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Alcohol Use and Cigarette Smoking as Risk Factors for Post-Endoscopic Retrograde Cholangiopancreatography Pancreatitis

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Abstract

Background & Aims—Alcohol use and cigarette smoking associate with various pancreatic diseases, but it is not known whether they associate with post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis (PEP). We performed a retrospective case-control study to determine if these activities increase the risk of PEP.

Methods—We identified 7,638 patients that had undergone ERCP in the University of Michigan Health System and applied exclusion criteria to identify 123 with PEP. We randomly selected 308 age- and gender-stratified controls (2.5-fold case sample); after applying exclusion criteria 248 remained. In a masked fashion, we collected data for alcohol use, cigarette smoking, and 5 internal control variables: suspected sphincter of Oddi dysfunction (SOD), pancreatic sphincterotomy, moderate/difficult cannulation, ≥ 2 pancreatic injections and pancreatic stent placement.

Results—The univariate model showed an increased frequency of PEP in current drinkers (P<0.001), former drinkers (P<0.001) and former smokers (P<0.001), as well as patients who were suspected of having SOD (P<0.001), had undergone pancreatic sphincterotomy (P<0.001), had a moderate/difficult cannulation (P=0.001), and/or had ≥2 pancreatic injections (P=0.007). The frequency of PEP was reduced in current smokers (P<0.001). The multivariate model showed that the only independent significant predictors of PEP were current drinking (OR=4.70, 95% CI 2.60–8.50, P<0.0001), former cigarette smoking (OR=3.29, 95% CI 1.28–8.44, P<0.013), suspected SOD (OR= 3.69, 95% CI 1.94–7.02, P<0.001), and pancreatic sphincterotomy (OR=5.91, 95% CI 2.04–17.14, P=0.001).

Conclusions—Current alcohol use and potentially former cigarette smoking are new risk factors for PEP. It is important to consider these variables in designing PEP prevention trials.

INTRODUCTION

Pancreatitis is a potential serious complication of endoscopic retrograde cholangiopancreatography (ERCP)[1,2–4]. Commonly reported risk factors include suspected

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sphincter of Oddi dysfunction (SOD)[5–10], pancreatic sphincterotomy[6], moderate/difficult cannulation[6, 7, 11, 12], ≥ 2 pancreatic duct contrast injections[6–8, 13, 14] and a prior history of post-ERCP pancreatitis (PEP)[5, 6]. Risk stratification of patients allows endoscopists to identify candidates who might benefit from the placement of a prophylactic pancreatic duct stent, the only intervention proven to reduce the incidence of PEP in high-risk patients[15, 16]. Unfortunately, this decision making is not always straight forward[17, 18] and evidence is inconclusive whether chemopreventive agents reduce PEP[17, 19, 20]. A potential consideration for all post-ERCP studies is that data may be confounded by the effects of unknown risk factors.

Alcohol use and cigarette smoking are known risk factors for various pancreatic diseases but they have escaped attention in PEP studies[21]. Alcohol use is a major risk factor for acute and chronic pancreatitis[22, 23] and alcohol exposure increases the risk of pancreatic necrosis in acute pancreatitis, independent of etiology[24]. Although there appears to be a dose-response relationship between alcohol use and the incidence of acute-[25] and chronic pancreatitis[26], there is no clear alcohol toxicity threshold on the human pancreas[26].

Cigarette smoking alters pancreatic secretion[27] and with few exceptions[28, 29] it increases the risk of developing acute[25, 30, 31] and chronic[30–35] alcoholic pancreatitis, idiopathic chronic pancreatitis (ICP)[31], pancreatic calcifications in alcoholic chronic pancreatitis (ACP)[36] and late-onset ICP[37], and pancreatic cancer[35, 38, 39]. Cigarette smoking also associates with an earlier onset of ACP[33] and an accelerated disease progression of both ACP[32] and late-onset ICP[40]. Finally, the dose-response relationship is strong between cigarette smoking and the incidence of acute alcoholic pancreatitis[25, 31, 41], but less so for idiopathic[25, 31] and "other or unknown[25, 41]" forms of acute pancreatitis, and absent for gallstone pancreatitis[25, 31, 34], with one exception[41].

