] Previously, it was understood that inflammation must be chronic in nature to lead to *KRAS*-driven pancreatic ductal adenocarcinoma.[12] However, more recent studies show that as few as 2 brief episodes of acute pancreatitis (AP) can cause rapid progression of pancreatic intraepithelial neoplasm lesions and acclerate the development of PC in the context of oncogenic *KRAS*, suggesting that even that small amount of inflammation can start a cascade of events that facilitates earlier malignant transformation.[13,14] Interestingly, evidence to date does not strongly support any theory of shared genetic risk factors between CP and PC.[15]

Acute pancreatitis is typically a self-limiting disease; most patients with AP have mild disease with resolution of inflammation within a few weeks. As AP is among the most common causes for inpatient gastrointestinal hospitalization in the United States, and its incidence is on the rise, it becomes even more imperative to define the relationship between AP and PC.[16,17] Acute pancreatitis can be the first manifestation of PC in up to 10.7% of new cases.[18]

In one recent study of 731 prospectively enrolled patients after a primary episode of AP, the risk of future development of pancreatic ductal adenocarcinoma (PDAC) was evaluated. Overall, the risk of PDAC was 0.7% after median of 55 months of follow-up.[19] Patients were then stratified by development of CP. Interestingly, the risk of PC was 9 times higher in patients who developed CP compared with those who did not develop CP. Although these results suggest that the risk of cancer may primarily be through CP development, the study is somewhat limited by its small sample size.

Another study evaluated administrative data for 41,000 patients with a first attack of AP and age- and sex- matched 208,000 comparison subjects without a history of AP: risk of PC for the patients with a history of AP was twice as high as those without a history of AP at 5 years of follow-up.[20] Interestingly, the median age of PC diagnosis was 5 years lower in patients with prior AP as compared with patients without a history of AP. Although this study suggests that AP both increases the risk of PC and results in PC diagnosis at a younger age, this study is limited by the use of administrative data and an inability to verify either the AP or PC history.

We hypothesized that patients with a remote history of AP, defined as greater than or equal to 2 years before PC diagnosis, would have an accelerated course of carcinogenesis, reflected by an earlier age of PC diagnosis. In this retrospective case-control study of PC patients, we evaluated the association of a history of

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pancreatitis with age at diagnosis of PC in a large prospectively ascertained cohort of patients.

MATERIALS AND METHODS

Study Population

The Pancreatic Adenocarcinoma Gene Environment Risk (PAGER) Registry was initiated at the University of Pittsburgh Medical Center (UPMC) in 2003. The PAGER has served as a universal study for enrolling subjects into the UPMC pancreatic cancer registry as either a case or control by all of the different medical and surgical disciplines involved in the care of benign and malignant pancreatic diseases.[21,22] It is used by gastroenterology, surgery, oncology, and pathology departments and allows for collection of biospecimens along with associated clinical data including a patient questionnaire. In addition, approved investigator(s) at UPMC have access to the subject's clinical records to allow for the collection of additional information regarding their disease. Coordinators recruit subjects in pancreatic cancer-related clinics including our multidisciplinary pancreatic cancer specialty care center, endoscopy units, and inpatient facilities located at Shadyside and Presbyterian Hospital. At the time of enrollment, patients are asked to complete a medical history questionnaire created for the PAGER study that contains questions on height, weight, racial background, alcohol use, tobacco use, comorbidity diagnosis including diabetes, pancreatic cancer date of diagnosis, family history, and pancreatitis history including type (acute or chronic) and date of diagnosis. Blood samples were collected on enrollment for future analysis; tissue samples were also obtained for future analysis in the event that the patient was undergoing a procedure including biopsy or resection and excess tissue was available.

Since initiation, 5228 patients have been enrolled in the PAGER study, 825 patients with a diagnosis of pancreatic malignancy including those with intraductal papillary mucinous neoplasm that degenerated into malignancy.

Data Abstraction and Collection

We manually reviewed histologic reports of all 825 patients, and 35 patients without histologically proven PC were excluded. Thus, 790 patients with histology proven PC formed the cohort for the present study.

