The Emerging Role of Smoking in the Development of Pancreatitis

Martine Alexandre^{a, c} Stephen J. Pandol^d Fred S. Gorelick^{a–c}
Edwin C. Thrower^{a, c}

^aDepartment of Internal Medicine, Section of Digestive Diseases, and ^bDepartment of Cell Biology, Yale University School of Medicine, New Haven, Conn., ^cVeterans Administration Connecticut Healthcare, West Haven, Conn., and

^dSouthern California Research Center for Alcoholic Liver and Pancreatic Diseases, Veterans Affairs Greater Los Angeles Health Care System and University of California, Los Angeles, Calif., USA

Key Words

Acute and chronic pancreatitis • Zymogen activation • Cellular injury • Nicotine • NNK • Tobacco smoking

Abstract

Background/Aims: Cigarette smoking has been linked to many diseases, including pancreatic cancer and more recently, pancreatitis. **Methods:** Electronic searches of primarily PubMed from 1990 to August 2011 were conducted and only articles published in English were reviewed. Original articles and reviews were selected based on screening of article abstracts and their relevance to tobacco smoking, its components, nicotine and its metabolites, and their effects particularly on the pancreas. **Results:** Smoking may affect the risk of developing chronic pancreatitis or its progression. Smoking may also affect the risk for developing acute pancreatitis. Its effects in pancreatitis appear to be dose dependent and its effects may be alcohol independent but synergize with alcohol. **Conclusion:** Specific constituents of cigarette smoke, including nicotine and its metabolites, could mediate effects on the pancreas.

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Smoking as an Independent and Dose-Dependent Risk Factor for Acute and Chronic Pancreatitis

Although numerous studies have shown that cigarette smoking increases the risk of developing pancreatic cancer, its contribution to the development of pancreatitis has only been appreciated recently. Many, but not all studies have identified tobacco smoking as a risk factor for developing chronic pancreatitis or as a factor that modifies disease phenotype and progression [1, 2]. Recent reports have demonstrated a direct relationship between the level of cigarette smoking and risk of developing pancreatic disease. The inclusion of subjects who smoked, but did not abuse alcohol, has helped to show that cigarette smoking can act as an independent risk factor for developing disease. More surprising has been the observation that cigarette smoke could also increase the risk of developing acute pancreatitis [1]. Although clinical advances have identified a role for cigarette smoke in the development of pancreatitis, there are little experimental data relating to its disease mechanism [3, 4]. In this review we summarize advances in both clinical and basic science research regarding the role of cigarette smoking and pancreatitis.

Clinical Evidence

Many clinical studies have implicated cigarette smoking in the progression of alcohol-related and chronic pancreatitis. A retrospective cohort study of chronic alcoholic pancreatitis showed that cigarette smoking affected the age at diagnosis and disease progression. The average age at diagnosis in smokers compared to nonsmokers was about 5 years earlier; smoking also significantly increased the risk of developing pancreatic calcification [5]. This study supported an earlier French study, which found that smoking correlated with a younger age at the time of diagnosis for chronic pancreatitis; on average, men were 41 years of age compared to 52 years of age in nonsmokers. The study also found that tobacco appeared to have an additive effect with alcohol on the risk for chronic pancreatitis [6]. However, others have interpreted these findings with caution, given that many of the smokers were also heavy drinkers, compared with nonsmokers [7]. Thus, the two groups under comparison had differences in two variables: alcohol intake *and* tobacco consumption. In addition, for a relatively large subset of the sample, no data were available for alcohol consumption (27%) or smoking habits (20%) [7]. In a separate study, which had controlled for alcohol consumption, no association was found between smoking and pancreatitis [7, 8]. However, as the participants in this study were very heavy drinkers, smoking may not have additionally impacted their risk for developing pancreatitis compared to individuals who drank less [1].

