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Alcohol, smoking and benign hepato-biliary disease

Daniel Mønsted Shabanzadeh [a, b, *], Srdan Novovic [c]

[a] Digestive Disease Center, Bispebjerg University Hospital, Copenhagen, Denmark
[b] Research Centre for Prevention and Health, Denmark
[c] Department of Gastroenterology and Gastrointestinal Surgery, Copenhagen University Hospital Hvidovre, Denmark

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ABSTRACT

Gallstone disease and pancreatitis are the most frequent benign hepato-biliary causes of hospital admissions. Gallstone disease is prevalent, but symptomatic disease develops only in about one out of five carriers. Alcohol intake seems to protect gallstone formation in cohort studies possibly through effects on bile cholesterol metabolism, the enterohepatic circulation, and gallbladder function. The impact of smoking on gallstone formation seems minor. Both alcohol intake and smoking do not alter the clinical course of gallstone disease carriers. Cholecystectomy is the preferred treatment for symptomatic gallstone disease. Studies about the impact of alcohol and smoking on the post-cholecystectomy state are few and future studies should be performed. Pancreatitis is associated with both excessive alcohol intake and smoking in observational studies. Interpretation of associations with pancreatitis is hampered by an incomplete understanding of underlying mechanisms and by the co-existence of excessive alcohol intake and smoking. Smoking cessation and alcohol abstinence is recommended in the treatment of pancreatitis, but higher-level evidence is needed.

1. Introduction

Benign hepato-biliary diseases include a variety of conditions including gallstone disease, gallbladder polyps, hepatitis, cirrhosis, autoimmune liver disease, and pancreatitis. Gallstone disease and pancreatitis are the two most frequent benign hepato-biliary causes for hospital admissions. Both diseases lead to high costs for health care providers due to morbidity and treatments [1,2]. Gallstone disease presents as either asymptomatic or symptomatic disease with the latter including both uncomplicated biliary colic and complicated disease such as acute cholecystitis, pancreatitis, common bile duct stones, cholangitis, and bowel obstruction. Pancreatitis presents as a symptomatic clinical manifestation and may be divided into acute or chronic pancreatitis. Due to the differing presentations of these benign hepato-biliary diseases, the risks of alcohol and smoking for the variety of entries in the clinic and in research of gallstone disease and pancreatitis will be treated separately in this chapter.

A number of limitations in the present evidence on associations for alcohol intake and smoking with gallstone disease and pancreatitis need to be addressed. Case-control and cross-sectional studies exist by plenty, but are hampered by not exploring temporal associations. Cohort studies, randomized controlled trials (RCT), or meta-analyses thereof are therefore given priority wherever possible in this chapter. Biochemical identification of present smoking exposure is available in clinical settings and RCTs [3], but quantifying exposures of smoking and alcohol intake is challenged by absence of specific and sensitive biomarkers. Information about smoking and alcohol intake is therefore dependent on self-report, with the risk of underreporting. Further, alcohol intake is not consistently reported due to variations in upper consumption limits, variations in definitions between studies, and due to alcohol use disorders ranging widely from a slightly excessive intake to

* Corresponding author.
E-mail addresses: daniel.moensted.shabanzadeh.01@regionh.dk (D.M. Shabanzadeh), srdan.novovic@regionh.dk (S. Novovic).

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alcohol dependency. These misclassification biases are unavoidable, based on the available evidence. Finally, there is a close coexistence between alcohol intake and smoking. People with excessive alcohol intake are three times more likely to also be smokers when compared to the general population, and smokers are four times more likely to have alcohol dependency when compared to the general population [4]. This may cause confounded associations and may also hamper explorations of additive effects of alcohol and smoking exposures.

Due to the frequency in clinical settings, this chapter will focus on gallstone disease and pancreatitis. A detailed discussion of cirrhosis is provided in another chapter of this special issue. The aim of this chapter is to describe identified associations and therapeutic implications for alcohol intake and smoking with gallstone disease and pancreatitis.