To test the hypothesis that alcohol use and cigarette smoking are risk factors for developing PEP, we performed a retrospective case-control study of 7,638 patients who had ERCP between 1/1/1998 – 6/30/2007 at the University of Michigan Health System. We collected and analyzed data to address two *a priori* aims: 1) to determine whether alcohol use and/or cigarette smoking in current and/or former drinkers/smokers influences the risk of PEP and 2) to determine whether a dose-response relationship exists between alcohol use and/or cigarette smoking and the risk of PEP.

MATERIALS AND METHODS

Ascertainment of Case and Control Samples

Permission to review patient records for a retrospective case-control study was granted by the University of Michigan Institutional Review Board. We performed an IDX cross-sectional search of our health system's databases and identified 7,638 patients who had ERCP performed between 1/1/1998 – 6/30/2007. Within this source sample we identified 1,334 patients who had an ICD-9 code (577.0) diagnosis of acute pancreatitis. Based on medical chart review, 247 patients met criteria by Cotton et al.[3] for PEP and 123 formed our case sample after applying the following exclusion criteria: age < 18, pregnancy, planned biliary stent removal or exchange without planned pancreatogram and factors that might confound the diagnosis of PEP, including 1) active pancreatitis pre-ERCP, 2) known chronic pancreatitis based on relevant symptoms, imaging modalities, and assessment of pancreatic function[42], 3) known pancreatic cancer, or 4) prior pancreatic surgery. We utilized a random-number generator program to select 308 age- and gender stratified controls from the remaining source sample, equivalent to 2.5-fold the number of cases. After applying these exclusion criteria, 248 remained to form our control sample (Figure 1). Age (either < 60 or ≥60) and gender were selected as stratification variables rather than other control variables because age and gender data were accessible in the demographic sections of the medical records and did not require opening and exposing the

entire medical record, which could introduce bias associated with the collection of the variables of interest.

Variable Selection and Definitions

We collected data for a set of five internal control variables and both alcohol use and cigarette smoking. The specific internal control variables were selected because they were consistent risk factors for PEP based on reported odds ratios in two multicenter, prospective trials[5, 6]. We included 4 of 5 identifiable risk factors (suspected SOD, pancreatic sphincterotomy, moderate/difficult cannulation, ≥ 2 pancreatic duct contrast injections) and one known prophylactic measure (pancreatic stent placement)[15, 16]. A history of prior PEP was not included because selection bias would have occurred in the process of choosing retrospectively one ERCP among all ERCPs performed for an individual patient. To this end, in those with multiple episodes of PEP, we selected the ERCP associated with the first episode of PEP.

We defined cigarette smoking and alcohol use as current, former, or never drinker/smoker. We defined cigarette smoking exposure as number of packs-per-day, years smoking, and pack-years. Quantitative information for alcohol use was commonly absent and inadequate for analysis. Suspected SOD was defined according to Cheng et al[5] as a clinically documented pre-ERCP suspicion of SOD independent of manometric findings. Cannulation difficulty was judged as moderate/difficult if the endoscopist performed ≥ 6 cannulation attempts on either the common bile duct or the pancreatic duct *or* if the endoscopist's report described a "difficult" or "tough" cannulation on either duct. We used common definitions for pancreatic sphincterotomy, pancreatic injections and pancreatic stent placement (see Supporting Documents).

Data Collection and Management

To limit bias, we pooled and masked the case and control electronic medical records. We utilized a computer program known as "EMERSE[43]" to electronically, automatically and reproducibly search the entire electronic medical record at our institution for our data of interest (see Supporting Documents).

During the timeframe of the study, ERCP reports were generated from one of two computer software driven template programs: EndoPRO (Pentax writer) from 1/1/1998 – 6/30/2006 and ProVation (ProVation Medical®, Inc) from 7/1/06–6/30/07 (see Supporting Documents).

