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The Deleterious Effects of Smoking on the Development and Progression of Chronic Pancreatitis

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Introduction

Chronic pancreatitis (CP) represents a fibro-inflammatory disease of the exocrine pancreas characterized by irreversible damage to the pancreas, and ultimately loss of pancreatic function.[1] With an estimated global incidence of 9.62 cases/100,000 person-years, the burden of CP is increasing as reflected by an increasing prevalence and hospital visits secondary to CP in the last decade.[1–4] In examining the etiology of CP, the role of cigarette smoking has garnered much interest due to emerging preclinical and epidemiological research.

The prevalence of smoking worldwide has decreased over several decades with estimates of 25% in men and 5.4% in women as of 2015, reflecting decreases of 28.4% in men and 34.4% in women since 1995.[5] Despite these global improvements, there remains a high rate of current smoking in the CP population with a prevalence of 51.1% reported in the North American Pancreatitis Study-2 (NAPS-2) population and 53% in a Scandinavian cohort.[6, 7]

This review will focus on the interplay between CP and cigarette smoking to: (i) provide an overview of how smoking contributes to the pathogenesis of CP, (ii) describe the association of smoking with disease progression, (iii) describe the association of smoking with patient-reported outcomes in CP, and (iv) highlight unique challenges for smoking cessation in CP.

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Search Strategy

We identified potential references for this narrative review using a search of PubMed for articles published until January 10th, 2022 with the following Medical Subject Headings (MeSH): (chronic pancreatitis or acute pancreatitis) AND (smoking OR nicotine OR tobacco). We identified additional articles by examining the references of selected articles. The final articles were selected with preference for original articles and those with high relevance to the goals of this review.

Smoking and the Pathogenesis of Chronic Pancreatitis

Of the approximately 4000 chemicals found in cigarettes, precisely which components contribute to the pathogenesis of CP is challenging to tease apart. In fact, there are multiple potential pathways, which may function additively or synergistically (Figure). One key mechanism is ductal dysfunction related to the dysregulation of the cystic fibrosis transmembrane conductance regulator (CFTR), which may occur through the elevation of cytoplasmic calcium which prevents normal sorting and degradation of CFTR.[8] CFTR in turn controls transport of chloride and bicarbonate ions, the dysfunction of which leads to decreased fluid secretion from the pancreas into the pancreatic duct, resulting into a low-flow, high protein concentration in the pancreas juice that can lead to premature activation of pancreatic enzymes and lead to acinar cell damage.[9] In both mice and humans, smoking has been found to lead to CFTR dysfunction, with one study finding smoking to be independently associated with low bicarbonate secretion into the duodenum (indicating impaired secretory function).[10–12]

Another pathogenic mechanism of smoking involves the activation of the inflammatory cascade and necro-inflammatory response, which ultimately results in fibrosis. Numerous studies have demonstrated how smoking damages pancreatic acinar cells, activating pancreatic stellate cells and thereby inducing fibrosis.[13–19] In a murine model, aryl hydrocarbon receptor ligands found in cigarette smoke increased levels of interleukin 22, which then upregulated pancreatic stellate cell extracellular matrix gene expression to promote fibrosis.[15] Smoking was also found to affect acinar cells by inhibiting X-box binding protein 1 (XBP1s) formation, thus leading to endoplasmic reticulum stress and eventually cell death.[16] In an autopsy study, smokers without CP were found to have significantly higher levels of total and intralobular fibrosis in the pancreas than non-smokers.[17] In regards to the decreased blood flow to the pancreas observed in CP, studies have found significantly higher levels of endothelin-1, a hormone related to vasoconstriction, in both the blood and pancreatic tissue in smokers with CP compared to non-smokers with CP.[20, 21] Thus, smoking may also compromise the vascular supply of the pancreas, with resultant ischemia damaging the pancreas.

