Published in final edited form as:

Curr Treat Options Gastroenterol. 2015 September ; 13(3): 332–346. doi:10.1007/s11938-015-0056-9.

Epidemiologic and Mechanistic Associations Between Smoking and Pancreatitis

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Opinion Statement

Alcohol has long been associated with pancreatitis. Although first described more than 3 decades ago, smoking has been widely accepted as an important risk factor for all forms of pancreatitis only in the past few years. Empiric data has confirmed smoking as an independent and dose-dependent risk for both acute and chronic pancreatitis. Smoking also increases the risk of recurrences and progression of established chronic pancreatitis. The effects of smoking are enhanced in the presence of alcohol consumption. Indirect evidence suggests that smoking cessation may be beneficial in preventing disease progression. Smoking cessation can therefore be an important strategy for primary as well as secondary prevention of pancreatitis. Therefore, in addition to alcohol, physicians should routinely counsel patients for the benefits of smoking cessation. The mechanisms through which cigarette smoke triggers pathological cellular events, resulting in pancreatitis, are unresolved. Although cigarette smoke contains greater than 4000 compounds, principally nicotine and the tobacco-specific nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), have been broadly studied with regard to pancreatic diseases. Both nicotine and NNK have been shown to induce morphological changes in the pancreas consistent with those seen in pancreatitis. Furthermore, nicotine affects pancreatic secretion and NNK induces premature zymogen activation, two well-known features of pancreatitis. These cigarette

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Conflict of Interest

Edwin Thrower declares that he has no conflict of interest.

Julia B. Greer has received a grant from Abbvie, Inc.

Dhiraj Yadav has received consultancy fees from Abbvie, Inc. and grants from the NIH.

Compliance with Ethics Guidelines

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

toxins may mediate both pro- and anti-inflammatory pathways and can induce changes in pancreatic acinar cell function at the level of transcription, leading to conditions such as thiamin deficiency and mitochondrial dysfunction. Such circumstances could leave the pancreas prone to the development of pancreatitis. This review summarizes relevant research findings and focuses on the epidemiologic links between smoking and pancreatitis, and the cellular pathways that may be significant in induction and evolution of smoking-related pancreatitis.

Keywords

alcohol; mechanism; nicotine; NNK; nicotine; acetylcholine

Introduction

Acute Pancreatitis (AP) is characterized by sudden inflammation of the pancreas due to injury from a variety of causes. Chronic pancreatitis (CP) is an inflammatory disease characterized by long-standing injury and irreversible structural and functional impairment of the pancreas. Pancreatitis is associated with increased morbidity, mortality, healthcare utilization and long-term disability.[1–3]

Cigarette smoking is one of the most common risk factors observed among CP patients. Until recently, alcohol consumption was the prevailing focus of basic science studies that assessed environmental influences underlying pancreatitis. Although reported over 30 years ago, cigarette smoking has been widely recognized as a risk factor for pancreatitis only in recent years. In this review, we discuss the epidemiologic evidence of the relationship between smoking and pancreatitis and the laboratory-based research data, which confirm that numerous mechanisms link tobacco smoking and pancreatitis (Tables 1 and 2).

Epidemiologic links between smoking and pancreatitis

Smoking and Risk of CP

While alcohol is more frequently recognized as a risk factor, the prevalence of cigarette smoking has been noted to be high among patients with CP. In the multi-institutional NAPS2 study, 47.3% of 540 CP patients were current smokers and 71.4% reported being ever smokers at study enrollment while 59.4% men and 28.1% women had CP attributed by their physicians to alcohol consumption.[4,5] The prevalence of smoking is even greater in studies with a higher prevalence of men and alcohol etiology. In a study of 132 men with alcoholic CP, over 90% were smokers.[6]

As early as 1982, cigarette smoking had been shown to be associated with the development of chronic or recurrent pancreatitis, especially among males.[7] Since then, several studies, mostly using a case control design, have assessed this relationship.[5–14] In addition to the number of subjects, studies have varied with regard to etiology of CP, proportion of men and the choice of controls, which have ranged from hospitalized patients to drinkers, alcoholic cirrhosis, and population controls. These differences explain the variability between studies of the magnitude of association observed between smoking and CP as reflected by wide measure of association (odds ratio, OR) after adjustment for age and sex in most studies.