2. Gallstone disease

Screen-detected gallstone disease has high prevalence of 10–20% in populations from Europe and the US [5] and the annual incidence rates range from 0.63 to 1.39% [6–9]. The prevalence depends to a large degree on age, female sex, and ethnicity where the Native Americans have one of the highest [5]. Modifiable determinants of gallstone disease formation such as body mass index, non high density lipoprotein cholesterol, and a number of lifestyle factors have also been identified [8]. The incidence of symptomatic gallstone disease has been determined through observing the natural history of screen-detected gallstone disease from general populations. Uncomplicated gallstone disease or cholecystectomy occurred in 7–25% and complicated gallstone disease occurred in 2–9% of screen-detected gallstone disease carriers [10]. Recently, a 20 year follow up of persons mostly unaware of their screen-detected gallstone disease identified that only 18% had hospital admissions due to symptomatic gallstone disease [10]. Thereby, screen-detected gallstone disease remains asymptomatic in most. Determinants for gallstone formation and for symptomatic disease are therefore best explored separately when assessing the risk of alcohol and smoking.

2.1. Biological effects of alcohol and smoking on gallstone formation

Gallstones are classified according to their composition of major constituents into cholesterol stones, pigment stones containing bilirubin, or mixed stones [11]. Cholesterol gallstones have been estimated to constitute 75–90% of gallstone disease in the US [12]. Recently, cholesterol was identified as the main constituent in 93.3% of gallstones removed at cholecystectomy in a German population and bilirubin in 5.5% only [13]. Due to the dominance of cholesterol gallstones in Western countries, most of the determinants for gallstone disease identified in epidemiological studies are assumed to apply to cholesterol gallstone disease [12].

Gallstone formation has been explored for centuries, and the most important mechanisms identified include:

1 Supersaturation of bile cholesterol.
2 Enterohepatic circulation of secondary bile salts.
3 Impaired gallbladder motor function.

The physical state of bile cholesterol from saturation to crystals is best described through the ternary diagram which describes the solubility of bile cholesterol relative to the amount of phospholipids and hepatic bile salts, the two other major constituents of bile [14]. The supersaturation of bile cholesterol and crystallization is believed to be the leading mechanism for cholesterol gallstone formation. Second, hepatic bile salts (cholate and chenodeoxycholate) are synthesized from cholesterol in the hepatocytes under normal physiological conditions, but may be degraded by colonic microbiota into secondary bile salts (deoxycholate and lithocholate) through the enzyme 7α-dehydroxylase [11]. Unlike the hepatic bile salts, secondary bile salts are hydrophobic, increase bile cholesterol saturation, and promote gallstone formation when absorbed to the enterohepatic circulation [15]. Higher amounts of secondary bile salts and the colonic microbiota producing them are found in gallstone disease [16,17]. A slower bowel transit also promotes absorption of secondary bile salts by the enterohepatic circulation [16,18]. Third, an impaired gallbladder motor function is believed to contribute to gallstone formation, but whether it causes bile stasis and thereby cholesterol crystallization or constitutes a secondary process to cholesterol crystallization is debatable [11].

Alcohol intake may protect against cholesterol gallstone formation by declining bile cholesterol saturation [19–21] and by elevating hepatic bile salt production and excretion [22,23]. Alcohol intake has also been attributed to elevate blood high density lipoprotein (HDL) cholesterol [19,24] which is associated with bile salt excretion [25] and inversely associated with bile cholesterol saturation [26]. The effects of alcohol intake on proximal bowel transit including oro-caecal transit in humans are controversial based on experimental studies [27–29]. However, an acute alcohol intake has been shown to suppress impeding Type I pressure waves in the jejunum and to stimulate propulsive Type III pressure waves in the ileum [30], and excessive everyday alcohol intake has also been associated with a faster self-reported whole bowel transit in a general population [31], all indicating that alcohol intake causes a faster distal bowel transit. The protective effects of alcohol intake on gallstone formation may thereby also be exerted by impeding the absorption of secondary bile acids to the enterohepatic circulation. Experimental study results on alcohol intake or chronic excessive alcohol intake on gallbladder motor function are also conflicting [29,32,33], but alcohol intake has been shown to stimulate post-prandial gallbladder emptying and refilling, indicating an enhanced gallbladder motor function with protective effect on gallstone formation [32].

Excessive alcohol intake causes hepatic injury and fibrogenesis and represents the most frequent aetiology of cirrhosis in European countries [34]. At cholecystectomy, the majority of patients with either cirrhosis or with excessive alcohol intake without cirrhosis have pigment gallstone disease [35]. This may be explained through elevation of bile unconjugated bilirubin excretion when administrating alcohol intravenously as demonstrated in humans [36]. Suggested mechanisms of pigment stone formation in cirrhosis include haemolysis and, consequently, elevated excretion of bile unconjugated bilirubin [35,37].