More recently, however, data emerging from several case-control and cohort studies strongly support an independent association between smoking and pancreatitis [1, 2, 9–12]. Key findings from these studies are shown in table 1. All studies conclude that the risk of developing chronic pancreatitis is increased by smoking independently of alcohol (table 1). For example, a recent US study showed that compared to never-smokers, the relative risk (OR) for developing chronic pancreatitis in smokers with <12 pack years was 1.34 (95% CI 0.90–2.01), with 12–35 pack years it increased to 2.15 (95% CI 1.46–3.17) and with >35 pack years, the OR increased to 4.59 (95% CI 2.91–7.25). In a stratified analysis, there was a direct relationship between the level of smoking and chronic pancreatitis for both men and women, whites and ‘ever drinkers’ (lifetime consumption of >20 alcoholic drinks) but not blacks. While there was a trend toward increased risk in blacks, the OR confidence intervals also increased, possibly due to the small number of black subjects [2].

A Danish population study with a mean follow-up of 20.2 years not only demonstrated a dose-dependent association between smoking and chronic pancreatitis, but identified a similar association with acute pancreatitis [1]. Another novel finding from this study was the risk for developing acute pancreatitis for former smokers was elevated (1.7; 95% CI 1.0–2.7), compared to those who had never smoked [1]. However, this study did not document the degree of smoking by former smokers (e.g. mild, moderate or heavy) or duration of smoking abstinence, both of which could affect risk. A more recent study, however, has focused on these factors and revealed that it is *duration* of smoking, rather than smoking intensity, that elevates the risk for non-gallstone-related acute pancreatitis. Two decades after smoking cessation, the relative risk (RR) was reduced to levels comparable to that seen in never-smokers (RR 1.20, 95% CI 0.66–2.15) [13]. Although smoking cessation altered the risk for acute pancreatitis, another study found that no significant risk was associated with former smoking in terms of chronic pancreatitis (OR 0.40, 95% CI 0.14–1.18) [11].

Although numerous clinical studies now support an independent role for smoking in pancreatitis, smoking is often not acknowledged by physicians as a risk factor for chronic pancreatitis. In a study of 535 patients diagnosed with chronic pancreatitis, 382 (71.4%) reported smoking, yet physicians listed smoking as a risk factor for only 173 (45.3%) patients. They were also more likely to do so if the patient was a current smoker, reported high levels of smoking and/or had a concurrent alcohol diagnosis [2, 14]. However, recognition of smoking as an independent risk factor, particularly for chronic pancreatitis, is becoming important for interventional purposes in light of these recent studies.

Although clinical studies have underscored the importance of smoking as an independent risk factor in development of pancreatitis, the underlying cellular mechanisms of smoking-related pancreatitis remain largely unexplored.

Animal Models of Smoking and Pancreatitis

To better understand the link between smoking and pancreatitis, a few animal models have been developed. Those that have been established expose rodents to cigarette smoke or its major component, nicotine. In one model of rat pancreatitis, tobacco smoke was delivered for 12 weeks and animals receiving high-dose smoke exposure (160 mg/m³) developed pancreatic damage with

Table 1. Summary of recent clinical studies on smoking as a risk factor in pancreatitis