Two large cohort studies have evaluated the relationship between smoking and pancreatitis. In one study of 129,000 health plan members, the relationship of smoking (any, amount) was evaluated for any pancreatitis (i.e. acute or chronic) that was further classified into etiology groups (gallstone, alcohol and idiopathic).[15] The association of smoking after adjusting for age, sex and coffee consumption for alcoholic pancreatitis increased from a relative risk (RR) of 2.6 for ex-smokers to 5.8 for <1 pack/day and 11.4 for 1 packs/day. Only borderline significance was noted with idiopathic pancreatitis and no association was noted with gallstone pancreatitis. In the other cohort study of 17,905 subjects, incident diagnosis of pancreatitis was subclassified into acute and chronic pancreatitis. The RR adjusted for age, sex, education level, alcohol consumption and body mass index for CP increased from 0.9 in former smokers to 3.3 for smoking 25 grams/day[16]

Ten case-control and two cohort studies were included in a meta-analysis that evaluated 1705 CP patients. The pooled risk estimate of CP associated with cigarette smoking after adjustment for alcohol consumption was 2.7 (95% CI 1.5–4.7) for ever smoking, 2.5 (95% CI, 1.3–4.6) for current smoking and 1.5 (0.9–2.5) for former smoking. Among participants who smoked <1 pack of cigarettes each day, the risk was more than two-fold at 2.4 (95% CI, 0.9–6.6) while amongst those smoking 1 packs per day it increased to 3.3 (95% CI, 1.4–7.9).[17]

Findings of these observational studies can be summarized as follows - smoking is independently associated with the risk of CP and the risk increases in a dose dependent fashion. The absolute risk of CP based on smoking is not much different than alcohol consumption.[18] Together, these habits may explain ~60–65% of all cases of CP.

Smoking and the Risk of AP

With smoking established as an important environmental risk factor for CP, investigators have begun to evaluate the association of smoking with acute pancreatitis. Until now, 12 observational studies, 6 being case-control and 6 being cohort studies, have evaluated this relationship.[13,15,16,19–27] Due to a wider spectrum of causes for AP, investigators often group patients based on physician defined etiology as alcohol, gallstones, miscellaneous/other and idiopathic.

Similar to studies on CP, selection of controls and patients in these studies has been variable. While most case-control studies report the association after adjustment for age and sex, some also adjusted estimates for additional confounders such as alcohol, medications, comorbidities, etc. The ORs range from 0.40 to 6.6 depending on status and amount of smoking. Cohort studies, often population-based have larger sample size of subjects with information on tobacco smoking habits at baseline, and diagnosis of AP determined by manual review of chart or use of administrative data. In the Danish study of 17,905 subjects mentioned earlier, the RR adjusted for age, sex, education level, alcohol consumption and body mass index for AP increased from 2.2 in former smokers to 3.8 for smoking 25 grams/day. Two separate cohort studies of 33,346 and 84,667 subjects were reported from Sweden with an observation period after initial ascertainment of 11.3 and 12 years respectively.[26,27] Lindkvist et al reported a RR for current vs. never smokers at baseline for AP to be 2.14 after adjusting for age, gender, body mass index (BMI) and alcohol

consumption. The association was even greater in heavy smokers (20–30 cigarettes/day) (RR 3.19). Smoking was associated with a RR of 3.57 for AP in subjects who reported no alcohol consumption. The risk of AP was 18.6 per 100,000 person years in never smokers and increased to 23.3 in former smokers, 42.2 in current smokers, 35 with smoking <1 pack/day, over 60 with smoking 1 packs/day.

Sadr-Azodi et al assessed the relationship between smoking status, smoking intensity and duration, duration of smoking cessation and the risk of AP.[27] The authors stratified AP etiologically by whether it was gallstone-related (234 cases) or not related to gallstones (307 cases). Compared to never smokers, the risk of non-gallstone-related AP was more than doubled (RR 2.29) among current smokers with a smoking history of 20 pack-years. There was no link between smoking and gallstone-related AP.