Oxidative stress may represent an additional mechanism of smoking induced pancreatic injury. In one study, smokers with CP had significantly higher levels of serum interleukin-6 (IL-6), a pro-inflammatory cytokine, than non-smokers with CP.[19] Furthermore, these patients also had higher levels of copper/zinc superoxide dismutase activity and glutathione

peroxidase activity in pancreatic fluid, further implicating smoking as a contributor to local oxidative stress of the pancreas and resultant systemic inflammation.[19]

Smoking and Progression from Acute to Chronic Pancreatitis

Pancreatic disease progression encompasses progression from acute pancreatitis (AP) to recurrent acute pancreatitis (RAP) to CP, as well as the advancement of CP in regards to morphology, endocrine insufficiency, and exocrine insufficiency. In population-based studies, patients' smoking status has typically been categorized as current smoker, former smoker, and no history of smoking (i.e., never).[22–26] Quantification of smoking exposure remains variable with some studies reporting the number of pack-years and others reporting the number of cigarettes or packs of cigarettes/day.[27] While self-reported smoking history may suffer from recall bias, it is generally considered reliable for assessment of long-term exposure, although accurately capturing a dose-dependent response to smoking exposure may prove challenging.[28, 29] Nevertheless, it remains unclear as to how prospectively collected smoking history compares to retrospectively ascertained smoking history. Biomarkers, such as cotinine or DNA methylation, represent an objective form of quantifying smoking exposure, but have not been measured in epidemiologic studies examining acute or chronic pancreatitis.[30] It is important to consider these limitations while interpreting the following epidemiological studies.

Patients can progress over time from having AP to CP, while many patients will present with CP without a prior documented episode of pancreatitis.[22, 31, 32] In examining 669 patients who presented with AP, the Dutch Pancreatitis Study Group reported that current smoking was an independent risk factor for development of CP (OR: 2.9, 95% CI, 1.4–5.9) when excluding recurrent acute pancreatitis (RAP) as a covariate.[22]

Numerous studies have identified smoking as an independent risk factor for CP (Table). A large study from Denmark found a dose-dependent relationship of smoking history with development of CP independent of alcohol.[23] Smokers who had ≥ 60 pack-years had the greatest risk (HR: 4.1, 95% CI, 1.9–9.7) with the risk decreasing with fewer pack-years; presence of recurrent pancreatitis was not recorded in this study. Similarly, the NAPS2 study demonstrated an independent, dose-dependent relationship of smoking and CP in men, women, and ever-drinkers, with CP subjects having a significantly higher amount of smoking and duration of smoking compared to those with RAP.[33] A sub-group analysis also found that smoking was independently associated with idiopathic CP, including ever-smokers (OR: 1.65, 95% CI, 1.08–2.52), current smokers (OR: 1.8, 95% CI, 1.10–3.05) and smoking ≥ 1 pack per day (OR: 1.87, 95% CI: 1.10–3.12).[25] A meta-analysis including 4 prospective studies with CP populations found a relative risk (RR) of 1.93 (95% CI, 1.60–2.32) for current smokers, RR of 1.30 (95% CI, 1.08–1.57) for former smokers, and RR of 1.59 (95% CI, 1.39–1.82) for ever-smokers.[27] Further analysis revealed a RR of 1.10 (95% CI, 0.99–1.21) per 10 pack-years. In summary, there is compelling evidence that cigarette smoking is independently associated with the progression from acute to chronic pancreatitis in a dose-dependent manner.

Smoking and Disease Progression of Chronic Pancreatitis

Several studies have linked accelerated disease progression with smoking in CP. In an international multicenter cohort of 934 patients, smokers showed earlier age of diagnosis as compared to non-smokers (mean difference of 4.7 years) and greater prevalence of calcifications at the time of diagnosis (OR: 2.0, 95% CI, 1.1–3.8).[34] Current smoking was also associated with the development of calcifications after initial diagnosis (HR: 4.9, 95% CI, 2.3–10.5) and strikingly, by the age of 60, 80% of smokers had calcifications compared to 40% of non-smokers. Similarly, in a Korean population, smoking was found to be an independent risk factor for progression of calcifications for both patients who smoked < 1 pack per day (OR: 6.1, 95% CI, 1.1–34.6) and ≥ 1 pack per day (OR: 36.6, 95% CI, 3.8–353.3).[35] A nationwide survey of Japan found that smoking, and not alcohol, was independently associated with calcifications (OR: 2.0, 95% CI, 1.5–2.8) in patients with CP.[36] Finally, a prospective study from Italy compared the development of calcifications by smoking cohorts, finding that calcifications developed in 57.8% of patients who had never smoked, 59.5% of patients who stopped smoking at the time of diagnosis, and 79.1% of patients who continued smoking ($p<0.001$).[37] The odds of developing calcifications followed a dose-dependent relationship with patients smoking > 1 pack per day having the greatest risk (OR: 1.79, 95% CI, 1.1–2.9).

