HHS Public Access

Author manuscript

Curr Opin Gastroenterol. Author manuscript; available in PMC 2019 July 23.

Published in final edited form as:

Curr Opin Gastroenterol. 2018 September ; 34(5): 355–361. doi:10.1097/MOG.0000000000000466.

Myths and Realities about alcohol and smoking in chronic pancreatitis

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Abstract

Purpose—Alcohol and smoking play an important role in pancreatitis. This review will address the myths and evidences about alcohol and smoking with pancreatitis to help improve the approach of health care professionals when managing of these patients.

Recent Findings—There is a growing recognition that chronic pancreatitis is a multifactorial disease. Eliciting an accurate history of alcohol consumption and smoking from patients, and if necessary, family members, can help determine their contribution to the patient's disease. In the absence of a convincing history, physicians should be open to consideration of other etiologies. The amount and duration of alcohol consumption is the most important determinant in increasing pancreatitis risk. Alcohol sensitizes the pancreas to other insults or injury and promotes disease progression. Smoking is an independent risk factor or chronic pancreatitis and has synergistic pathogenic effects with alcohol. The natural history of chronic pancreatitis is highly variable. A patient with alcoholic pancreatitis can have symptoms, recurrences or exacerbations from disease-related complications or non-pancreatic causes. Novel strategies are needed to enable patients quit smoking.

Summary—Obtaining accurate history, appropriate evaluation and management can help to achieve meaningful improvement in symptoms in patients with chronic pancreatitis. Abstinence from alcohol and smoking cessation, when applicable, should be recommended in all patients to prevent disease recurrences and progression.

Keywords

Pancreatitis; abstinence; cessation; drinking; risk

Introduction

The relationship between alcohol and pancreatitis is known for over a hundred years. While there was initial skepticism that smoking also contributed to chronic pancreatitis, the association between smoking and pancreatitis is now well-established. Despite these known associations, physician routinely come across patients who do not fit into the "typical

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clinical profile" of chronic pancreatitis. This review aims to highlight some of the prevailing myths about the association of alcohol and smoking with pancreatitis. We hope to dispel these myths with empiric data, where available, and suggest areas where further research is needed.

MYTH #1: Chronic Pancreatitis patients are all alcoholics.

This concept is the residual effects of the dogma of previous generations when alcohol was the only identifiable risk factor for chronic pancreatitis in the majority of patients. In many medical and surgical subspecialties this misperception prevails, with substantial negative consequences. Preconceived notions can affect a physician or healthcare professionals' approach and interactions with patients, their ability to consider a thorough work up for other potential etiology or the cause of symptoms, and an opportunity to choose a therapy that may result in meaningful improvement in the condition. It is not uncommon to come across patients who are believed to be underreporting their drinking or are labeled as *closet alcoholics*.

The proportion of patients in whom alcohol was identified as the primary cause in several recent large cross-sectional studies from the US, Europe and Japan range from 44–68% (Table 1)[1–7]. In other words, in 32–56% patients, alcohol was not considered to be the major factor for the patient's disease – of particular importance being that only a minority of all cases among women are explained by alcohol. In developing countries, although alcohol-related pancreatitis appears to be on the rise, the majority of cases are related to idiopathic or genetic causes[8–10]. Finally, there is growing recognition of pancreatitis as a distinct disease in children, in whom alcohol is rarely a factor in disease causation[11, 12].

The evolving conceptual framework is that chronic pancreatitis is a multifactorial disease – while alcohol is the most commonly identified risk factor, environmental factors other than alcohol, genetics and other known or yet unknown factors may be important in subsets of patients[13].

Reality: Pancreatitis is a multifactorial disease. Alcohol is the most commonly identified risk factor for chronic pancreatitis, but many cases of chronic pancreatitis may occur independent of any alcohol.

MYTH #2: Alcohol *causes* pancreatitis.

Interestingly, administration of alcohol alone, irrespective of dosage, is unable to elicit pancreatitis responses in experimental and animal models[14]. The most commonly used model is hyperstimulation with cholecystokinin or its analogue caerulein, where supraphysiologic doses of these agents are needed to initiate pancreatitis responses. However, in the presence of alcohol, these agents can initiate pancreatitis even with physiologic doses. This observation has led investigators to suggest that heavy alcohol consumption "sensitizes" the pancreas to another injury or insult[15–17].