Author	Type of study	No. of subjects total	Gender	Alcohol intake	Smoking status/ cigarette consumption	Observations
Talamini et al., 1999 [9]	case-control	1,330 CP = 571 Con = 700	M	0 to 80 g/day	0 to >10 cigarettes/day	CP patients drank and smoked more than controls Smoking (1–10 cigarettes/day) greater risk factor for CP than drinking 41–80 g alcohol/day
Lin et al., 2000 [10]	case-control	266 CP = 91 Con = 175	M	0 to ≥100 g/day	nonsmokers ^a ex-smokers current smokers mild moderate heavy	Smoking associated with an independent and dose-dependent increase in risk for CP Cigarette smoking associated with higher risk at two alcohol consumption levels (0–28, ≥29 g alcohol/day)
Tolstrup et al., 2009 [1]	cohort	17,905 P = 235	M, F	Abstainer <7 to >20 drinks/week	never ^b ex (former) current mild moderate heavy	A roughly 2–3-fold increased risk of pancreatitis associated with moderate and heavy smoking Dose-dependent association between smoking and P Former smokers showed elevated risk (~2-fold) for AP but not CP Alcohol intake associated with increased risk of P P cases (46%) attributed to smoking
Yadav et al., 2009 [2]	cohort (NAPS2)	1,695 CP = 540 RAP = 460 Con = 695	M, F	Abstainer <0.5 to ≥5 drinks/day	never ^c ever mild moderate heavy	Heavy smoking and alcohol intake are independent risk factors for CP Cigarette smoking was an independent, dose-dependent risk factor for CP and RAP
Law et al., 2010 [11]	cross-sectional	235 CP = 79	M, F	Abstainer 0 to ≥10 drinks/week	never ex-smoker current	Current smoking but not former smoking significantly associated with CP Approximately 2-fold increased risk associated with current smoking
Cote et al., 2011 [12]	epidemiological (NAPS2)	1,234 CP = 539 Con = 695	M, F	Abstainer <0.5 to ≥5 drinks/day	never ^c ever mild moderate heavy	Independent association between smoking and idiopathic CP
Sadr-Azodi et al., 2011 [13]	cohort	84,667 AP = 307	M, F	0 to ≥400 g/month	never ^d former current	Duration of smoking increases risk for non-gallstone-related AP Two decades of smoking cessation decreases risk for AP

CP = Chronic pancreatitis, AP = Acute pancreatitis, Con = controls, P = pancreatitis (acute and chronic), RAP = recurrent acute pancreatitis; M = males, F = females.

^a Mild (<20 cigarettes/day), moderate (20–39 cigarettes/day), heavy (≥40 cigarettes/day).

^b Mild (1–14 g/day), moderate (15–24 g/day), heavy (>24 g/day).

^c Never (<100 cigarettes in lifetime), ever (>100 cigarettes in lifetime): mild (<12 pack years), moderate (12–35 pack years), heavy (>35 pack years); pack year = average number of cigarettes/day and duration of smoking.

^d Never (not defined), former (<20 or ≥20 pack years), current (<20 or ≥20 pack years).

Fig. 1. Pancreatic acinar cell damage in response to treatment with cigarette smoke components. Clinical and experimental evidence suggests that components of cigarette smoke, particularly nicotine, sensitize the pancreatic acinar cell to injury. Injurious responses include decreased amylase secretion, increased vacuolization and pyknotic nuclei. Alcohol has been shown to worsen smoking-related pancreatitis responses. Direct effects shown as black arrows; sensitizing effects shown as grey arrows.

features of chronic pancreatitis. In addition, elevated pancreatic levels of trypsinogen and chymotrypsinogen were increased. Furthermore, these animals developed focal pancreatic lesions with areas of increased extracellular matrix, although pancreatic damage was less compared to that seen in human chronic pancreatitis. These differences from human chronic pancreatitis may be due to the relatively short experimental period [15]. Another study reported that environmental tobacco smoke induced altered gene expression in the exocrine pancreas, which affected the ratio of trypsinogen to its endogenous inhibitor (pancreas-specific trypsin inhibitor; PSTI). Although trypsinogen was elevated in smoke-exposed animals, the expression of PSTI was not upregulated. These changes resulted in increased susceptibility of the smoke-exposed animals to pancreatitis [4].

Nicotine is a major component of tobacco and is rapidly absorbed through the lungs with an elimination half-life of 120–180 minutes [16]. Experiments with ^3H -nicotine have demonstrated a prominent accumulation in the pancreas and intestine of rats [17, 18]. Further, in samples of human pancreatic juice from smokers, metabolites of nicotine have been detected including cotinine (129–156 ng/ml) and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butane

