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Title: Bidirectional relationship between acute pancreatitis and pancreatic cancer

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Abstract:

Purpose of review: The burdens of pancreatic ductal adenocarcinoma [PDAC] and acute pancreatitis [AP] are increasing globally. We reviewed current literature on whether AP is a causal factor for PDAC and examined clinical manifestations of PDAC-associated AP.
Recent findings: Recent findings detail the timing of AP before and after PDAC occurrence, further solidifying the evidence for PDAC-associated AP and for AP as a causal risk factor for PDAC. The risk of PDAC remains elevated above the general population in patients with distant history of AP. PDAC risk also increases with recurrent AP episodes, independent of smoking and alcohol. Mechanisms linking AP to PDAC include inflammation and neutrophil infiltration, which can be attenuated by suppressing inflammation and/or epigenetic modulation. There is also a role for regulating pancreatic serine and arginine-rich splicing factor 1 [SRSF1], which promotes acinar-to-ductal metaplasia. Clinical presentation and management of AP in the context of PDAC are discussed, including challenges AP poses in the diagnosis and treatment of PDAC, and novel interventions for PDAC-associated AP.
Summary: PDAC risk may be reduced with improved AP prevention and treatment, such as anti-inflammatories or epigenetic modulators. Increased AP and PDAC burden warrant more research on better diagnosis and management of PDAC-associated AP.

Keywords: acute pancreatitis, pancreatic cancer, pancreatic adenocarcinoma, pancreatic inflammation

Introduction

Acute Pancreatitis (AP) is the third leading gastrointestinal diagnosis for adults in US hospitals, accounting for 288,220 admissions per year and contributing to healthcare costs of almost $5 billion US dollars annually (1). Pancreatic cancer is the third-leading cause of cancer deaths in the US, with an estimated annual incidence of 66,000 new cases, and over 50,000 deaths (2). Approximately 90% of pancreatic cancers are histologically consistent with pancreatic ductal adenocarcinoma (PDAC). Unfortunately, the prognosis remains poor for PDAC: 5-year survival is currently estimated at 13% (2). The incidence of PDAC is increasing worldwide (3), concomitant with a rise in AP incidence (4). Understanding the association between AP and PDAC is important to assist with early PDAC detection to improve prognosis for this deadly disease. Previously, the association between AP and PDAC was thought to occur as a consequence of the development of chronic pancreatitis (CP), a well-established independent risk factor for PDAC (5), or as a reflection of PDAC-induced AP. Recent work suggests that AP itself may increase long-term risk of PDAC development (6). This review explores the implications of recent work evaluating the relationship between AP and PDAC, focusing on the role of AP on PDAC, independent of CP.

Incidence of Acute Pancreatitis in Pancreatic Cancer

Approximately 10% of patients with PDAC present with AP, thought to be largely due to obstruction of the pancreatic duct by tumor (7, 8). A retrospective cohort study by Munigala et al. of almost 500,000 veterans further clarified this timeline (8). Of the studied population, 710 patients were diagnosed with PDAC, and 76 of those had AP within 2 years of receiving their cancer diagnosis. The subsequent time to diagnosis of PDAC after AP was variable though the majority presented within 2 years: 34 patients were diagnosed in ≤ 2 months, 35 patients received diagnoses within 3-12 months, 7 patients received diagnoses within 12-24 months. This study also examined incident PDAC following AP diagnosis. While the absolute risk of

pancreatic cancer in the 12 months after AP was highest in patients aged >70 years old, the relative risk of PDAC attributable to AP was highest in younger patients between 41 and 50 years old (RR 104.78, 95% CI 43.43-252.79), demonstrating a stronger link between AP and PDAC among younger individuals.

Incidence of Pancreatic Cancer in Acute Pancreatitis

The impact of prior AP history on subsequent PDAC development has been less clear. Retrospective studies have demonstrated that statistical associations between AP and PDAC are driven mostly by AP diagnosed proximal to PDAC. A 2020 meta-analysis by Liu et al (9) showed a markedly increased association of PDAC and AP within the first year after AP (attributable to tumor causing ductal obstruction and subsequent AP), with decreasing relative risks at subsequent timepoints (23.47 at 1 year after AP, then 2.47, 1.69, and 1.17 at 5 years, 10 years, and >10 years after AP, respectively). However, several recent studies have pointed to an increased risk of PDAC in patients with a history of AP compared to the general population. A large retrospective study of 7,147,859 US veterans, 35,550 of whom had AP and 16,475 had PDAC, showed that the cumulative risk of PDAC 3-10 years after AP diagnosis was *>3 times higher* than controls who had no history of AP (6). The study also demonstrated that 1) PDAC risk increases with each additional episode of AP (HR of 1.28, 2.48 and 3.71 for 1, 2 and 3+ episodes of AP vs. no-AP controls) and 2) this risk was additive to the underlying risk of CP, suggesting that AP confers a unique risk outside of that characterized by CP. A smaller retrospective study of 790 patients with PDAC by Evans et al showed that those with remote history of AP (>2 years before PDAC diagnosis) presented approximately 4.7 years earlier with PDAC than those who did not have an AP history (10). A population-based study by Kirkegard et al, showed a similar difference in median age at time of cancer diagnosis (67.6 years in patients with history of AP versus 72.6 in comparison subjects), suggesting possible accelerated carcinogenesis in the AP population (11). This study showed that the risk of PDAC in patients