A recent meta analysis summarized the results of observation studies.[28] The RR of AP was 1.54 (95% CI 1.31–1.80) for ever smokers, 1.71 (95% CI 1.37–2.14) for current smokers and 1.21 (1.02–1.43) for former smokers. The risk was limited to non-gallstone related, alcohol, drug and idiopathic etiologies. Findings of these observational studies can be summarized as follows - smoking is independently associated with the risk of AP, the risk increases is higher in current smokers than former smokers and appears to be dose dependent. The risk is limited to subsets of etiologies including all non gallstone-related causes, alcohol, and idiopathic causes but not for gallstone-related AP.

Combined Cigarette Smoking and Alcohol Consumption

The habits of drinking and smoking often co-occur and dependence on alcohol and tobacco is also highly correlated.[29] People who are dependent on alcohol are three times more likely than those in the general population to be smokers, and people who are dependent on tobacco are four times more likely than the general population to be dependent on alcohol. [30] The prevalence of smoking was noted to grow incrementally with quantity of alcohol consumed, which reflects that these two habits often co-exist.[5]

Because heavy drinkers are usually smokers, it is difficult to separate out the effects of these two behaviors. In addition to being an independent risk factor for CP, the pathophysiologic effects of cigarette smoking on the pancreas seem to be greatest for patients with alcohol-related CP, which supports the theory that smoking enhances the effects of alcohol consumption.[5] In a case-control study that compared patient variables between 103 male patients with alcoholic cirrhosis of the liver, 145 with CP patients and 264 control participants, 94% of the CP patients were both smokers and drinkers compared with 83% of liver cirrhosis patients.[6] While drinking alcoholic beverages was a risk factor for both conditions, smoking was selectively related to the development of CP and the average age at onset of pancreatitis was lower among smokers than non-smokers. In the NAPS2 study, when an analysis was performed after stratification of subjects as ever and never drinkers, a disproportionate increase in the OR for CP was observed in ever when compared with never drinkers. A similar observation for the association for alcohol was noted in ever when compared with never smokers. Although a formal interaction analyses was not significant, likely due to small number of very heavy drinkers and smokers, these analyses suggest that the effects of smoking and alcohol are likely synergistic. Combined effect of smoking and

alcohol was also evaluated in patients with established alcoholic CP in a retrospective five-country study. Among 934 individuals with chronic alcoholic pancreatitis patients, the diagnosis came an average of 4.7 years earlier in smokers than in non-smokers ($p = 0.001$). [31]

Smoking and Progression of Pancreatitis

AP, recurrent acute pancreatitis (RAP) and CP are believed to represent a disease continuum. After the first episode of AP, about 20% patients develop one or more recurrences and about 20% patients with RAP transition to CP.[32,33] Although the majority of patients with CP have one or more episodes of AP during their disease course, a small subset can have only abdominal pain without AP, or can be asymptomatic with/without exocrine and/or endocrine insufficiency.

A population-based study from Germany investigated the circumstances that influence the progression of pancreatitis from the acute to the chronic stage.[34] Over 20 years, they assessed the development of CP and all-cause mortality among 532 individuals (289 men, 243 women) who were hospitalized for an initial attack of AP and were followed up for an average of 7.8 years. Nineteen (4%) individuals progressed to have CP, and all were alcoholics. Information on tobacco exposure prior to the first attack of AP was available for 73% of the alcoholics. Among this subgroup, heavy smoking (>30 cigarettes/day) was associated with a higher risk of developing CP (log-rank $p=0.011$). The association remained significant after adjustment for age, gender, and usual alcohol consumption level before the first-attack (hazard ratio, HR 4.30, 95% CI 1.11–6.6). In another US based population study of 7456 patients, the risk of RAP (HR 1.47, 95% CI 1.30–1.67) and CP (HR 1.76, 95% CI 1.30–2.39) were noted to be significantly higher among subjects who were tobacco abusers after controlling for demographic factors and etiology.[35]

The effect of smoking on disease progression has also been assessed in patients with established CP. Tobacco smoking was noted to significantly increase the risk of pancreatic calcifications (HR 4.9, 95% CI 2.3–10.5 for smokers versus non-smokers) and to a lesser extent the risk of diabetes (HR 2.3, 95% CI 1.2, 4.2) during the course of alcoholic CP.[31] A study evaluating the effects of smoking on nonalcoholic idiopathic CP among 83 Italian and 83 Swiss patients found that smoking increased the risk of pancreatic calcifications and shortened the time to appearance of these calcifications among Italian patients.[36] Additionally, smoking >1 pack/day was associated with the incidence of diabetes (HR 3.94, 95% CI 1.14–13.6). Another study examined factors related to cigarette smoking and early or late-onset idiopathic CP in 66 patients diagnosed between 1976 and 1982 who were then followed until 1985.[37] In late-onset idiopathic CP, smokers developed pancreatic calcifications faster ($p < 0.001$) and more frequently (83 vs. 13%, $p < 0.001$) than nonsmokers, independent of gender, body mass index, and exocrine or endocrine insufficiency.