Exocrine pancreatic insufficiency (EPI) is frequently encountered in CP and can develop due to loss of functioning acini, ductal dysfunction, and/or duct obstruction.[1] Numerous studies have linked smoking with development of EPI in CP. In a Scandinavian cohort of 1071 subjects with CP, smoking was associated with both exocrine and endocrine insufficiency (OR: 1.42, 95% CI, 1.0–2.0).[7] In a study from Spain which used a ^{13}C-mixed triglyceride breath test to assess exocrine function, smoking was the only independent risk factor for development of EPI (OR: 2.5, 95% CI, 1.2–5.2).[38] Lastly, a large study from China focusing on CP patients with known genetic factors such as *SPINK1*, *PRSS1*, *CTRC*, and *CFTR* mutations also identified smoking as an independent risk factor for development of steatorrhea (HR: 1.56, 95% CI, 1.1–2.3).[39]

The development of diabetes represents one of the later complications of CP, typically occurring 10–20 years after diagnosis.[1] One multicenter cohort study found that CP patients who smoked had a greater risk (HR: 2.3, 95% CI, 1.2–4.2) of developing diabetes during the course of follow-up.[34] The aforementioned survey study from Japan also found smoking to be independently associated with diabetes, independent of a history of heavy alcohol consumption.[36] Whether smoking affects the risk of diabetes by means of insulin secretion, insulin signaling, insulin sensitivity or by beta cell loss remains to be investigated.[40] In a US cohort, men who smoked ≥ 25 cigarettes/day carried a greater risk of developing diabetes (RR: 1.94, 95% CI, 1.25–3.03), which was also seen in a Chinese cohort, where men who smoked ≥ 20 cigarettes/day had a greater risk (HR: 1.28, 95% CI, 1.04–1.57) of developing diabetes than non-smoking men.[41, 42] Further investigation is needed to delineate how smoking contributes to the development of diabetes.

Chronic pancreatitis is a known risk factor for pancreatic cancer with the risk of cancer varying based on etiology.[43, 44] At the same time, smoking is also well-established as

increasing the risk of pancreatic cancer in a dose-dependent manner with a relative risk of at least 1.5 in most studies.[45, 46] It follows that smoking further increases the risk of pancreatic cancer in patients with CP. One study found that patients with CP who smoked had a significantly increased risk (OR: 20.3, 95% CI, 2.7–158) of developing pancreatic cancer during follow-up.[47] In a landmark study involving patients with hereditary pancreatitis, smoking doubled the risk (OR: 2.1, 95% CI, 0.7–6.1) of pancreatic cancer and was associated with earlier development of cancer by nearly 20 years although it remains important to note that in a follow-up study of 217 patients with *PRSS1* mutations, only five patients developed pancreatic cancer, two of which were smokers.[48, 49] In a large multicenter cohort study involving 2,015 patients with CP, however, only increasing age, and not smoking, was associated with an increased risk of pancreatic cancer.[44] The primary limitation of these studies, however, remain the relatively low number of patients who do develop pancreatic cancer within these cohorts and larger studies with long-term follow-up are ideally needed to elucidate the potential additive effect of smoking on the risk of pancreatic cancer in CP.