The impact of tobacco smoking on gallstone formation is not sufficiently explored. Smoking causes a decline in blood HDL cholesterol [38] only indicating possible opposite effects of those of alcohol through the mechanisms described above. Although smoking has been shown to increase post-prandial bile salt excretion [39], studies exploring the effects of smoking on bile composition are lacking. Smoking attenuates both oro-caecal transit and colonic transit, indicating an overall slowing down of bowel transit [40,41]. Effects of smoking on postprandial gallbladder emptying and refilling have been identified as both slower and to have no effects, indicating a possible impaired gallbladder motor function [42,43]. Biological mechanisms of gallstone formation are summarized in Table 1.

Table 1
Biological mechanisms for alcohol, smoking, and gallstone formation.

Exposure	Mechanism	Effects on gallstone formation ↑ ↓	Key references
Alcohol intake	Cholesterol metabolism		
	Bile cholesterol saturation decline	↓	[19–21]
	Hepatic bile salt incline	↓	[22,23]
	High density lipoprotein cholesterol incline	↓	[19,24–26]
	Stimulates distal bowel transit	↓	[30,31]
	Stimulates gallbladder motor function	↓	[32]
	Unconjugated bilirubin bile excretion incline	↑ pigment gallstone	[36]
Cirrhosis	Haemolysis + unconjugated bilirubin bile excretion incline	↑ pigment gallstone	[35,37]
Smoking	Cholesterol metabolism		
	High density lipoprotein cholesterol decline	(↑)	
	Slowing of gut transit	↑	[40,41]
	Impairs gallbladder motor function	(↑)	

Parenthesis refer to associations not sufficiently explored.

2.2. Alcohol, smoking, and risk of clinical gallstone disease in studies without gallstone disease screening

Several larger population-based cohort studies have explored outcomes of clinical gallstone disease by obtaining information about hospital admissions or cholecystectomy. Two meta-analyses have explored associations for alcohol intake and smoking where six out of eight and nine out of ten studies, respectively, assessed clinical gallstone disease only [44,45]. Alcohol intake was inversely associated with incident clinical gallstone disease when highest consumption was compared to lowest (Relative Risk 0.58, 95% confidence interval (CI) [0.45; 0.73]). A significant dose-response relative risk reduction of 12% for every 10 g increase in daily alcohol intake was found [44]. Ever smoking was associated with incident clinical gallstone disease when smokers were compared to non-smokers (Relative Risk 1.15, 95% CI [1.13; 1.18]). A significant dose-response relative risk increase of 11% for every 10 cigarettes per day was found [45].

However, assessment of clinical gallstone disease, only, without systematically screening for gallstone disease represents a small fraction of the total prevalence in a population, and most carriers will be misclassified as not having gallstone disease. Studies may, therefore, be hampered by misclassification and selection bias. Further, determinants for gallstone formation and for development of symptomatic gallstone disease cannot be distinguished in these studies.

2.3. Alcohol, smoking, and risk of incident screen-detected gallstone disease

The systematic gallstone disease screening of an entire cohort through ultrasound examination is the superior method when exploring determinants for gallstone formation. General population-based cohort studies have identified incident screen-detected gallstone disease to be inversely associated with weekly alcohol intake (weekly versus no weekly intake, Odds Ratio 0.29, 95% CI [0.09, 0.98]), with wine consumption (glasses per day, Odds Ratio 0.71, 95% CI [0.54; 0.92]), and with a rising alcohol intake in females throughout follow-up (per 1 increase unit alcohol per week, Odds Ratio 0.94, 95% CI [0.90; 0.98]) [6,9,46]. However, no linear (continuous) dose-response association for alcohol intake and incident screen-detected gallstone disease was found in a meta-analysis of two studies (per 1 unit alcohol per week, Odds Ratio 0.99, 95% CI [0.98; 1.00]) [8]. Another meta-analysis of pooled exposures, but restricted to include only studies with ultrasound screening of incident gallstone disease did also not find a significant association (Relative Risk 0.68, 95% CI [0.44; 1.03]) [44]. Altogether, alcohol intake seems to protect against gallstone formation, but its effects are currently not generalizable across studies in meta-analysis. This may be due to sex-dependent effects of alcohol as previously suggested [46] or due to bias caused by the heterogeneity in defining alcohol exposure or in obtaining data in studies.