In summary, smokers have an increased risk of both a relapse of AP and of developing CP, and smoking accelerates the morphological and functional changes in patients with established CP.

Smoking related changes in the Pancreas in asymptomatic individuals

At a tissue level, cigarette smoking has been shown to cause parenchymal changes that are similar to those seen in CP. In a study that evaluated 111 autopsy specimens in subjects with no history of excessive drinking (>21 drinks/week in men, >14 drinks/week in women) or pancreatic disease, ever smoking was associated with increased total and intralobular pancreatic fibrosis.[38] In another study of 2,614 patients who underwent endoscopic ultrasound for an indication unrelated to pancreaticobiliary disease, patients who were cigarette smokers were more likely to have hyperechoic parenchymal foci.[39] Patients who drank alcohol, even at low levels, also showed pancreatic changes, indicating that alcohol and cigarette smoking may cause pancreatic injury prior to being clinically recognized. We have also recently learned that past and current smokers have decreased pancreatic bicarbonate secretion, indicative of duct cell secretory dysfunction, when compared to never smokers. Using endoscopic pancreatic function testing, the risk of low peak bicarbonate flow in smokers was slightly greater than twice (RR 2.2) that of never smokers among a group of 131 individuals evaluated for pancreatic disease at a tertiary pancreas center.[40] The cellular mechanism of how cigarette smoke reduced secretion was not determined. Excessive alcohol consumption and alterations to the gene encoding the cystic fibrosis transmembrane conductance regulator (CFTR) are known causes of pancreatitis. One recent investigation determined that alcohol disrupted expression and localization of CFTR, resulting in reduced secretion of pancreatic fluid and bicarbonate, leading to development of pancreatitis.[41] It is interesting to speculate that cigarette smoke toxins may reduce pancreatic secretion through a similar mechanism, by disrupting CFTR.[42]

Physicians Underestimate the Impact of Cigarette Smoking

There is definitive variation among physicians in the recognition of smoking as a risk factor for pancreatitis. In the NAPS2 study evaluating 19 US academic medical centers, smoking status as well as amount and duration of smoking were recorded. While 71.4% of CP patients reported being current or previous cigarette smokers, physicians reported that smoking was a risk factor in fewer than half (45.3%, 173/382) of these self-identified ever smokers. Additionally, physicians identified smoking as a CP risk factor among 53% of current smokers, 49.8% of heavy smokers and in 54.5% of patients whose etiology was described as being alcohol.[43] These findings highlight the need for educating physicians and the public on the potential benefits of smoking cessation.

Mechanistic links between smoking and pancreatitis

Animal Models of Smoking-related Pancreatitis

The cellular mechanisms through which smoking causes pancreatitis remain vague. From a scientific perspective, it has been difficult to develop appropriate animal models to explore relevant pathways, as cigarette smoke contains more than 4000 chemicals, over 60 of which have been acknowledged as carcinogens.[44] With such a range of toxins, it is challenging to distinguish which components may initiate pancreatitis or sensitize the pancreas to development of the disease. A small number of animal models looking at effects of cigarette smoke and its toxins on the pancreas have been established.[45–62] Some have assessed effects of whole tobacco smoke whereas others focused on specific constituents, including

nicotine, the tobacco specific nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), and other NNK derivatives.[45,61–66] Polycyclic aromatic hydrocarbons (PAHs) are also toxic components of smoke although their potential role in pancreatic disease has not been sufficiently explored.[41,67] In this next section we will give an overview of these models and discuss what has been learned recently about cellular events and mechanisms that may participate in smoking-mediated pancreatitis.