with history of AP was consistently elevated above the control population throughout a 10-year follow-up period. Moreover, a recent single-center study combined with a meta-analysis showed that high grade dysplasia in the pancreas was more commonly observed in intraductal papillary mucinous neoplasms (IPMNs) with AP as compared to IPMN without AP (12). These lines of evidence collectively support a causal role for AP as an inflammatory, pro-neoplastic event prior to PDAC development.

Role of Shared Risk Factors of Acute Pancreatitis and Pancreatic Cancer

Deciphering if AP increases PDAC risk independently or through shared risk factors like alcohol and smoking has clinical implications for prevention strategies. Careful examination of confounders is warranted, especially for alcohol and smoking which increase PDAC risk in a dose-dependent manner (13, 14). Of studies that compared the long-term (≥ 2 years) risk of PDAC after AP diagnosis compared to a control population without AP (6, 11, 15-17), three have modeled the risk of PDAC by AP accounting for potential confounders of the relationship (Table 1), all pointing to an increased risk of PDAC attributable to AP with heterogeneous relative risks ranging from 1.27 to 5.4. Studies controlling for smoking and drinking categorized the behaviors in broad categories, such as never, former, current smoking, or as smoking-associated conditions or diagnosed alcoholism. In these studies, residual confounding may remain, because PDAC risk in smokers and drinkers varies by intensity (18, 19). However, given the relatively stronger associations of AP with PDAC (mostly RR >2), and the more modest association of smoking and alcohol with PDAC (mostly <RR 2) (18-21), residual confounding is unlikely to fully explain the link. Consistent with this, a recent study by Munigala et al. (6) demonstrated no difference in risk of PDAC by smoking or alcohol etiology of AP, thereby attributing the elevated PDAC risk to AP itself. While toxic risk factors have been accounted for epidemiologic associations of AP with PDAC, metabolic factors such as triglycerides, BMI or fatty pancreas (22) have received less attention as confounders, and may contribute to the risk

of PDAC (23, 24). Munigala et al. (6) demonstrated a non-statistically significant increased risk of PDAC among patients with gallstone-associated AP vs. non-gallstone-associated AP after 5 years of AP diagnosis, suggesting that shared risk factors of gallstones and PDAC, such as obesity, could have tumorigenic consequences. Future studies that investigate the role of shared metabolic factors between AP and PDAC with robust sample sizes and longitudinal measurements are warranted.

Preclinical Studies Linking Acute Pancreatitis to Pancreatic Cancer

PDAC often derives from precursor lesions arising initially from regions of acinar to ductal metaplasia (ADM), a process whereby acinar cells trans-differentiate to ductal-like cells. ADMs can eventually progress to form pancreatic intraepithelial neoplasia (PanIN), and then to PDAC. AP in humans is known to be associated with acinar cell death, edema, and neutrophil/macrophage infiltrates.

Evidence that AP accelerates precursor lesion progression to PDAC was initially demonstrated with caerulein-induced AP, using genetically engineered mouse models (GEMMs) expressing mutant $Kras^{G12D}$ in the pancreas (25). In GEMMs expressing mutant $Kras^{G12D}$ driven by Pdx1-Cre recombinase (KC mice), ADMs and early-stage PanIN appeared at age 2 months and slowly increased in number (25). When the mice were 6-7 months old, there was an increase in high grade PanIN, and several months later some mice developed PDAC. In contrast, one month following caerulein-induced AP in 2-3 month old KC mice, there was a rapid appearance of numerous ADMs and high-grade PanIN, and 80 days post-AP readily evident PDAC developed in 2 of 5 mice (25).

This slow progression of early PanIN to high grade PanIN has been attributed to oncogene-induced senescence (OIS) (26), which can be bypassed in GEMMs through additional manipulations such as deletion of Smad4, Cdkn2a, Trp53 (transformation related

protein 53), or insertion of a $Trp53^{R172H/+}$ gain of function mutated p53 allele (27). The latter model was recently shown to exhibit increased neutrophil accumulations within the tumor microenvironment (TME) due to increased expression of the neutrophil chemokine CXCL2 in conjunction with attenuated cancer-directed immune mechanisms (28), underscoring the role of intra-pancreatic neutrophils.