The following data were abstracted from the PAGER database: demographics (age, date of birth, sex), biometrics (weight, height, usual body mass index [BMI], BMI at age of 18 years), and PC history (age at diagnosis, type of pancreatitis [acute or chronic], age at first episode, age of diagnosis), current smoking or past smoking, alcohol history, and history of diabetes mellitus (DM). Patients were stratified by smoking (ever/never), alcohol use (past use, current use, never), and obesity (BMI, ≥30 kg/m^2).

Pancreatitis History

Pancreatitis history (history of AP or CP, number of prior episodes, date of first known episode, age at diagnosis of CP) was initially retrieved from the patients' self-reported medical history (n = 114). Electronic medical records of all patients who reported a history of AP or CP as well as those with missing information for pancreatitis history were reviewed for supporting documentation to confirm the history and the age at diagnosis. Patients who did not report a prior history of pancreatitis were determined not to have had pancreatitis. To ensure that we were not underestimating prior history of pancreatitis, we reviewed records of 100 randomly chosen patients out of the 676 patients with no reported history of pancreatitis; none of these patients had a history of pancreatitis on review of records.

All available imaging studies for patients with a remote history of pancreatitis and those in whom the timing of pancreatitis in relation to PC diagnosis was unclear by record were reviewed by an expert abdominal radiologist with an interest in pancreatic diseases (A.A.B.) to assess for evidence of AP and/or underlying CP. Of these 49 patients, 46 had triphasic pancreatic mass protocol computed tomography (CT) performed within 1 month of diagnosis, which consisted of noncontrast, late arterial, and venous phases. Axial images with 2.5 mm thickness were reviewed on a picture archiving and communication system. Among the 3 patients who did not have CT images available, 2 had contrast-enhanced magnetic resonance imaging (MRI) and noncontrast CT, which was used for interpretation, whereas 1 patient only had written reports of contrast-enhanced CT and MRI available for review. Maximal pancreatic duct size was measured for all available images to evaluate for dilatation. Because PD dilatation and upstream atrophy could be caused by tumor effect causing ductal obstruction, we used parenchymal calcifications as the diagnostic criteria for definitive evidence of CP. Changes of AP including enlargement of the gland, peripancreatic stranding, and peripancreatic fluid were noted. Classification of patients into AP or CP was based on review of imaging studies by our radiologist; a diagnosis of CP was assigned only to patients with morphologic evidence of CP on CT or MRI, based on presence of parenchymal calcifications. Patients with history of pancreatitis but no evidence of CP were classified as AP. The scans evaluated were performed at the time of PC diagnosis, and so changes of AP were not required to be present at that time for patients to be classified as having had history of AP.

Statistical Analysis

Descriptive analyses for continuous variables are presented as mean (standard deviation [SD]) or as median (interquartile range) and for categorical variables, as percentages. Univariate analyses were performed between PC patients with no prior history of pancreatitis and those with a remote history of AP using a 2-sided *t*-test for continuous variables and χ^2 or Fisher's exact test for categorical variables. To evaluate independent effect of a remote history of AP on the age at PC diagnosis, multivariate linear regression analysis was conducted where the age at PC diagnosis was considered as a dependent variable and a remote history of AP was considered as the primary predictor variable. In this analysis, we controlled for other factors that could potentially confound this relationship including sex, smoking (ever or never), alcohol use (exposed vs never exposed), diabetes (yes or no), and obesity (yes or no). All statistical tests were done in Stata version 14.2 (StataCorp LLC, College Station, Tex). Statistical significance was set at $\alpha < 0.05$.