Associations for cirrhosis of unspecified aetiology and incident screen-detected gallstone disease in general populations are reported with conflicting results [6,7]. A number of studies have performed regular ultrasound screenings in clinical cohorts of patients with cirrhosis mostly caused by excessive alcohol intake and report annual gallstone disease incidence rates in 3.4–5.5% [47–49] which is about a four-fold increase when compared to incidence rates in general populations [6–9]. Determinants for incident gallstone disease in a cirrhosis cohort included alcohol aetiology, a more severe Child-Pugh classification at baseline (Risk Ratio 6.19 to 12.1, $P < 0.01$) [47], and decompensated cirrhosis defined as altered liver function test and ascites when compared to compensated (34.6% versus 6.50, $P < 0.002$) [49].

Smoking was not associated with incident screen-detected gallstone disease in meta-analysis including three studies (Odds Ratio 1.07, 95% CI [0.84; 1.36]) [8]. Changes in smoking habits during follow-up also did not determine incident screen-detected gallstone disease in a cohort [46].

2.4. The impact of alcohol and smoking on the natural history of screen-detected gallstone disease

Two cohort studies have explored the impact of baseline alcohol intake and smoking on symptom development in screen-detected gallstone disease [50,51]. In a Swedish screen-detected gallstone disease cohort, 7.6% had gallstone disease related hospital admissions at 5 years follow-up. The distributions of weekly alcohol intake (versus no intake) and smoking at baseline did not differ between persons admitted or not admitted [50]. In a larger Danish cohort where participants were unaware of their screen-detected gallstone disease, 17% developed clinical gallstone disease requiring hospital admission during median 17.5 years follow-up. Baseline alcohol intake (per 1 unit per week, Odds Ratio 0.98, 95% CI [0.96; 1.01]) or smoking (current or past smoking versus never, Odds Ratio 1.12, 95% CI [0.71; 1.73]) did not determine symptomatic gallstone disease hospital admissions [51].

Cirrhosis has not been found to determine the clinical course of gallstone disease in a cohort with screen-detected gallstone disease [52].

Epidemiological risk estimates for alcohol, smoking, and gallstone disease are summarized in Table 2.

2.5. Gallstone disease clinical treatment guidelines for alcohol and smoking

Cholecystectomy is the preferred treatment for symptomatic

Table 2
Epidemiological risk estimates for alcohol, smoking, and gallstone disease.

Author, Year, reference	Study design	Exposure	Risk estimate for outcome [95% CI]
Clinical gallstone disease incidence in general populations			
Alcohol			
Wang 2017 [44]	Meta-analysis	Highest vs lowest alcohol consumption	RR 0.58 [0.45; 0.73]
Smoking			
Aune 2016 [45]	Meta-analysis	Ever smoking	RR 1.15 [1.13; 1.18]
Screen-detected gallstone disease incidence in general populations			
Alcohol			
Misciagna 1996 [6]	Cohort	Wine glasses per day	OR 0.71 [0.54; 0.92]
Halldestam 2009 [9]	Cohort	Alcohol intake weekly versus no weekly intake	OR 0.29 [0.09, 0.98]
Shabanzadeh 2017 [46]	Cohort	Per 1 increase unit alcohol per week in females	OR 0.94 [0.90; 0.98]
Shabanzadeh 2016 [8]	Meta-analysis	Per 1 unit alcohol per week	OR 0.99 [0.98; 1.00]
Wang 2017 [44]	Meta-analysis	Alcohol consumption	RR 0.68 [0.44; 1.03]
Cirrhosis			
Fornari 1994 [47]	Cohort	Child-Pugh classification C vs B, C vs A	RR 6.19, RR 12.1
Smoking			
Shabanzadeh 2016 [8]	Meta-analysis	Smoking	OR 1.07 [0.84; 1.36]
Impact on the natural history of screen-detected gallstone disease			
Alcohol			
Shabanzadeh 2017 [51]	Cohort	Per 1 unit alcohol per week	OR 0.98 [0.96; 1.01]
Smoking			
Shabanzadeh 2017 [51]	Cohort	Current or past smoking	OR 1.12 [0.71; 1.73]

CI, confidence interval; OR, Odds Ratio; RR, Relative Risk.

gallstone disease [53]. Smoking has been associated with prolonged hospital stay following cholecystectomy when compared to non-smokers in an observational study [54]. However, general recommendations for smoking and laparoscopic cholecystectomy must await further trials.