Variations in the data recorded in the electronic medical record were reconciled by extracting the data most consistently reported in the medical record or if necessary the data from the most current medical document. Microsoft Excel spreadsheets were utilized for data management.

Statistical Analyses

The primary outcome analyzed was PEP. Descriptive statistics were compiled on all variables to evaluate variable distribution prior to modeling. Univariate analyses were conducted prior to multivariate logistic regression analyses, which contained variables with P values < 0.2 from the univariate analysis. Categorical and dichotomous variables were assessed by χ^2 tests and continuous variables were assessed using either two sample t-tests for normally distributed variables or the Kolmogorov-Smirnov two-sample tests for non-normal variables. Broad frequency age and gender stratification was used in the selection of controls with all results adjusted for age < 60 and gender. The multivariate analysis examined the risk of PEP associated with substance status (current and former drinkers/smokers), cumulative cigarette exposure (represented as continuous pack-years), suspected SOD, pancreatic sphincterotomy, moderate/difficult cannulation, ≥ 2 pancreatic injections, and pancreatic stent placement. The model was

used to estimate odds ratios and associated 95% confidence intervals. All statistical analyses were performed using SAS version 9.1.3 (SAS Institute Inc., Cary, NC).

RESULTS

Univariate Analysis

The case and control samples had similar mean ages (52.4 years vs. 52.2 years, P=0.928), persons < 60 years old (74.0% vs. 75.4%, P=0.767), and women (74.0% vs. 73.8%, P=0.968), indicating successful age and gender stratification (Table 1). Similar to prior studies, the frequency of PEP was greater for the internal control variables known to be associated with PEP – suspected SOD (39.8% vs. 16.1%, P<0.001), pancreatic sphincterotomy (20.3% vs. 4.4%, P<0.001), moderate/difficult cannulation (39.8% vs. 23.4%, P=0.001), and ≥ 2 pancreatic injections (11.4% vs. 4.0%, P=0.007).

The frequency of PEP was greater in both current (55.8% vs. 25.2%, P<0.001) and former (11.7% vs. 7.7%, P<0.001) drinkers. Former smokers had a greater frequency of PEP (27.6% vs. 10.3%, P<0.001) and current smokers had a lesser frequency of PEP (13.3% vs. 19.4%, P<0.001).

Multivariate Analysis

According to the multivariate logistic model, the only independent significant predictors of PEP were current drinking (Table 2, OR=4.70, 95% CI 2.60–8.50, P<0.0001), former cigarette smoking (OR=3.29, 95% CI 1.28–8.44, P<0.013), suspected SOD (OR= 3.69, 95% CI 1.94–7.02, P<0.001), and pancreatic sphincterotomy (OR=5.91, 95% CI 2.04–17.14, P=0.001). We could not examine an alcohol dose-response relationship because there was insufficient quantitative data for alcohol use. There was no dose response relationship between continuous pack-years of cigarette smoking with PEP in either current or former smokers.

Interaction Analysis

We were not able to analyze interactions between alcohol use and cigarette smoking, which frequently co-associate[44, 45], because subgroups of drinkers and smokers had few persons, which prevented a meaningful interaction analysis. For example, the combined group of former drinkers and current smokers had three persons in the control sample and two persons in the case sample. Further, the combined group of current drinkers and former smokers had only 18 persons in the case sample and five persons in the control sample.

DISCUSSION

The multivariate analysis of our data reveals that current drinking, former cigarette smoking, suspected SOD and pancreatic sphincterotomy are risk factors for PEP. Of these the most important new finding is the association of current alcohol use with PEP. Perhaps surprising and open to other interpretations are the association of former cigarette smoking with PEP and the lack of association of former drinkers and current smoking with PEP (and potential protection from PEP).