Effects of chronic alcohol consumption on the brainstem result in adaptive responses in the neurohormonal control of pancreatic secretion to maintain normal pancreatic enzyme output despite inhibitory effects of alcohol on neurohormonal reflexes. Sudden withdrawal of

alcohol from rodents that have adapted to continuous elevated blood levels of alcohol can lead to sudden release of the inhibitory effects of alcohol on pancreatic secretion resulting in pancreatic hyperstimulation[18], which can cause acute pancreatitis. In one well-conducted human epidemiologic study, 69% patients with first-attack of alcoholic pancreatitis were noted to have stopped drinking shortly before developing the first symptom – in 33% between 7–24 hours, and 28% more than 24 hours before the onset of symptoms[19]. Interestingly, 54% reported that they had stopped continuous drinking before the start of acute abdominal pain.

Alcohol also has effects on the pancreas at many other levels. Some of these include facilitation of pancreatic injury through signaling pathways, non-oxidative metabolism to form fatty acid ethyl esters which could lead to mitochondrial toxicity, activation of pancreatic stellate cells directly or through other mechanisms,the way pancreas responds to stress, and how alcohol alters the immune response to injury. These effects explain greater severity of alcohol-related acute pancreatitis, and its progression to chronic pancreatitis. A detailed discussion of these is beyond the scope of this article, and the reader is referred to excellent reviews on mechanisms of alcohol-related pancreatic disease and animal models of pancreatitis[14, 20, 21].

Reality: Alcohol does not *cause* pancreatitis directly. Heavy alcohol consumption has a variety of effect on the pancreas, brain and the immune system. These effects *sensitize* the pancreas to injury and promote disease progression after initiation of pancreatic injury.

MYTH #3: Most people who drink heavily develop pancreatitis.

The absolute risk of pancreatitis with alcohol consumption was evaluated in two studies using different study designs. In a study of 1,409 veterans who received care in the Veterans Administration System and attended an outpatient detoxification clinic for alcoholism, prevalence of pancreatitis diagnosis was used as a surrogate for lifetime risk. In these veterans, the prevalence of pancreatitis diagnosis at any time during their care was 5.9% for any, 4.7% for acute, and 3.0% for chronic pancreatitis. This prevalence was ~6 folds greater when compared with the prevalence of any (0.98%), acute (0.76%) and chronic (0.41%) pancreatitis diagnosis in 59,378 veterans treated in the same healthcare system who did not receive an alcoholism diagnosis[22].

In a cohort study of 17,905 subjects who enrolled in the Copenhagen City Heart Study in Denmark from 1976 to 2007, during a mean of 20.1 years of follow-up, the overall risk of any pancreatitis was noted to be 1.3%[23]. Participants completed a detailed questionnaire at the time of ascertainment which included information about their drinking and smoking habits. The risk of pancreatitis increased with the amount of alcohol consumption – the absolute risk in subjects who reported drinking ≥5 drinks/day was ~2.9%, which was ~3 folds greater when compared to abstainers.

Two meta analyses have evaluated the risk of pancreatitis with the amount of alcohol consumption[24, 25]. Although a clear association is noted with higher amount of consumption, i.e. ≥4–5 drinks per day, the role of lower amounts of alcohol consumption is less clear and needs further study. One likely reason is an overall small increase in absolute

risk of disease at lower levels of consumption, thereby limiting power to detect statistical significance. Moreover, in addition to the amount and intensity of drinking, i.e. drinks on a drinking day, pattern of consumption, e.g. regular vs. binge drinking may also be important determinants in increasing the risk. We consider regular drinking at lower levels to be a co-factor in disease development and progression.

A recent provocative epidemiologic study, supported by experimental data, reported that smaller amounts of alcohol may even be protective for incident acute pancreatitis[26]. Whether there truly is a safe limit for alcohol consumption with regard to incident pancreatitis or in patients who have suffered an episode of mild non-alcohol related acute pancreatitis needs further study. Individuals who have had an episode of alcohol-related pancreatitis, and those with recurrent acute or chronic pancreatitis from any cause should be cautioned to avoid alcohol consumption, as even smaller amounts of consumption result in disease progression[27–29].

Since only a small fraction of heavy drinkers ever develop pancreatitis, there must be other co-factors that result in an individual's susceptibility to pancreatitis. These likely vary between individuals, and include known factors, such as smoking[30], hypertriglyceridemia[31], genetic polymorphisms (e.g. *CLDN2*, alcohol or aldehyde dehydrogenase)[32–34] or yet unknown factors. This concept is reinforced by findings that lifetime drinking habits and cumulative consumption do not differ significantly between alcoholics who do and do not develop pancreatitis[35].