Meta-analysis of observational studies has found that patients with cirrhosis have higher rates of conversion to open surgery, intraoperative bleeding, pooled postoperative complications, and require longer time for laparoscopic cholecystectomy when compared to patients without cirrhosis [55]. Cirrhosis was also attributed to postoperative complications requiring antibiotic treatment or blood transfusions [56]. This study was based on data from a Swedish register of laparoscopic cholecystectomy which is considered one of the largest and most comprehensive registers of biliary surgery. A more severe cirrhosis classification of Child-Pugh C is attributed to post-laparoscopic cholecystectomy complications [57].

The postoperative course following specifically cholecystectomy has not been explored sufficiently and more studies are needed, preferably through randomized controlled trials. It is therefore, necessary to explore the impact of alcohol intake and smoking across pooled general surgical procedures [3,58–60]. Alcohol, smoking and surgical management of gastrointestinal patients will be discussed in detail by Kennedy & Winter in this issue.

3. Acute pancreatitis

The annual incidence of acute pancreatitis ranges from 13 to 45/100,000 [61,62]. However, the incidence of acute pancreatitis varies considerably throughout both Europe and the rest of the world [63]. Furthermore, an increasing trend has been reported in the incidence of acute pancreatitis and the number of hospital admissions for both acute and chronic pancreatitis [64,65]. The two major aetiologies to acute pancreatitis are gallstone disease and excessive alcohol intake, accounting for approximately 80% of the cases. The majority of episodes are mild and self-limiting without development of distant organ failure or pancreatic necrosis, requiring only brief hospitalization. Approximately 20% of the patients will develop severe disease, characterized by organ failure that may lead to death [66]. Unfortunately, at current time there is no targeted treatment for acute pancreatitis, mainly because of lack of understanding of the underlying pathophysiology.

3.1. Biological effect of alcohol and smoking on acute pancreatitis

The exact induction mechanism of acute pancreatitis by alcohol

Table 3
Biological mechanisms for alcohol, smoking, and pancreatitis.

Exposure	Mechanism	Assumed effect in pancreas	Key references
Acute pancreatitis			
Alcohol intake	Production of reactive oxygen species	Auto digestion of pancreatic acinar cells	[67,68]
	Transcription factor nuclear factor-κB activation	Inflammation	[69]
	Intracellular calcium increase		
	Extracellular matrix proteins inhibition		
	Mitochondrial dysfunction		
	Endoplasmatic reticulum stress		
Smoking	Probably cholecystokinin-mediated pathway	Auto activation in pancreatic acinar cells	[71]
Chronic pancreatitis			
Alcohol intake	Pancreatic stellate cells activation	Fibrogenesis	[89–91]
	Secretion of type-1 collagen and matrix metalloproteinases		[90,92]
Smoking	Pancreatic zymogens elevation	Morphological changes	[93–95]
	Trypsinogen and chymotrypsinogen elevation		
	Extracellular matrix increase		
	Nicotine elevation		

intake is not clear, but ethanol-derived toxic metabolites are believed to induce oxidative stress and production of reactive oxygen species, which in turn induces the process of auto digestion in acinar cells with subsequent induction of pro-inflammatory mediators. Only a minor part of individuals with excessive alcohol intake develop acute pancreatitis, suggesting that other factors must be present in order to initiate inflammation in pancreas [67,68]. Alcohol intake probably sensitizes the pancreas to injury and lowers the threshold for triggering the inflammation. Thus, in combination with another internal or external stimulus, alcohol intake causes the onset of inflammation and acute pancreatitis. Increasing understanding of alcohol derived effects on initiation and progression of acute pancreatitis comes especially from experimental studies and involves both activation of key transcription factors nuclear factor-κB, sustained increased intracellular calcium, inhibition of extracellular matrix proteins, mitochondrial dysfunction, and endoplasmatic reticulum stress [69].