Current alcohol use may enhance the vulnerability of the pancreas to injury via disruption of normal pancreatic neurohormonal control mechanisms[46], dysregulation of the immune system[47], reduction in pancreatic microperfusion[23], and/or triggering multiple pathological changes in pancreatic acinar cells recently reviewed by Pandol et al.[23], such as increased intracellular calcium concentrations, mitochondrial damage, increased activation of the inflammatory transcription factor NF-kB and trypsinogen activation. In addition, drinking alcohol may predispose to pancreatic diseases by uncoupling NO production from the enzyme

endothelial NO synthase (eNOS)[21, 48]. eNOS helps maintain normal endothelial function and has protective effects on acute pancreatitis[49], possibly by maintaining pancreatic exocrine secretion[48], augmenting pancreatic blood flow[49] or indirectly inhibiting intracellular trypsinogen activation[49].

Why former drinking does not and former smoking does increase the risk of PEP is uncertain. Possibly former drinkers developed subclinical pancreatic damage that reduced the risk for PEP, analogous to patients with established chronic pancreatitis, who appear to have a lower risk of PEP[6]. It is unknown whether pancreatic damage persists after cessation of smoking, although cigarette smoke in experimental studies increases pancreatic inflammation and reduces pancreatic blood flow[50, 51]. A possible explanation for increased risk of PEP in former smokers is that they may be predisposed to PEP on the basis of ischemia as they were older than the cohorts and current smokers (60.3 vs. 52 vs. 45.7 years old, see Supporting Documents) and had a greater frequency of coronary heart disease compared to current and never smokers (27% vs. 19% vs. 6%, see Supporting Documents), which is associated with increased pancreatic microvascular atheroma[52, 53]. The association of age, independent of smoking, is unclear. One multicenter prospective trial[5] showed that younger age associated with greater PEP but another trial[6] made no such association; neither trial considered smoking (or drinking) in statistical analyses.

Whether current cigarette smokers had less PEP is uncertain. Only by univariate analysis we found that current smokers had less PEP (Table 1, OR 13.3% vs. 19.4%, P=0.001) but by multivariate analysis this was a nonsignificant trend (Table 2, P=0.055). If however, current smoking reduces PEP, a possible explanation may be that nicotine activates the nicotinic anti-inflammatory pathway, which reduces pancreatic inflammation and ameliorates experimental pancreatitis[54].

We performed an observational retrospective case control study, which has inherent disadvantages such as confounding (unrecognized differences in the drinkers and/or smokers vs. the control populations might explain the associations with PEP rather than the risk exposure) and incorrect reporting of the risk factors, particularly if the factors are deemed socially undesirable (alcohol use, cigarette smoking).

To address incorrect reporting of risk factors, we point out that our data reporting was interview-based, which is more reliable than self-reporting[55]. Secondly we obtained a statistically acceptable rate of missing data (7.8%)[56], showed that the site of data collection (inpatient versus outpatient) had a nonsignificant effect on study outcome and in subgroup analyses that former and current smokers compared to never smokers had a greater frequency of Chronic Obstructive Pulmonary Disease (COPD) and a greater odds of Coronary Artery Disease (CAD), giving support for the accuracy of the smoking data. Thus, although data reporting bias is possible, such an effect was likely minimal in our study, as suggested by the analyses of data reliability in this paragraph (please see Supporting Documents for additional results and discussion).

In addition we provide supporting evidence that our data is reliable by confirming that recognized risk factors increased the odds of PEP. Specifically, we showed that suspected SOD[5–10] and pancreatic sphincterotomy[6] are independent risk factors for PEP. Also, we showed that as a prophylactic intervention[15, 16], pancreatic stent placement occurred more frequently in the case sample (26% vs. 12.5%), and, as expected, was not a risk factor for PEP. Moderate/difficult cannulation associated with increased risk of PEP in several studies[6, 7, 11, 12] but not in our study. As a possible explanation, we expanded our definition of the difficulty of the cannulation to include the endoscopists' subjective interpretation of the cannulation in addition to a preset number of cannulation attempts (≥ 6 attempts), because the

number of attempts was lacking in the majority of ERCP reports. Similarly, we speculate that non-standardized reporting by the endoscopists may explain why ≥ 2 pancreatic duct contrast injections was not a significant risk factor for PEP in our study as it is in other studies[6–8, 13, 14].