RESULTS

Study Cohort

The study population consisted of 790 patients with a histologically confirmed diagnosis of PC. Of these patients, 426 (53.9%) were male. At time of diagnosis of PC, mean (SD) age was 67.2 (10.8) years. Mean (SD) BMI at enrollment was 28.8 (6.1) kg/m^2; 253 (30.3%) were obese (BMI, >30 kg/m^2) at enrollment. Mean (SD) BMI at 18 years was 22.8 (4.04) kg/m^2; 21 (2.7%) were obese at age of 18 years. Diabetes was present in 296 (37.5%) of patients. Of the whole cohort, 385 (48.7%) were previous or current smokers (>100 cigarettes in their lifetime), 242 (30.6%) were current drinkers, 224 (28.4%) were past drinkers, 218 (27.6%) were never drinkers, and 106 (13.4%) had an unknown alcohol history.

Group Assignment

Pancreatic adenocarcinoma patients were stratified into 4 groups based on patients' history of pancreatitis (Fig. 1). History of any pancreatitis was noted in 114 patients (14.4%). Of these,

1. Thirty-two (4.1%) had a history of pancreatitis greater than or equal to 2 years before PC diagnosis (with 4 of these having CP on imaging) and therefore, 28 (3.5%) having a history of AP greater than or equal to 2 years before PC diagnosis.
2. Sixty-nine (8.7%) had history of pancreatitis less than 2 years before PC diagnosis.
3. Thirteen (1.6%) had a history of pancreatitis where age of diagnosis relative to PC diagnosis was unknown.

Univariate Analysis

Compared with the 676 patients (53.7% male) without a history of pancreatitis, the 28 patients (53.6% male) with a remote history (≥2 years before PC diagnosis) of AP had a similar mean (SD) BMI (28.9 [6.1] vs 31.3 [7.8], $P < 0.063$), proportion of obese patients with BMI greater than 30 kg/m^2 at time of enrollment (32.4% vs 39.3%, $P < 0.4$), mean (SD) BMI at age of 18 years (22.8 [4.08] vs 23.3 [4.46], $P < 0.58$), proportion of patients who were obese at age of 18 years (2.5% vs 3.6%, $P < 0.10$), smoking prevalence (326 [48.8%] vs 16 [57.1%], $P < 0.36$), and drinking prevalence (current drinkers, 207 [30.6%] vs 6 [21.4%]; never drinkers, 189 [28.0%] vs 7 [25.0%]; past drinkers, 182 [27.0%] vs 12 [42.9%]; unknown drinking history, 95 [24.5%] vs 3 [10.7%] [$P < 0.37$]) (Table 1). Diabetes mellitus was seen in 247 (36.5%) of the patients with no history of pancreatitis and 18 (64.3%) of patients with remote history of pancreatitis ($P < 0.003$). The mean (SD) age of PC diagnosis in patients with remote history of AP (n = 28; 63.0 [10.5]) was significantly lower compared with patients with no history of pancreatitis (n = 676; 67.6 [10.8]) ($P < 0.027$). Median age of PC diagnosis in patients with remote history of AP was 62 years and in patients with no history of pancreatitis 68 years.

Multivariable Analysis

Complete data for sex, smoking, alcohol, diabetes, and BMI were available for 561 patients (patients with no history of pancreatitis, n = 539; patients with remote history of AP, n = 22). After controlling for sex, smoking, alcohol exposure, obesity, and diabetes, multivariable regression analysis revealed that patients with pancreatitis greater than or equal to 2 years before PC diagnosis presented 4.7 years earlier than did patients with no history of pancreatitis ($P < 0.035$).

DISCUSSION

In a large, prospectively collected, retrospectively analyzed cohort of patients with PC, we found that patients who have a remote history of pancreatitis (≥2 years before PC diagnosis) present with PC approximately 4.7 years earlier than their counterparts without a history of pancreatitis. This was confirmed as an independent association after controlling for sex, smoking, alcohol exposure, obesity, and diabetes, factors all traditionally associated with PC. This represents an accelerated onset of carcinogenesis in those patients with a remote history of pancreatitis. Although the mechanism of this finding remains unclear, the inflammatory nature of AP suggests a link to acute inflammation.