Cigarette smoke exposure

In an early model of smoking-related pancreatitis in rats, animals exposed to high-dose smoke tobacco smoke (160mg/m³) for up to three months incurred pancreatic damage comparable to CP. Elevated levels of pancreatic zymogens trypsinogen and chymotrypsinogen and focal pancreatic lesions demonstrating areas of amplified extracellular matrix accompanied the injury. Pancreatic injury was less severe than that observed in CP in humans, although this could have been related to the short duration of the rodent study. [61] Another report observed that levels of trypsinogen were elevated in smoke-exposed animals whereas its endogenous inhibitor (pancreas-specific trypsin inhibitor; PSTI) was not. With this protective mechanism compromised, smoke-exposed animals were noted to be more predisposed to pancreatitis.[62] Another study demonstrated that cigarette smoke exposure worsened pancreatic ischemia initiated by ethanol.[59] In addition, cigarette smoke alone increased leukocyte-endothelium interactions and, upon combination with ethanol, increased pancreatic sequestration.[59] These models thus defined a synergistic effect of smoking with alcohol and further supported clinical observations.

Models with cigarette smoke treatment have made evident the existence of biochemical and morphological effects on the pancreas but they have uncovered little about the specific components of tobacco and the pathological cellular mechanisms potentially activated in the course of the disease. In the subsequent sections, we describe studies that have focused on potent constituents of cigarette smoke, namely nicotine and its metabolite NNK, and we further explore underlying cellular pathways that may participate in pancreatitis.

Nicotine exposure

Nicotine is a significant constituent of tobacco and cigarettes and potentially mediates the development of pancreatic disease. A number of rodent models exploring the effects of nicotine on the pancreas have been implemented. When rats were given ³H-nicotine it accumulated in their pancreas and intestine, demonstrating that cigarette toxins can become concentrated in the pancreas.[48,54] Nicotine exposure (either to whole animals or isolated acinar cells) resulted in morphological changes in the exocrine pancreas including cytoplasmic swelling, vacuolization, pyknotic nuclei and karyorrhexis.[45,50,55,68] The pathological changes observed in these studies reflect those seen in AP.[45]

Nicotine has also been found to alter pancreatic secretion. In rats, nicotine exposure resulted in decreased pancreatic amylase secretion, particularly after cholecystokinin (CCK) stimulation, and increased retention of pancreatic pro-enzymes.[47,50,52,57,60,68] Furthermore, a recent study has shown that the secretory effects induced by nicotine in

isolated rat acini are abolished upon treatment with a nicotinic receptor antagonist and calcium channel antagonists.[57] These pharmacologic findings indicate that the nicotine effect could be initiated through a nicotinic acetylcholine receptor (nAChR) and calcium is a downstream effector of these events. Nicotine has also been shown to alter circulating levels of the hormones gastrin and CCK in rats;[51] such changes have been linked with the morphological damage which occurs during pancreatitis.[48,58] Oxidative stress and lipid peroxidation are also modulated by nicotine, and these processes might be involved in the pathophysiology of pancreatitis.[58]

NNK

The tobacco-specific nitrosamine known as nicotine-derived nitrosamine ketone (NNK), constitutes one of the most toxic carcinogens found in tobacco and related products.[69] Other nitrosamines include N'-nitrosornicotine (NNN) and diethylnitrosamine (DEN), although they are somewhat less toxic than NNK.[70] Previous studies assessing the effects of NNK on the pancreas have focused on its potential involvement in pancreatic cancer, [71,72] but a role in pancreatitis has recently been considered.[73]

Alexandre et al were the first to define effects of NNK on AP responses in rats using isolated acinar cells and *in vivo* models of pancreatitis.[73] They showed that NNK, at levels a smoker would likely be exposed to, caused premature activation of digestive zymogens (trypsinogen and chymotrypsinogen) within the acinar cell, a key initiating event in pancreatitis. Cerulein is an orthologue of the hormone cholecystokinin (CCK) and, when given to isolated cells or animals in supraphysiologic concentrations (10–100x that which are required to induce physiological responses), causes experimental pancreatitis. Pre-treatment of cells or animals with NNK in a cerulein model of the disease lead to elevated activation of zymogens above that seen solely with NNK or cerulein treatment. NNK was also shown to cause cellular injury in the pancreas (vacuolization, pyknotic nuclei, and edema) after a two-week treatment period in rats. By using these models, Alexandre et al. were able to further explore underlying mechanisms of these NNK-mediated effects in the pancreas. Those findings and additional mechanistic studies are outlined below.