How does environmental and genetic factors impact the clinical presentation and phenotype of pancreatitis? We agree with the hypothesis proposed by DiMagno et al that alcohol and tobacco affect the expression of disease, and that genetic susceptibility underlies the development of chronic pancreatitis[36]. An earlier age of onset of alcoholic pancreatitis than late-onset idiopathic chronic pancreatitis, and acceleration of disease course by alcohol and smoking demonstrated by them and others provides empiric data to support this hypothesis[36–39]. The age at presentation for genetic, early-onset and late-onset idiopathic chronic pancreatitis reflect the strength of underlying genetic influence, in that mutations with stronger effects result in an earlier age at the onset of symptoms/diagnosis (e.g. *PRSS1*, *SPINK1*, *CFTR*)[40] (Figure 1). Presence of environmental influences in these subjects will further reduce the age of presentation and accelerate disease course.

Reality: Clinical pancreatitis develops in ~5% of individuals who drink heavily. Consumption of ≥4–5 drinks per day increases the risk of developing pancreatitis. Regular consumption of alcohol at lower levels is likely a co-factor in disease development. Safe limit of alcohol consumption for incident pancreatitis is currently not established. Alcohol consumption affects the clinical presentation and course of disease.

MYTH #4: The risk of pancreatitis is lower with beer (or wine) drinking.

Studies have used different designs to assess the impact of beverage type on the risk of pancreatitis. In a cohort study of ~85,000 Swedish subjects followed for a median of 10 years, Sadr-Azodi et al reported that, when compared with wine or beer, the risk of incident acute pancreatitis was 1.52-fold greater for each increment of 5 drinks of spirits consumed

on a single occasion[41]. In another cohort study from Denmark, drinking 14 or more beers per week increased the risk of pancreatitis by 2-folds, but no association was noted with wine or spirits[23]. Similarly, case-control studies have also shown discordant results[42, 43]. In a Japanese study evaluating lifetime drinking habits among patients with alcoholic acute and chronic pancreatitis, beer drinking was less frequent among men when compared with women, and in patients with chronic pancreatitis when compared with those who had acute pancreatitis[29]. Epidemiology studies focusing on alcohol may also be confounded by diet, since in at least one study people who drank wine had a significantly healthier diet than people who drank beer[44]. Definitive studies on the relationship between beverage type with the risk of pancreatitis are awaited.

Alcohol consumption is universal and the type of alcoholic beverage consumed varies between and within geographic regions. However, occurrence of pancreatitis is not limited by geography. While beverage type may influence risk, we believe that the amount and duration of alcohol consumption is the most important determinant for the risk of pancreatitis.

Reality: The role of beverage type on the risk of pancreatitis needs further study. The amount of alcohol consumed likely has a far greater impact in the risk of pancreatitis than beverage type.

MYTH #5: Patients with alcoholic acute pancreatitis either have or will progress to chronic pancreatitis.

Historically, it was believed that acute pancreatitis in alcoholics was the first manifestation of pre-existing alcoholic chronic pancreatitis and that progression from acute pancreatitis to chronic pancreatitis was extremely rare[45]. In 1999 the Sentinel Acute Pancreatitis Event (SAPE) hypothesis was proposed as an alternative, suggesting that acute pancreatitis was an important starting point in the process leading to chronic pancreatitis[46]. Since then several studies followed the natural course after the first attack of acute pancreatitis and observed that a subset of patients clearly develop recurrences or transition to clinical chronic pancreatitis, and this risk is greater in patients with alcohol etiology[39]. Taking one representative population-based study from Germany as an example, the risk of a subsequent attack after an attack of acute alcoholic pancreatitis was 33%, and the risk of progression to chronic pancreatitis after one recurrence was 42%[47]. Equally important is to recognize that the risk of disease progression is directly linked to continuation of alcohol consumption after the initial presentation[27, 28].

Reality: Progression to chronic pancreatitis after an episode of alcoholic pancreatitis occurs in a subset of patients. The risk of disease progression is directly linked to continuation of alcohol consumption (and smoking).

MYTH #6: A patient with alcoholic pancreatitis is unlikely to give up drinking.

Although physicians and other health care professionals regularly counsel for abstinence from alcohol, they often feel that patients will not follow their advice and continue to drink. However, in published studies, a significant fraction of patients are noted to have stopped or

significantly reduced their drinking during follow up[27, 48]. The impact of continuing alcohol consumption on the natural history should be discussed with patients. It is important to offer structured services for counseling[49] and other professional services for alcohol rehabilitation.

Reality: Patients with alcoholic pancreatitis often stop or reduce their drinking, which is associated with a reduction in symptoms and disease progression.

MYTH#7. Most patients with chronic pancreatitis have chronic pain and are narcotic seeking.