In our study, median age of patients with no history of pancreatitis was 68 years, whereas those with a remote history of pancreatitis was 62 years. It is known that the risk of pancreatic cancer increases with age, although with slightly different peaks in incidence among several different populations.[23] In the United States, median age of PC diagnosis is 71 years.[17] Our focus was therefore on evaluation of risk factors, both modifiable (smoking, alcohol, obesity) and dose-dependent for alcohol and smoking,[24–29] and non-modifiable (age, sex).

We suspect that inflammation is the link that can explain the acceleration of carcinogenesis in patients who have a remote history of AP. Acute pancreatitis progresses to CP via recurrent episodes of inflammation and fibrosis,[30] and chronic inflammation in CP is postulated to be a major contributor to PC development in those patients.[31,32] Both AP and CP have been long confounded with PC diagnoses in the setting of active inflammation.[18,31,33] Our study, by instituting a 2-year gap between AP diagnosis and PC diagnosis, ensures a more accurate characterization of AP as separate from PC diagnosis. By removing CP patients, we were able to solely focus on the effects of the remote AP episode, a severe inflammatory event for these patients who subsequently developed PC. Whether the severe inflammatory event is truly self-limited as has previously been thought or instead serves as an activator of downstream oncogenic pathways is a question for further analysis.

We did note a significant difference in the number of patients with diabetes between those with no history of pancreatitis (247, 36.5%) and those with a remote history of pancreatitis (18, 64.3%) ($P < 0.003$). A previous pooled analysis of 1102 patients has shown the prevalence of prediabetes, DM, and insulin therapy

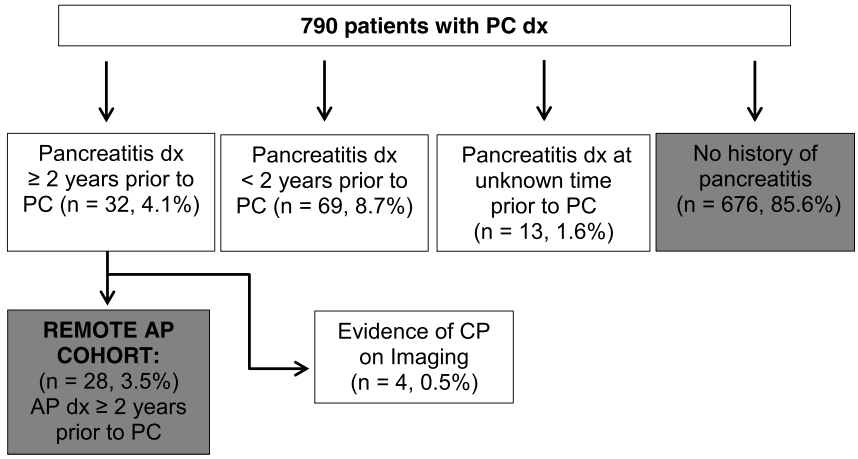

FIGURE 1. Study flow chart. dx indicates diagnosis.

TABLE 1. Characteristics of Study Cohort

	No History of Pancreatitis (n = 676, 85.6%)	AP dx ≥2 y Before PC dx (n = 28, 3.5%)	*P*
Sex, male, n (%)	363 (53.7)	15 (53.6)	0.989
Age at dx of PDAC, mean (SD), y	67.6 (10.8)	63.0 (10.5)	0.027
Ever smoker,* n (%)	326 (48.2)	16 (57.1)	0.355
Alcohol use, n (%)			0.37
Past user	182 (26.9)	12 (42.9)	
Current user	207 (30.6)	6 (21.4)	
Never user	189 (28.0)	7 (25.0)	
Unavailable	98 (14.5)	3 (10.7)	
BMI at enrollment, mean (SD), kg/m^2	28.9 (6.1)	31.3 (7.8)	0.063
Obese, BMI at time of enrollment >30 kg/m^2, n (%)	219 (32.4)	11 (39.3)	0.419
BMI at age of 18 y, mean (SD), kg/m^2	22.8 (4.08)	23.3 (4.46)	0.58
Obese at age of 18 y, BMI >30 kg/m^2, n (%)	17 (2.5)	1 (3.6)	0.10
Diabetes, n (%)	247 (36.5)	18 (64.3)	0.003