(NNK) (1.37–600 ng/ml) [19]. In a rodent model, rats were exposed to graded doses of nicotine either by aerosol, intragastric or ad-libitum feeding over 3 to 16 weeks. Exocrine pancreatic cells from these animals showed cytoplasmic swelling and vacuolization, pyknotic nuclei and karyorrhexis. Furthermore, isolated acinar cells either treated with nicotine or harvested from nicotine-exposed animals showed a decreased secretory response and similar morphological changes to those described above. These changes are comparable to those seen in acute or experimental pancreatitis (fig. 1) [3, 20–24]. Nicotine has also been shown to affect circulating levels of gastrin and CCK in rats [22]. In this context, studies have linked changes in basal levels of GI hormones, and serum enzymes such as amylase and lipase, with the morphological changes of pancreatitis [17, 25]. Nicotine has also been shown to modulate oxidative stress and lipid peroxidation and these processes might be involved in the pathophysiology of acute and chronic pancreatitis [26].

The nicotine metabolite, NNK, is one of the most abundant and potent tobacco-specific carcinogens. Studies of NNK and the pancreas have focused on its effects in pancreatic cancer, but a role in pancreatitis has not yet been determined [27, 28]. NNK has been found to bind with high affinity to human β -1 and β -2 adrenergic receptors (β 1R; β 2R) and the α 7 nicotinic acetylcholine receptor (α 7nAChR) (EC_{50} for β 1R = 5.8 nM; EC_{50} for β 2R = 128 nM; EC_{50} for α 7nAChR = 30 nM) [29, 30]. Additionally, non-neuronal α 7nAChRs have been shown to be upregulated in the organs of smokers, and experimentally in the pancreas and lungs of rodents upon chronic exposure to nicotine or NNK [30, 31]. Whether these receptors play a role in smoking-related pancreatitis remains to be investigated.

Approach to Studies Investigating the Mechanism of Smoking-Induced Pancreatic Injury

As with other forms of pancreatitis, a key assumption is that understanding the mechanism of disease will provide opportunities for the development of therapeutic strategies for pancreatitis. Further, finding key steps in the mechanism of smoking-induced disease will lead to better understanding and potential treatments of all forms of pancreatitis. At this time, there is very little information on the pathogenesis of smoking-induced pancreatitis compared to other forms of the disease including those related to alcohol abuse, gallstones and lipid disorders.

There are a host of issues that must be addressed to develop research approaches for smoking-induced pancreatic injury that are meaningful and lead to potential treatments. Overall, data from improved animal models, as well as human studies, will be important cornerstones for advancing our understanding of the disease.

Because cigarette smoke is a complex mixture of compounds, the development of reliable animal models must consider which compounds and mixtures most likely are responsible for human disease. Further, the route of administration (i.e. inhalational vs. systemic), dosing and combinations of smoke compounds with ethanol administration are all issues that need to be considered to best approximate the human model/experience. It is also likely that there will be animal species and strain differences in pathologic responses that will emerge as the field develops. One cannot propose a specific model at this time because of the limited amount of information available. However, as research progresses in this area, there will be findings that help improve models that provide meaningful information.

The pancreas and its cellular constituents are unique in many respects compared to other organs [32, 33]. For example, the protein synthetic and export capacity of the exocrine pancreas and its acinar cell far exceed that of any other organ. The ductal system has a unique ability to generate fluid with very high concentrations of bicarbonate for transporting digestive enzymes to the small intestine. Disorders in protein synthesis, processing, trafficking and secretion from the acinar cell and water and bicarbonate secretion from the duct cell are implicated in the pathobiology of pancreatitis. These unique functions

of the exocrine pancreas may present specific vulnerabilities to smoking compounds not encountered in other organs [34]. As is becoming evident with respect to alcohol, there may be other environmental and/or genetic factors that may promote pancreatic injury with smoking. Studies designed to reveal how smoking alone, or in combination with other environmental or genetic factors, affects key cell biologic processes will allow the most important insights into the mechanism of smoking-induced pancreatic damage.

There are well-identified roles for the pancreatic circulation, immune system, nervous system and stellate cells in the mechanism of pancreatitis [35, 36]. It is highly likely that all of these pancreatic constituents play key roles in development of pancreatic disease with smoking. However, well-designed and relevant research studies will reveal which ones play central roles in the initiation and promotion of pathologic processes.

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