Although increasing epidemiological evidence points towards direct relationship between smoking and acute pancreatitis, the underling pathogenic mechanisms are only partially revealed. Smoking is known to interact with cholecystokinin, one of the main hormones responsible for the stimulatory effect on pancreatic exocrine function [70]. The cholecystokinin-mediated pathway is, therefore, believed to mediate the effect of smoking on the development of acute pancreatitis. Also, smoking affects the ductal system, pancreatic microvasculature, the inflammatory system, neurotransmitters, and causes oxidative stress [71]. Biological mechanisms of acute pancreatitis are summarized in Table 3.

3.2. Alcohol, smoking, and risk of acute pancreatitis

It has long been recognized that excessive alcohol intake is a risk factor for acute pancreatitis. In a meta-analysis including 146,517 individuals with 1671 cases of acute pancreatitis, an excessive alcohol intake of more than 4 drinks per day was significantly associated with the pancreatitis (Relative Risk 2.5; 95% CI [0–3]) when compared to non-drinkers [72]. A more recent meta-analysis comprising 157,026 participants and 2490 cases of first episode of acute or recurrent acute pancreatitis, and 1128 cases of chronic pancreatitis found a linear dose-response relationship between average volume of alcohol intake and acute pancreatitis in men, but a non-linear one (J-shaped) in women [73]. Alcohol intake below 40 g/day was inversely associated with acute pancreatitis in women. Although it is well established that chronic excessive alcohol intake can lead to acute pancreatitis, short-term excessive alcohol intake and even binge drinking can induce acute pancreatitis [74].

The term binge drinking has been frequently mentioned as a possible cause of acute pancreatitis [75]. However, there exists no consensus on the amount of alcohol needing to be ingested or the duration of binge drinking.

In a prospective cohort study, a relative risk of 2.14 (95% CI [1,3,9,48]) for developing acute pancreatitis in current smokers was found. In this study, a dose-response effect was also observed after controlling for alcohol intake [76]. A recent meta-analysis based on 12 observational studies (six case-control and six cohort studies) including a total of 3690 incident cases of acute pancreatitis supported the evidence of the association between smoking and the risk of developing acute pancreatitis which was independent of body mass index and alcohol intake [77]. The likelihood of developing acute pancreatitis was proportional to the amount of tobacco use, suggesting that smoking exerts a dose-related effect. Interestingly, the same study found a small, but significantly higher risk for previous smokers as compared to current smokers, which could indicate a persistent effect of smoking even after cessation.

Existing evidence suggest that aetiology does not influence the disease course of acute pancreatitis [78], nor does there exist a dose-response relationship between alcohol and smoking exposure, and severity of pancreatitis.

Traditionally, late complications of acute pancreatitis such as walled-off necrosis and pseudocysts have been managed surgically. During recent years a number of minimally invasive techniques have been developed. Whether alcohol and smoking have an impact on the timing or the outcome of these techniques remains to be investigated. Epidemiological risk estimates for alcohol, smoking, and acute pancreatitis are summarized in Table 4.

4. Chronic pancreatitis

Chronic pancreatitis is a fibro-inflammatory disease characterized by irreversible destruction of the pancreatic tissue, which may lead to exocrine and/or endocrine insufficiency as the disease evolves [79]. Chronic pancreatitis is often diagnosed in the late stage of the disease, and for the time being, early diagnosis is difficult to establish. More precise epidemiological estimates are thus difficult to perform, but the incidence is probably increasing world-wide, with great geographical variation. A population-based study from Mayo Clinic found increased incidence from 2.94/100,000 during 1977–1986 to 4.35/100,000 during 1997–2006 [80]. Reports on prevalence of chronic pancreatitis vary between 3 and 125/100.00 [81–83]. Abdominal pain is the cardinal symptom, often in combination with malnutrition, osteoporosis, and psychiatric comorbidity [84,85]. The clinical features and complex symptomatology is associated with reduced quality of life and

Table 4
Epidemiological risk estimates for alcohol, smoking, and pancreatitis.