*Smoked ≥100 cigarettes in their lifetime.
dx indicates diagnosis.

after AP to be 16%, 23%, and 15%, respectively (95% confidence interval [CI], 9%–24%, 16–31%, and 9–21%, respectively) with newly diagnosed DM developing in 15% of individuals within 1 year of the first episode of AP.[34] In the same study, this risk increased 2.7-fold at 5 years after the first episode (risk ratio, 2.7; 95% CI, 1.9–3.8); notably owing to limitations of the included studies, they were unable to perform additional subgroup analysis evaluating new-onset DM based on severity of AP. A later study of 162 patients did show that risk of new-onset DM increased in the presence of organ failure and pancreatic necrosis, estimating the risk of new-onset DM after mild AP to be 10% to 15% and after severe AP (or necrosis) to be 30% to 50% over a 3- to 5-year period.[35] In our cohort of PC patients, a higher presence of diabetes in the patients who had remote history of AP may suggest that the inflammation was bad enough in these individuals to concomitantly cause islet cell destruction. Without more detailed information on their earlier AP courses (such as pancreatic necrosis and severity), why these individuals spared their pancreatic parenchymal cells (and avoided progression to CP) then becomes more difficult to explain.

Long-standing adult-onset diabetes has been shown to increase risk of PC by approximately 2-fold,[36] but diabetes is also well known as an early manifestation of PC. Timing of diabetes onset, temporal association with PC diagnosis, and most importantly information on type of diabetes were limited. Although patients were asked in the medical history questionnaire whether their diabetes was type I or type II and when they had received their diagnosis, many patients chose not to answer. This information was also incomplete in many electronic medical records charts given the focused reason for patient referral to this center. In addition, type 3c diabetes, which occurs secondary to islet cell destruction patients with pancreatic damage (most often secondary to pancreatitis), was not included in the patient history questionnaire. Given these considerations and the small group size of the patients with remote history of pancreatitis, a meaningful interpretation of this difference was not feasible. The role that diabetes plays in development or progression of PC is also linked to obesity given the common co-occurrence of these conditions.[26] It has been suggested by some that increased fasting insulin levels have been causally linked with increased risk of PC (odds ratio, 1.66; 95% CI, 1.05–2.63).[24] In a previously published analysis, it has been shown that increased exposure to insulin in DM patients does not accelerate PC development.[21]

Limitations of this study include the small number of PC patients with remote history of AP and the use of patient-obtained histories. The size of this cohort limited our ability to perform in-depth assessment of prior alcohol use, tobacco use, and the effects of diabetes and obesity. We performed multivariable regression analysis in an effort to adjust for these factors and found evidence that is largely consistent with prior literature in addition to the new and significant findings discussed above. Although we could not exclude type I error with regard to the age of presentation being significantly younger in PC patients with remote AP, our findings were mirrored by the larger study of administrative data of over 40,000 patients.[20] In addition to this, the limitations of retrospective data collection from a database precluded in-depth evaluation of the timing and process of pancreatitis diagnosis in these patients. Recollection bias may have altered some patients' report of AP and CP history: wherever possible, this history was supported by extensive chart review and additionally corroborated by radiologic evidence. Acute pancreatitis, as a common gastroenterological diagnosis, is an important piece of clinical history in any patient with PC. Elucidating the aspect of its role as an accelerator in the carcinogenic process for this deadly helps to inform our history taking for each PC patient as we struggle to understand the influential aspects of the affected person's history.

CONCLUSIONS

In summary, these findings suggest that a remote history of any pancreatitis accelerates carcinogenesis with PC diagnosed 4.7 years earlier than patients without a history of pancreatitis. The mechanism of this remains unclear. Future studies are needed to evaluate additional PC patients with remote history of pancreatitis to validate the multivariate analysis findings and elucidate potential mechanisms by which this may be occurring.

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