Recently, expression of serine and arginine rich splicing factor 1 (SRSF1) splicing factor was shown to increase in pancreata of caerulein-induced AP (29). SRSF1 caused AP in a tetO-Srsf1; LSL-rtTA; Pdx1-Cre GEMM (called SC mice) after doxycycline induced the expression of pancreatic SRSF1 to levels observed in the caerulein AP model. SC mice developed all the features of AP, including neutrophil infiltrates. SRSF1 acted by enhancing the expression of interleukin 1 receptor type 1 (IL1R1), prompting enhanced MAPK signaling (29). A negative feedback loop that dampened MAPK activity was counteracted by endogenous MYC activity. The importance of IL1R1 in this AP activation pathway was confirmed by a conditional Il1r1 knockout SC GEMM and demonstrating that AP induction, ADM formation, and immune cell infiltration were markedly attenuated (29). Given that MYC is a potent oncogene that facilitates SRSF1's actions to induce AP and ADM-PanIN progression, as well as PDAC progression and metastasis (30, 31), the novel SRSF1 findings provide compelling evidence for an AP-to-PDAC roadmap that could yield novel preventive strategies, perhaps in conjunction with non-steroidal anti-inflammatories (32) and epigenetic modulators (33) that impede ADM formation.

Mechanism of Pancreatic Cancer-Induced Pancreatitis

1. Pancreatic duct obstruction

Patients with PDAC may sometimes present with findings suggestive of an obstructed pancreatic duct and AP due to the inability of the pancreatic juice to flow into the duodenum. In a review by Delhaye et al, the authors summarized a variety of etiologies that may be

associated with pancreatic duct obstruction and AP or RAP (34). These include obstruction of the main pancreatic duct by a PDAC compressing the duct, pancreatic duct stricture, blocked pancreatic duct juice flow due to an obstruction by an ampullary cancer near the major or minor papilla, and rare duodenal cysts that when encumbered with stones and secretions can compromise pancreatic juice flow.

IPMNs may occur in the main or branch pancreatic duct or at both sites (35), exhibit regions of obstructive flow of pancreatic juice due to its mucinous nature, and have the potential to undergo malignant transformation (36, 37). IPMNs can also be associated with AP and recurrent AP, as shown in an analysis of 150 patients whose IPMNs were resected (38). Notably, 10 patients had AP and 9 had RAP, and their incidence of cancer was higher than in the non-pancreatitis group.

2. Pancreaticobiliary union

An anomalous pancreaticobiliary junction (APBJ) between the pancreatic and bile ducts outside the duodenal wall occurs in ~3% of the population and may result in aberrant pancreatic juice and bile flow, choledochal cysts, bile-induced AP, and a higher incidence of gall bladder cancer and PDAC (39-41).

Clinical Manifestations of Acute Pancreatitis associated Pancreatic Cancer

As noted above, PDAC and AP may be related in multiple ways including delayed PDAC development in patients with a prior history of AP (without CP), as the initial presentation of PDAC in the setting of a first AP episode (PDAC-AP), and as iatrogenic AP in the setting of interventions in PDAC e.g. after endoscopic retrograde cholangiopancreatography (ERCP) or after PDAC resection. The clinical manifestations of PDAC-AP will be discussed here.

Patients with AP generally present with abrupt pain onset, classically described as severe upper abdominal pain radiating into the back or to the left, often with nausea and/or

vomiting. The clinical presentation of patients with PDAC-AP compared to AP alone may be similar, however PDAC-AP has been associated with an older age (42-44). In general, AP secondary to a biliary stone or PDAC may present with jaundice in addition to AP-associated pain. However, pain is typically more indolent and may occur later in patients with PDAC without AP. Other symptoms associated with PDAC such as poor appetite, diarrhea or loose stool secondary to steatorrhea, unintentional weight loss, and recent or new onset diabetes, should raise the concern for malignancy in patients presenting with AP (42). Although studies have reported that most PDAC-AP patients present with mild AP, based on clinical or imaging criteria for the classification of AP, in some patients, the presentation of PDAC-AP may be associated with severe necrotizing pancreatitis (7, 43, 45-48).

The imaging findings in PDAC-AP include the presence of a pancreatic mass or a pancreatic duct stricture with dilation of the pancreatic duct upstream from the stricture and findings suggestive of metastatic disease e.g., abnormal lymphadenopathy or liver metastasis (44, 49) The exact etiology of AP is not clear in an estimated 7-27% of patients presenting with AP and is defined as idiopathic (50). A challenge associated with PDAC-AP is a delay in diagnosis of patients presenting with AP (43, 44). In one study of 18 PDAC-AP patients, the mean number of episodes prior to a malignancy diagnosis was 2 with a range of 1 to 15 and a mean time from AP to PDAC diagnosis of 34 weeks (43). An important step in the evaluation of recurrent seemingly idiopathic AP is to repeat imaging including CT (Computerized Tomography), MRI/MRCP (Magnetic Resonance Imaging/Magnetic Retrograde Cholangiopancreatography) and/or EUS (endoscopic ultrasound) as this strategy is associated with identification of the etiology of AP including PDAC-AP in up to 64% of patients, including a small but important subset of those with PDAC (43, 50, 51). However, even with all these diagnostic modalities, severe pancreatic necrosis may obscure PDAC [Figure 1].