Smoking and Patient-Centered Outcomes in Chronic Pancreatitis

Incorporating patient-centered outcomes in assessing patients with CP remains critical in understanding the holistic impact of the disease yet are often not assessed as part of standard of care. A large Scandinavian/Baltic cohort of individuals with CP found that smoking was associated with the presence of pain.[50] Furthermore, smokers reported higher rates of constant pain, as opposed to intermittent pain, which has been shown to have a greater reduction of quality of life.[51–53] Part of these associations may reflect that some people smoke to alleviate pain although current smoking has been associated with a negative impact in both physical and mental quality of life.[6, 52] Similarly, a cross-sectional study from the U.S. found smoking to be independently associated with worse quality of life in CP patients.[54] While pain and quality of life represent important patient-centered outcomes, further qualitative research is needed to further understand the effect of smoking in this patient population.

Smoking Cessation in Chronic Pancreatitis

Given the consequences of smoking in CP, smoking cessation represents a critical target for potential therapy in this population, particularly given the lack of treatment options for reversing the disease course.[55] Smoking cessation, however, remains challenging for any population of patients, including those with CP. Smoking cessation strategies generally consist of a combination of behavioral and pharmacotherapies as only 3–6% of unaided smokers will remain abstinent when attempting smoking cessation.[56, 57] A single-center prospective study utilizing these strategies in a CP population, found that out of 27 subjects enrolled in a smoking cessation program, none had quit smoking at 18 months, illustrating the immense challenge in these patients.[58] Notably, among study participants, there was a high rate of unemployment and disability, which mirror the factors associated with high smoking prevalence in the general population and represent important barriers to smoking cessation within the CP population. Similarly, a large prospective study from Italy found that among 592 smokers, 37 (3.7%) quit smoking within 5 years of diagnosis.[37] More

encouragingly, a retrospective cohort study demonstrated that in 127 smokers, 56 (44.1%) were compliant with recommendations to stop smoking, with higher rates seen when recommendations were made by gastroenterologists or pancreas specialists.[59] Birth cohort analyses of the NAPS2 data have demonstrated that tobacco policies have had an impact in changing smoking practices in male CP patients, but prevalence of smoking among female CP patient have not decreased over time.[6]

There are no prospective data to determine whether smoking cessation alters the natural history of CP. In a cohort of patients with alcoholic CP who received pancreatic surgery for chronic pain, post-operative smoking cessation was independently associated with narcotic cessation at 6 months post-surgery and was the only independent risk factor for narcotic cessation at 12 months post-surgery.[60] Furthermore, smoking cessation was also associated with improved quality of life at 6 and 12 months post-procedure, which point towards the potential short-term benefits of smoking cessation, particularly in patients undergoing pancreatic surgery where other benefits such as decreased perioperative complications should be considered. Further investigation is also warranted to determine how smoking cessation affects the efficacy of other treatments, such as pancreatic endotherapy.

Future Directions

Smoking has deleterious effects on the pancreas along all aspects of the pancreatitis spectrum. Additional research is needed to further improve our understanding of the effects of smoking and importantly, help patients across the pancreatitis spectrum quit smoking. Further studies are needed to elucidate the pathways by which smoking contributes to the pathogenesis of CP and progression of AP to CP, which may help identify potential therapeutic targets. In our clinical experience, smoking cessation is extraordinarily challenging in patients with pancreatitis, and novel strategies are greatly needed. Once smoking cessation is achieved prospective studies will be helpful to understand how this affects the course of the disease. Non-pharmacological treatments such as disease-specific and culturally-tailored educational interventions and mindfulness represent alternative approaches that may improve smoking cessation rates within this patient population.[61, 62] In line with this, with the growing use of e-cigarettes, also known as vaping, as a smoking cessation tool, much remains to be seen regarding its efficacy within this population along with its safety profile.[63] The effect of second-hand smoke, while challenging to measure, also warrants further investigation given how it may even affect children presenting with pancreatitis.[64] Lastly, additional research is needed to understand the effects of marijuana in CP. Marijuana is becoming increasingly available due to varying degrees of legalization in the United States and worldwide, and is commonly considered for non-opioid analgesia. In fact, one small study has demonstrated opioid sparing effects in CP.[65] However, additional studies are needed to understand if the potential benefits are isolated to symptom relief or if there is also disruption of the pathophysiological mechanisms of CP.