An additional limitation of our study is failure to include all variables possibly associated with PEP. Of statistical necessity we had to limit the number of variables because the number of variables a statistical model can accommodate is directly proportional to the sample size. Hence, we excluded variables that had a doubtful or unclear association to PEP such as miscellaneous indications for ERCP, an endoscopist's experience, trainee involvement, a patient's body-mass index, or the presence of co-morbidities like diabetes, anemia, and hemodialysis[5–8, 13, 14, 57–60]

In summary, this study is the first to attempt to examine the relationship between alcohol use, cigarette smoking, and other established risk factors in PEP. We report that current alcohol use and potentially former cigarette smoking are new risk factors for PEP. Because of inherent limitations of the retrospective study design, including the reliability of former smoking and drinking data, these findings require validation, preferably by a large, prospective multi-center study of detailed drinking and smoking habits, which could also address interactions between alcohol use and cigarette smoking and further elucidate dose-response relationships. Nevertheless, our findings are potentially important because if confirmed by prospective studies, drinking and smoking status may aid assessing the risk of PEP prior to ERCP and guide implementation of risk lowering strategies for PEP such as prophylactic pancreatic stent or chemoprevention.

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Abbreviations

ACP	alcoholic chronic pancreatitis
ERCP	endoscopic retrograde cholangiopancreatography
ICP	idiopathic chronic pancreatitis
post-ERCP pancreatitis	PEP
SOD	Sphincter of Oddi

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Figure 1.
Methodological Summary

Table 1

Univariate Analysis

Variable	Case (%)	Control (%)	*P*-value
Mean Age (std dev)	52.4 (15.4)	52.2 (16.1)	0.928*
Age < 60 years old	91/123 (74.0%)	187/248 (75.4%)	0.767
Female	91/123 (74.0%)	183/248 (73.8%)	0.968
Suspected SOD	49/123 (39.8%)	40/248 (16.1%)	<0.001
Pancreatic Sphincterotomy	25/123 (20.3%)	11/248 (4.4%)	<0.001
Mod./Diff. Cannulation	49/123 (39.8%)	58/248 (23.4%)	0.001
≥ 2 Pancreatic Injections	14/123 (11.4%)	10/248 (4.0%)	0.007
Pancreatic Stent Placement	32/123 (26.0%)	31/248 (12.5%)	0.001
Alcohol Use Status			
Current drinker	67/120 (55.8)	56/222 (25.2)	<0.001
Former drinker	14/120 (11.7)	17/222 (7.7)	<0.001
Cigarette Smoking Status			
Current smoker	16/120 (13.3)	43/222 (19.4)	<0.001
Former smoker	33/120 (27.5)	23/222 (10.3)	<0.001
Mean pack–years for smokers (std dev)	28.1 (31.4)	19.2 (19.3)	0.171†

*Two Sample T-Test

†Kolmogorov-Smirnov Two-Sample Test

Table 2

Multivariate Analysis

Variable	OR	95% CI	*P*-value
Suspected SOD	3.69	1.94–7.02	<0.001
Pancreatic Sphincterotomy	5.91	2.04–17.14	0.001
Mod./Diff. Cannulation	1.70	0.92–3.14	0.091
≥ 2 Pancreatic Injections	1.52	0.53–4.34	0.439
Pancreatic Stent Placement	0.70	0.29–1.70	0.430
Alcohol Use Status			
Current drinker	4.70	2.60–8.50	<0.0001
Former drinker	2.33	0.87–6.22	0.091
Cigarette Smoking Status			
Current smoker	0.30	0.09–1.03	0.055
Continuous pack-years	1.04	0.99–1.09	0.098
Former Smoker	3.29	1.28–8.44	0.013
Continuous pack-years	1.00	0.98–1.02	0.978

All results adjusted for stratified variables of age < 60 and gender.