The natural history of chronic pancreatitis is highly variable. Age at presentation or diagnosis, sex, etiology, genetic factors, and integrity of the pancreatic duct are important determinants of the natural history of disease. Patients may have episode(s) of acute pancreatitis interspersed with variable periods of pain or pain free intervals. The severity and temporal nature of pain can also be highly variable. Pain symptoms and acute pancreatitis attack(s) could be related to treatable causes, such as pancreatic ductal stricture and/or stones, local complications, etc. that can be addressed by available therapies. Therefore, an understanding of the natural history of disease is critical to making treatment decisions. It is also important to recognize that morphological findings may not always correlate with the presence, severity of temporal nature of pain[50].

In recent cross-sectional studies, the proportion of patients who reported having pain ranges from 63 to 86%, suggesting that a subset of patients were pain free at the time of assessment[2, 4, 6, 7, 50]. Variability of pain experience was captured in a large multicenter US study of >500 patients – in the year preceding enrollment, 16% patients reported no pain, 53% reported constant and 32% intermittent pain; pain was mild-moderate in 18% and severe 67% patients. Narcotics was used intermittently by 23% and constantly by 36%. Interestingly, the proportion of patients treated with narcotics is much lower in Europe (stronger opioids used in 31%)[6].

Reality: Understanding the natural history can help in making management decisions (also see Myth #8).

MYTH #8: Pain, disease flares and hospitalizations in patients with alcoholic pancreatitis are always related to ongoing alcohol consumption.

A patient with established alcoholic pancreatitis can be symptomatic due to disease-related manifestations independent of alcohol consumption. In addition to counseling for behavior modification, evaluation and addressing potentially treatable causes should be considered, especially in a patient who reports significant reduction or abstinence from alcohol consumption.

Development of obstructive disease related to pancreatic ductal structure and/or stones, duct blowout due to obstructive disease, ductal disruption, inflammatory mass in the head of the pancreas, disconnected duct after an episode of acute pancreatitis, groove pancreatitis or nonpancreatic diseases such as symptomatic gallstone disease, peptic ulcer disease,

gastroparesis and small bowel bacterial overgrowth are examples of conditions where appropriate management can lead to prolonged symptomatic improvement and quality of life.

Reality: A patient with alcoholic pancreatitis can have symptoms from disease-related manifestations that may be independent of alcohol consumption or have non-pancreatic cause for symptoms. Appropriate evaluation and management may lead to meaningful improvement in symptoms and quality of life.

MYTH #9: Smoking has no relationship with pancreatitis.

Since patients with alcohol also have a high prevalence of tobacco smoking, for years, it used to be believed that the relationship between smoking with pancreatitis is spurious because one could not separate between the effects of alcohol from smoking. However, several well-conducted studies have confirmed conclusively that smoking is an independent risk factor for the risk of acute and chronic pancreatitis, as well as for disease progression[39, 51]. The risk of pancreatitis is greater with current smoking and the amount of smoking. While studies have primarily evaluated the relationship with cigarette smoking, it is reasonable to assume that the effects of smoking apply to all forms of tobacco exposure.

Reality—Smoking is a dose-dependent risk factor for susceptibility and progression of pancreatitis

MYTH #10: Counseling for smoking cessation in patients with pancreatitis can be effective.

Increasing awareness can improve physician recognition of smoking as a risk factor for pancreatitis. This will hopefully translate into increased counseling and facilitating enrollment of patients into smoking cessation programs. However, a recent small study found that such programs may have suboptimal results in terms of achieving smoking cessation[52] highlighting the needs for novel strategies to achieve this goal.

Reality—Counseling for smoking cessation may have limited success in helping patients to quit. Innovative strategies are needed to promote smoking cessation in patient with pancreatitis.

Conclusion

Alcohol and smoking play an important role in increasing the risk as well as progression of pancreatitis. Eliciting an accurate history from patients, and if necessary, family members, can help to determine their contribution to the patient’s disease. In the absence of a convincing history, physicians should be open to consideration of other etiologies. A patient with alcoholic pancreatitis can have symptoms, recurrences or exacerbations from disease-related complications or non-pancreatic causes. Appropriate evaluation and management often helps to achieve a durable and meaningful improvement in symptoms. In addition to abstinence from alcohol, smoking cessation, when applicable, should be recommended in all

patients to prevent disease recurrences and progression. Novel strategies are needed to enable patients quit smoking.

Acknowledgements

Dr. Yadav is supported by the National Institute of Health under award number - U01 DK108306. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

The authors thank David C. Whitcomb, MD PhD for critical review of the manuscript and helpful comments.