Conclusions

In summary, a high proportion of patients with CP actively smoke or have a prior history of smoking. Smoking likely contributes to the development of CP and is independently

associated with the progression of AP to CP. Furthermore, it acts as a disease accelerant in CP and adversely effects patient-centered outcomes such as pain and quality of life. Smoking cessation, therefore, remains a prime target for the management of this disease, but novel treatments and approaches are needed to reduce the contribution of smoking-related pancreatic injury to the progression of pancreatitis.

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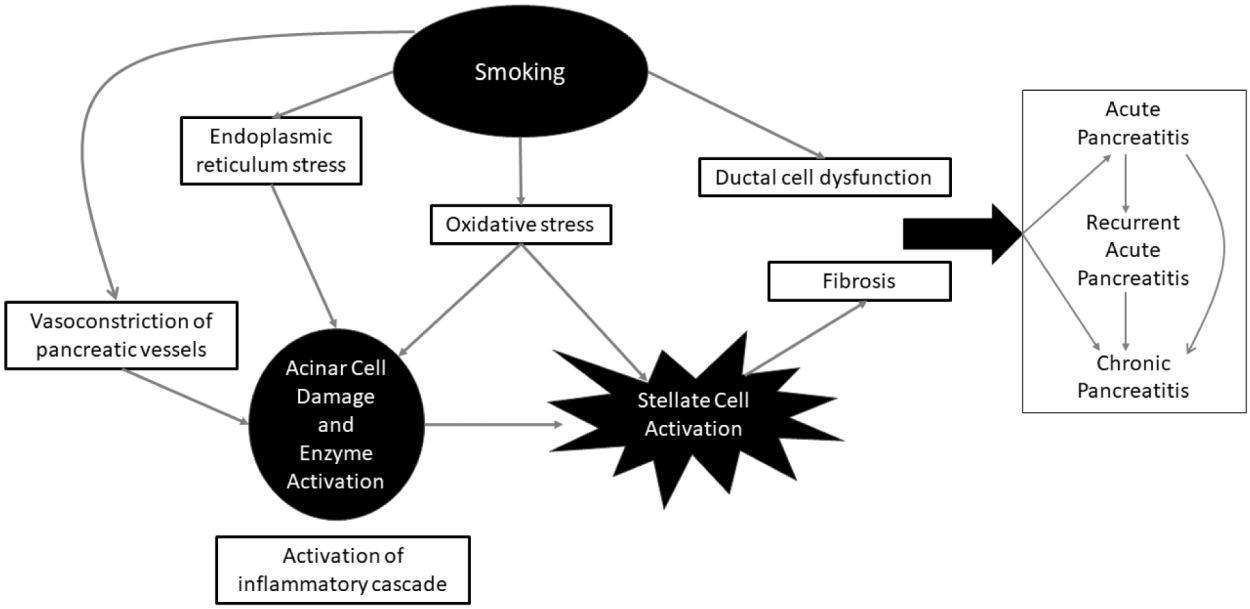

Figure.

Conceptual framework of cigarette smoking and its contribution to the pathogenesis and disease progression of chronic pancreatitis

Table.

Selected studies depicting the negative effects of smoking on disease progression in chronic pancreatitis

	Smoking contributes to progression
Progression from acute pancreatitis to chronic pancreatitis	Ahmed et al. 2016 Tolstrup et al. 2009 Coté et al, 2011 Rebours et al, 2012[66]
Morphologic progression of chronic pancreatitis	Maisonneuve et al, 2005 Lee et al, 2016 Hirota et al, 2014 Talamini et al, 2007
Exocrine pancreatic insufficiency	Olesen et al, 2019 Luaces-Reguiera et al, 2014 Ru et al, 2021
Pancreatic endocrine insufficiency (ie, diabetes)	Maisonneuve et al, 2005 Hirota et al, 2014 Olesen et al, 2019