Study Author, Year	Study design	Exposure	Risk estimate for outcome [95% CI]
Acute pancreatitis			
Alcohol			
Irving 2009 [72]	Meta-analysis	More than 4 weeks per day	RR 2.5 [0–3]
Smoking			
Sun 2015 [77]	Meta-analysis	Ever smokers vs. never smokers	RR 1.54 [1.31-0.80]
		Current smokers vs. never smokers	RR 1.71 [1.37–2.14]
		Former smokers vs. never smokers	RR 1.21 [0.02–1.43]
Lindkvist 2008 [76]	Cohort	Current smoking	RR 2.14 [1,3,9,48]
Chronic pancreatitis			
Alcohol			
Samokhvalov 2015 [73]	Meta-analysis	100 g of alcohol per day	RR 6.29 [3.04–13.02]
Smoking			
Maisonneuve 2005 [99]	Cohort	Smokers vs. non-smokers	HR 4.9 [2.3–10.5]
Raphael 2017 [100]	Cross-sectional	The effect of smoking on pancreatic insufficiency	OR 4.34 [1.37–13.75]

CI, confidence interval; OR, Odds Ratio; RR, Relative Risk; HR, Hazard Ratio.

increased disease burden [86,87]. It is estimated that chronic pancreatitis costs the US healthcare system over 150 million dollars yearly [88].

4.1. Biological effect of alcohol and smoking on chronic pancreatitis

Pancreatic stellate cells are the key mediators of pancreatic extracellular remodelling. They regulate the deposition and degradation of extracellular matrix. Abnormal, persistent activation of pancreatic stellate cells can lead to altered extracellular matrix environment, which may play a key role in the development of fibrosis and eventually chronic pancreatitis [89]. Alcohol and its metabolites contribute to the activation of pancreatic stellate cells [90,91]. In addition, alcohol intake induces secretion of type-1 collagen and matrix metalloproteinases, thus further contributing to increased fibrogenesis [90,92]. Pancreatic ductal cells, repair mechanisms, and inflammatory response are other potential targets for the action of alcohol and its substrates [69].

It can be difficult to explore the exact cellular pathways and mechanistic explanations of the role of smoking in chronic pancreatitis, as cigarette smoke contains several thousand substances. In an experimental rat model, high-dose tobacco smoke for up to three months induced elevated levels of pancreatic zymogens trypsinogen and chymotrypsinogen and increase in extracellular matrix in focal areas of pancreas [93]. Nicotine has been shown to be able to accumulate in pancreas [94] and to induce substantial morphological changes [95]. Biological mechanisms of chronic pancreatitis are summarized in Table 3.

As previously mentioned, it may be difficult to assess the independent effect of smoking on chronic pancreatitis, as smoking often is strongly associated with alcohol intake. In a recently published cross-sectional study 44% of the chronic pancreatitis cases were classified as being due to concomitant alcohol and tobacco use [96].

4.2. Alcohol, smoking, and risk of chronic pancreatitis

The most common cause for developing chronic pancreatitis is chronic excessive alcohol intake which accounts for about 50% of all chronic pancreatitis cases in the Western world [80]. However, smoking is increasingly recognized as an independent aetiological factor, and recent studies on the topic of chronic pancreatitis report smoking as being one of the most frequent causes of chronic pancreatitis [96]. Acute pancreatitis, recurrent acute pancreatitis, and chronic pancreatitis probably represent different stages of the same disease. Among 669 patients admitted with their first episode of acute pancreatitis, 17% developed recurrent acute pancreatitis and 8% progressed to chronic pancreatitis within five years [97]. Progression to chronic pancreatitis was associated with alcohol intake, smoking, recurrent acute pancreatitis, and development of pancreatic necrosis. Similar numbers were found in a meta-analysis performed by Sankaran et al., in which 10% of patients with their first episode of acute pancreatitis and 36% with recurrent acute pancreatitis progressed to chronic pancreatitis. The risk of progression to chronic pancreatitis was greater in patients who smoked, had a high alcohol intake, and were men [98].

In a retrospective cohort of 934 patients with chronic alcoholic pancreatitis where information on smoking was available, tobacco smoking increased significantly the risk of pancreatic calcifications (Hazard Ratio 4.9, 95% CI [2.3; 10.5]) for smokers vs. non-smokers [99].