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Keypoints

1. Chronic Pancreatitis is a multifactorial disease. The natural course of chronic pancreatitis is highly variable.
2. Alcohol and smoking increase the risk and progression of pancreatitis. The amount and duration of alcohol consumption is the most important factor in increasing the risk of pancreatitis. Clinical pancreatitis develops in ~5% individual who drink heavily.
3. Alcohol sensitizes the pancreas to other insults or injury.
4. Pain, disease flares and hospitalizations may be disease-related manifestations independent of alcohol consumption or from non-pancreatic causes
5. Novel strategies are needed to enable patients quit smoking.

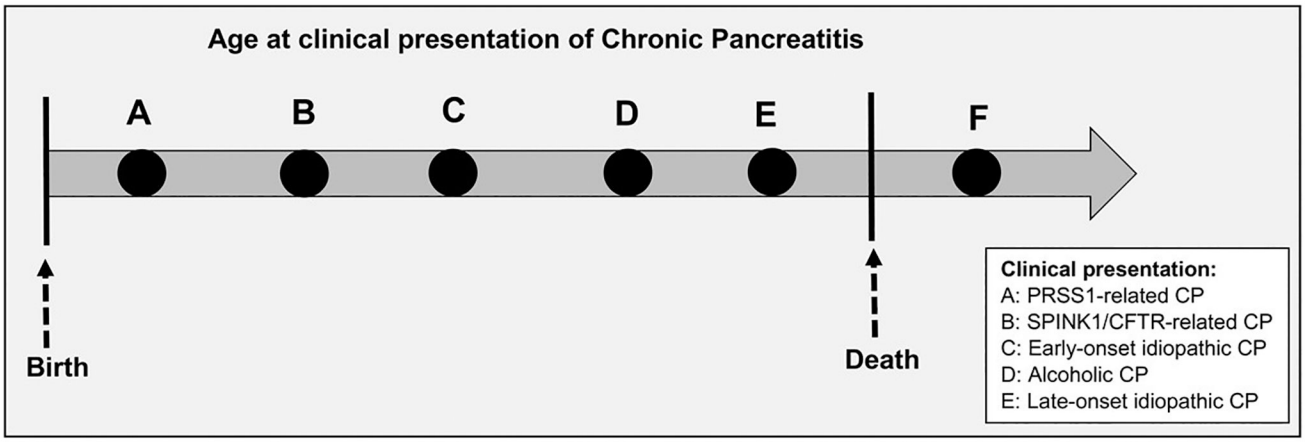

Figure 1:

Impact of alcohol, smoking and genetic factors on the clinical presentation and phenotype of pancreatitis.

The arrow represents time in years from birth and extends beyond death to represent a hypothetical scenario (F) for an inherent risk to develop chronic pancreatitis in all individuals. In subjects with no alcohol use (but may be presence of other environmental factors such as smoking and/or weak genetic effects), pancreatitis can manifest during lifetime which would otherwise not have manifested (E – late-onset idiopathic chronic pancreatitis). Exposure to alcohol (usually in combination of smoking) results in acceleration of late-onset idiopathic disease by several years (D – alcoholic chronic pancreatitis). Presence of genetic factors result in acceleration of disease expression depending on the strength of influence (e.g. C – early-onset idiopathic chronic pancreatitis; B – *SPINK1* or *CFTR* gene mutations; A – *PRSS1* gene mutations). Environmental influences in patients with more penetrant genetic factors will further impact disease expression (concepts elaborated from Ref. 36).

Table 1:

Alcohol etiology and prevalence of abdominal pain in recent cross-sectional studies from US, Europe and Japan

Country	Study name	Time period	Sample size	Male (%)	Alcohol etiology (%)			Pain (%)
					All	Male	Female	
USA	NAPS2[2, 53]	2000–2006	540	53	45	59	28	86
USA	NAPS2-CV[1, 46]	2008–2011	521	55	46	58	30	84
Italy	PanCroInAISP[4]	2000–2005	892	74	43	55	14	63
Hungary	HPSG[7]	2012–2014	229	74	62	N/A	N/A	68
Belgium	Belgian National Registry[3]	2014–2015	809	74	65	N/A	N/A	N/A
Scandinavia	SBPC[6]	As of 12/2016	910	67	59	N/A	N/A	69
Japan	National survey[5]	2011	1,734	68	76	30	N/A	N/A

NAPS2: North American Pancreatitis Study; NAPS2-CV: NAPS2-continuation and validation study; SBPC: Scandinavian Baltic Pancreatic Club; NA – not available