Underlying Cellular Mechanisms of Smoking-related Pancreatitis

This section focuses on NNK-mediated mechanisms in smoking-related pancreatitis and highlights potential signaling pathways that should be considered when developing therapies for the disease.

β -adrenergic receptors

NNK structurally resembles classic β -adrenergic agonists, such as adrenaline and noradrenaline, and binds with high affinity to human β -1 and β -2 receptors (EC_{50} for β 1= 5.8 nM; EC_{50} for β 2 = 128 nM).[74] In most mammalian cells, activation of β -adrenergic receptors causes elevations of the intracellular second messenger, cAMP, which mediates some pancreatitis responses including zymogen activation and secretion.[75] Alexandre et al identified β -1 and β -2 adrenergic receptors in rat acini through PCR analysis, although pharmacologic inhibition of these receptors with the β -blocker propranolol did not block

NNK-mediated zymogen activation.[73] Whether these receptors contribute to other pancreatitis responses is currently unresolved.

Nicotinic acetylcholine receptors (nAChRs)

In previous studies examining nicotine's effects in pancreatic acinar cells, nicotine-mediated secretion was abrogated by the nicotinic acetylcholine receptor (nAChR) blocker mecamylamine, implicating this receptor as a potential target.[57] NNK is also capable of binding with high affinity to nAChRs, particularly the α -7 isoform (EC_{50} = 0.03 μ M). Although nAChRs were primarily described in the nervous system, they have since been identified in non-neuronal cells.[70] The study from Alexandre et al detected α -7 nAChR in rat acini by PCR analysis.[73] Pre-treatment of isolated acini with mecamylamine nullified NNK-mediated zymogen activation, highlighting a role for α -7 nAChR in smoking-related pancreatitis. This potential role was further emphasized by studies in which NNK-induced zymogen activation was absent in α -7 nAChR^{-/-} mice versus the wild type.[76] These findings are the first to characterize a direct effect of a cigarette toxin on the acinar cell in initiating pancreatitis responses through a receptor-mediated mechanism. Whether other stages of NNK-induced pancreatitis are potentiated through α -7 nAChR remains a topic for future research.

Inflammation

NNK and nicotine may, in part, mediate the risk of pancreatitis through the activity of inflammatory cells. Nicotine binds to α 7nAChR localized on macrophages and inhibits production of pro-inflammatory cytokines by blocking the NF κ B pathway, which is involved in macrophage activation.[77,78] Furthermore, blockage of α -7 nAChR in mice with mecamylamine increased disease severity during experimental pancreatitis and reduced passage of neutrophils and macrophages to pancreatic tissue.[79] In another investigation, both prophylactic and delayed-therapeutic treatment with nicotine diminished severity of acute experimental pancreatitis via stimulation of the cholinergic anti-inflammatory pathway.[80]

Ultimately though, extended exposure to cigarette smoke causes chronic inflammation in the pancreas, suggesting that an anti-inflammatory effect may only be a transient response which switches to a chronic inflammatory phase.[81] Such pro-inflammatory effects of NNK may occur through absorption and metabolism of NNK by macrophages. This process, known as "bioactivation," is further detailed in the next section. In U937 human macrophages, bioactivation of NNK caused NF κ B activation and release of TNF α , promoting an inflammatory response.[65] Therefore, in terms of pancreatitis, it would seem that NNK-signaling can induce early events through direct interaction with α -7nAChRs on the acinar cell (zymogen activation, cell damage) and macrophages/neutrophils (anti-inflammatory) whereas later pro-inflammatory responses may be a result of NNK uptake and metabolism by macrophages.

Bioactivation

It is uncertain whether bioactivation of NNK takes place in pancreatic acinar cells and influences smoking-related pancreatitis. Cytochrome P450 (CYP 450) enzymes (isoforms

2B6, 3A5 and 2A3) responsible for bioactivation of NNK, have been discovered in rodents, although there have been ambiguous findings in human pancreas [71]. Cytochemical techniques could not locate CYP450 enzymes in pancreatic samples from smokers and non-smokers.[41] Immunohistochemical methods, however, detected CYP450 enzymes in human pancreatic tissue, with elevated levels in samples from patients with CP and pancreatic cancer.[82] Therefore NNK uptake and metabolism within pancreatic cells could contribute to smoking-related pancreatitis and other pancreatic diseases.