Another interesting effect of smoking on benign pancreatic disease comes from a recently published study which enrolled patients with and without a history of heavy tobacco exposure to examine the cross-sectional relationship between smoking and pancreatic insufficiency (characterized by faecal elastase) in patients with no prior history of pancreatic disease [100]. This study identified pancreatic insufficiency in a high proportion of smokers with a prior history of pancreatic disease. The prevalence in smokers (18%) significantly exceeded the prevalence in the non-smoking control population (6%). The rate of severe pancreatic insufficiency was also significantly increased in the tobacco exposure cohort. The relationship seemed to be independent of alcohol intake. Epidemiological risk estimates for alcohol, smoking, and chronic pancreatitis are summarized in Table 4.

4.3. Pancreatitis clinical treatment guidelines for alcohol and smoking

There is increasing evidence of direct relationship between alcohol and smoking, and risk of acute and chronic pancreatitis. As both smoking and alcohol are modifiable risk factors, improvement in preventive measures and better education is warranted. Alcohol abstinence has beneficial effects on disease progression in patients with alcoholic chronic pancreatitis [101]. Increasing evidence suggests that smoking accelerates disease progression [102]. Recommendations on alcohol abstinence and smoking cessation are both included in the newest European guidelines [103].

5. Summary

Gallstone disease and pancreatitis are some of the most frequent benign hepato-biliary diseases causing hospital admissions.

Gallstone disease is prevalent when screening general populations, but rarely causes hospital admissions. Mechanisms of gallstone formation include bile cholesterol supersaturation, enterohepatic circulation of secondary bile salts, and impaired gallbladder function. Observational and experimental studies support gallstone formation to be inversely determined by alcohol intake but whether there exists a dose-response relationship has not been clarified yet. However, cirrhosis caused by excessive alcohol intake is a determinant of gallstone formation. The effects of smoking on gallstone formation have not been sufficiently explored in experimental or observational studies, but do currently not indicate a strong causal association. Neither alcohol intake nor smoking seems to significantly alter the clinical course in cohorts with screen-detected gallstone disease.

Cholecystectomy is the preferred treatment of symptomatic gallstone disease. Studies exploring alcohol intake, smoking, and the specific post-cholecystectomy course are few and experiences therefore have to be drawn from observations in general surgery.

Pancreatitis is a clinical condition that is believed mostly caused by alcohol intake or gallstone disease. Acute pancreatitis is associated with organ failure and mortality. The continuum to chronic pancreatitis is associated with high morbidity due to endocrine and exocrine pancreatic insufficiency. Development of specific treatments is hampered by an incomplete knowledge of underlying mechanisms.

Acute pancreatitis is associated with both excessive alcohol intake and binge drinking and smoking may exert a dose-related effect. Chronic pancreatitis also seems associated with both alcohol intake and smoking. Effects from smoking and alcohol intake often co-exist in chronic pancreatitis, but recent cross-sectional studies suggest smoking to be independently associated with pancreatitis progression. Alcohol abstinence and smoking cessation are recommended in the treatment of chronic pancreatitis.

Practice points

- Gallstone formation is inhibited by alcohol intake at responsible levels, however excessive consumption may stimulate gallstone formation
- Alcohol intake and smoking do not seem to alter the natural history of gallstone disease carriers
- Cirrhosis and cirrhosis severity is attributed to a more complicated operative and post-operative course of laparoscopic cholecystectomy
- Both chronic excessive alcohol intake and binge drinking can cause acute pancreatitis
- Smoking probably exerts a dose-related effect on the risk for acute pancreatitis
- The majority of chronic pancreatitis is due to either alcohol intake, smoking, or both
- Smoking and alcohol intake are independent risk factors for chronic pancreatitis, and they both accelerate its progression
- Smoking cessation and alcohol abstinence are highly recommended, although much of the evidence comes from cross-sectional studies

Research agenda

- A causal association for smoking and gallstone formation is currently not supported by higher level of evidence, and mechanisms may be further explored
- High quality clinical trials on the impact of lifestyle habits on surgical outcomes in patients specifically undergoing laparoscopic cholecystectomy are needed, preferably through randomized controlled trials
- A better understanding of the mechanisms by which alcohol and smoking alter pancreatic physiology is needed
- High quality clinical studies designed to investigate how smoking or alcohol alone or in combination mediate pathological processes in acute and chronic pancreatitis are requested
- Large, prospective clinical studies should investigate the progression from acute to chronic pancreatitis and the independent and synergistic role of alcohol and smoking in this process

Conflict of interest statement

None.

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