The overall management of PDAC-AP is similar to that of de novo PDAC patients, though there are conflicting data regarding the impact of AP on PDAC-AP survival (43, 52). A

recent population-based study reported lower rate of metastasis at presentation and higher overall survival in PDAC-AP patients potentially attributable to an earlier presentation secondary to AP (53). An additional single center study of patients with moderate or severe PDAC-AP reported earlier disease recurrence and shorter overall disease-free survival in PDAC-AP patients (42). In the presence of PDAC-AP, the presence of moderately severe or severe AP has been associated with a higher risk of tumor recurrence. Symptomatic management of jaundice secondary to biliary obstruction in the setting of PDAC-AP is similar to that of patients without AP patients with biliary drainage via ERCP and stent placement being recommended in patients who are not candidates for immediate surgical resection (52). However, ERCP itself is associated with a risk of pancreatitis which is greater with metal compared to plastic stents although how this affects patients with PDAC-AP is not known (54). While pancreatic duct stent placement is not typically performed, it has been shown to be efficacious for pain relief in PDAC patients with pancreatic duct obstruction, likely due to decompression of the obstructed pancreatic duct resulting in resolution of acute and smoldering pancreatitis (55). Celiac plexus neurolysis, via a percutaneous or EUS guided approach, has been shown to be efficacious for severe or refractory pain symptoms in PDAC patients in general, and is applicable to patients with PDAC-AP as well (56, 57).

Conclusion

Both AP and PDAC are increasing globally. Recent data suggests that AP increases PDAC risk in a dose-dependent manner. Inflammation and epigenetic modulation mediate AP-driven PDAC carcinogenesis, which may involve IL-1 signaling. While AP potentially delays the diagnosis of PDAC, AP does not necessarily worsen PDAC outcomes.

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Conflicts of Interest: There is no conflict of interest to report.

Figures and Tables:

Table 1. Studies investigating relative long-term (>2 years) risk of pancreatic cancer following acute pancreatitis with adjustment for confounders.

Figure 1.

72 year old man with a 7 year history of acute relapsing pancreatitis

A . Note areas of walled off necrosis in the setting of disconnected pancreatic duct syndrome. B. The patient was treated with dual modality (endoscopic and percutaneous) drainage. Note percutaneous drain and a lumen-apposing metal stent [LAMS] with 2, 7Fr pigtail stents placed into the necrotic cavity. C. Contrast injection through the percutaneous tube 6 weeks later demonstrating ongoing communication to the stomach through the stents and a small residual cavity. D. Following removal of his percutaneous drain, the patient presented 3 months later with pancreatic adenocarcinoma growing through the original percutaneous tract (arrow).

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Table

Table 1. Studies investigating relative long-term (>2 years) risk of pancreatic cancer following acute pancreatitis with adjustment for confounders.

First author and year	Study design and Setting	Adjusted hazard ratio attributable to AP	Confounders modeled	Limitations
Kirkegard et al. 2018 (11)	Retrospective cohort study of Danish National Patient Registry and Danish Cancer Registry	HR = 2.43 (1.73–3.41) for AP 2-5 years ago HR = 2.02 (1.57–2.61) for AP >5 years ago	Age, sex, year of AP diagnosis, alcohol- and smoking-related conditions, and Charlson Index	Potential for residual confounding by alcohol and smoking; no control for obesity
Sadr-Azodi et al. 2018 (17)	Retrospectively cohort study of Swedish Inpatient Register, Swedish Cancer Register	HR = 5.43 (3.01–9.80) for AP 2-3 years ago HR = 2.68 (1.50–4.76) for AP 3-4 years ago HR = 2.70 (1.37–5.30) for AP 4-5 years ago HR = 1.91 (1.30–2.82) for AP 5-10 years ago HR = 1.27 (0.69–2.33) for AP >10 years ago	Age, sex, municipality, calendar year, education level, birthplace, the Charlson Index and alcohol abuse	No control for smoking; potential for residual confounding by alcohol; no control for obesity
Munigala et al. 2023 (6)	Retrospective cohort study of VA Health System in U.S.	HR = 2.00 (1.67-2.38) for AP >2 years ago HR = 4.71 (3.80, 5.82) for AP > 2 years ago and developed CP	Age, Sex, race, smoking status, alcoholism, diabetes, gallstone disease	Potential for residual confounding by smoking and alcohol; no control for obesity

Figure