More recent findings have demonstrated effects of NNK within the pancreatic acinar cell at the genetic level [83], although whether this is via a “bioactivated” derivative of NNK or another pathway is unknown. The vitamin thiamin is crucial for pancreatic function and pancreatic cells sustain high levels via uptake from their environment through thiamin transporters-1 and -2 (THTR-1 and THTR-2). One study looked at the effects of NNK on pancreatic thiamin uptake and found that protein and mRNA levels of THTR-1 and THTR-2 were significantly decreased when pancreatic acinar 266-6 cells were exposed to NNK. These changes were linked with a reduction in thiamin uptake and thiamin transporter promoters- SLC19A2 and SLC19A3. Long-term treatment (2 weeks) of NNK in mice gave similar findings.[83] This study demonstrates that cigarette toxins can alter pancreatic function at the genetic level causing, in this circumstance, thiamin deficiency. Thiamin deficiency, followed by a decline in cellular ATP concentration, could leave the pancreas vulnerable to a secondary insult, resulting in pancreatitis.

Conclusion

Smoking is now an established risk factor for all forms of pancreatitis. The relationship between smoking and pancreatitis is dose dependent and its effects are more pronounced in the presence of alcohol consumption. Smoking is associated with progression of disease. Efforts are needed to increase awareness of the effects of smoking on pancreatitis among physicians as well as in the general public as smoking cessation has the potential for primary as well as secondary prophylaxis in pancreatitis.

Data on the pathogenesis of smoking-related pancreatitis is scarce. Developing trustworthy human and animal models of the disease is necessary if successful therapies are to be employed in its treatment. Models focusing on tobacco toxins, such as nicotine and NNK, have identified promising cellular targets and pathways. In addition, cigarette smoke toxins may combine with other environmental and/or genetic factors to further promote pancreatic injury. Studies designed to investigate how smoking alone, or in combination with other factors, mediates pathological pancreatic processes will improve our understanding of mechanisms in smoking-induced pancreatic diseases.

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Table 1

Key epidemiologic observations on the relationship between smoking and pancreatitis

1	Smoking is an independent and dose-dependent risk factor for acute and chronic pancreatitis.
2	The effects of smoking may be enhanced in the presence of alcohol consumption.
3	Smoking is associated with progression of all forms of pancreatitis.
4	Physicians often underestimate the role of smoking in pancreatitis.
5	Smoking cessation has the potential for primary and secondary prophylaxis in pancreatitis.

Table 2

Mechanisms of smoking and pancreatitis

Pancreatitis Response	Cause	Tentative cellular mechanism
Morphological changes	Cigarette smoke/nicotine/NNK	Unknown
Acinar cell secretion	Nicotine	$\alpha 7$ nAChR? Ca ²⁺ signaling? Blockers of nAChR and Ca ²⁺ channels abrogate nicotine-mediated secretory effects
Duct cell secretion	Cigarette smoke toxins?	Pancreatic secretion from duct cells is reduced by smoking Alcohol (a cause of pancreatitis) disrupts expression/localization of CFTR causing reduction in secretion Smoking may mediate effect through similar mechanism
Zymogen activation	NNK	$\alpha 7$ nAChR; blockage of nAChR abrogates NNK-mediated zymogen activation
Anti-inflammatory	Nicotine/NNK	$\alpha 7$ nAChR localized on macrophages Nicotine/NNK binds to receptor and initiates signals to prevent an inflammatory response Blockage of nAChR increases macrophage infiltration of pancreatic tissue during experimental pancreatitis
Pro-inflammatory	Nicotine/NNK	Bioactivation: NNK is absorbed and metabolized by macrophages Initiates pro-inflammatory signals May lead to chronic inflammation seen during the course of pancreatitis
Thiamin deficiency/loss of mitochondrial function	NNK	Bioactivation: NNK may be absorbed and metabolized by the pancreatic acinar cell; NNK metabolites can effect changes at the level of gene transcription NNK has been shown to reduce levels of the thiamin transporters-1 and -2 (THTR-1 and THTR-2) leading to thiamin deficiency It is unclear whether "bioactivated" NNK mediates this process Thiamin deficiency can lead to mitochondrial dysfunction and reduction in ATP levels, conditions which can predispose to pancreatitis