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The Effect of Cigarettes on Acute Pancreatitis Among Patients in Saudi Arabia

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ABSTRACT

Background and purpose: Questions remain unclear about the association of smoking status and the development of acute pancreatitis (AP). We performed a meta-analysis of observational studies to explore this association. **Materials and Methods:** A computerized literature search was performed in MEDLINE and EMBASE through October 15, 2016. We also searched the reference lists of pertinent articles. We used a rand om-effects model to calculate the summary relative risks (SRRs) and their corresponding 95% confidence intervals (CIs).

Results: A total of 8 observational studies (4 case control and 4 prospective cohort/nested case control studies) were identified. Compared with never smokers, the summary RR estimates were 1.49 (95% CI, 1.29-1.78) for ever smokers, 1.69 (95% CI, 1.42-2.21) for current smokers, and 1.19 (95% CI, 1.11-1.52) for former smokers. Smoking is found to be a potential risk factor for alcohol use, idiopathic factors and drugs related AP, but not for gallstone related AP, in the ever and current smokers. A dose response effect of tobacco use on the risk was ascertained: current smokers had a 40% (95% CI, 30%-50%) increased risk of AP for every additional 10 cigarettes per day.

Conclusion: The current analysis suggests that smokers have an elevated risk of AP development. Further studies, however, are warranted before definitive conclusions can be drawn.

Keywords: pancreatitis, cigarettes, smoking, meta-analysis.

INTRODUCTION

The occurrence of acute pancreatitis (AP) has increased worldwide in latest years [1, 2]. Most incidences of AP are self-limiting and mild, necessitating only a short hospitalization [3]; nevertheless, nearly 20% of acute pancreatitis patients will progress to a life-threatening condition with local and extra-pancreatic complications categorized by the early progress of multi-organ failure [4].

In the overall population, 80-90% of AP cases happen due to either gallstone disease or alcohol abuse [5]. Numerous other risk factors as well have been suggested, containing high levels of triglycerides, diabetes mellitus (DM), hypercalcemia, drugs, and a high body mass index (BMI) or obesity [6].

The role of smoking in the threat of pancreatic cancer and chronic pancreatitis has been clarified [7], though, its role in the threat of acute pancreatitis has not been established. Some earlier studies that have examined the association between smoking status and risk of acute pancreatitis have yielded inconsistent results [8-15].

When we were arranging this manuscript, we have taken into consideration studies which reported AP related to alcohol use [8], antihypertensive medications [9, 15], endoscopic retrograde cholangiopancreatography pancreatitis (ERCP) [10], or reported only of persons who had ever smoked (ever-smokers) [11] and other factors. The aim of the current study was to examine the important epidemiological observations linking tobacco smoking to acute pancreatitis development.

MATERIALS AND METHODS

This meta-analysis was carried out following the meta-analysis of observational studies in epidemiology (MOOSE) guidelines [16]. Two independent reviewers carried out a computerized literature search in MEDLINE (from January 1, 1965) and EMBASE (from January 1, 1974), up to 15 October, 2016.

We searched the relevant studies, additional studies were retrieved by hand searching reference lists of original studies and review articles on this topic. Only articles written in English were included.

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- **Data searches and study selection**

Studies were included in case that they met all of the following criteria:

- based on an observational design,the outcome of interest was AP,the exposure of interest was tobacco smoking; and providing relative risk (RR) estimates and their 95% confidence intervals (CIs) or sufficient data to calculate these numbers.

Disagreement was resolved by discussion between the investigators. Excluded articles included non-peer- reviewed articles, ecological and prevalence studies, case reports, and molecular researches. We also excluded studies which reported risk estimations for recurrent AP, or AP and chronic pancreatitis (CP) combined. To carry out a more inclusive etiologic subgroup analysis, we included studies for post-ERCP related AP (PEP).

In cases of studies appeared in more than one article, only the most recent study was included. Two authors independently evaluated all potentially relevant articles from the databases.

- **Data extraction**

Data were abstracted independently by 2 reviewers using a standardized data collection form to increase the uniformity and to decrease reporting bias. In the case of discrepancy, a consensus decision was made with the help of the senior author. The following data were extracted from each study included: first author's last name, country where the study was performed, year of publication, year of study conducted, study design, ascertainment of outcome, sample size, duration of follow-up, variables adjusted for in the analysis, and the relative risk estimates with their corresponding 95% CIs.

The study was done according to the ethical board of Umm Al Qura university.

Statistical analysis

We divided epidemiological studies of the relationship between smoking status and AP risk into two general types according to design: (nested) case control studies (OR), cohort studies (rate ratio). In practice, these two measures of effect yield similar estimates of RR because the absolute risk of AP is low. All statistical analyses were performed with STATA, version 11.0 (STATA, College Station, TX, USA). A two-tailed P value <0.05 was considered to be significant.

Summary relative risk (SRR) estimates with their corresponding 95% CIs were calculated with a random-effects model that considers both within- and between-study variation [17]. In case that studies reported risk estimations for several levels of smoking, but did not report results for smoking status, we combined the risk estimates for each exposure level according to a fixed-effects model.

RESULTS

The detailed search steps are described in Figure 1. Briefly, from the initial literature search, we identified and screened 1429 articles. Twenty four articles were considered to be of interest and their full text was retrieved. Sixteen of these 24 articles were subsequently excluded for different reasons.

Therefore, a total of 8 articles (4 case control and 4 cohort/nested case control studies) were used in this meta-analysis (Table 1). These 8 studies were published between 1996 and 2014. Acute pancreatitis was defined as upper abdominal pain with a serum amylase level of more than two times the upper limit of normal within 72 h after admission to the hospital, and/or with confirmatory evidence of AP on ultrasonography, computerized tomography in 5 studies [8-12]. In the remaining five studies, the ascertainment of AP was based on medical claims or diagnostic codes.

Table 1: Characteristics studies of smoking status and the risk of AP development

Author	year	Cases/ control or participants, n	Acute pancreatitis assessment	Smoking status	Estimate (95% CI)	Follow-up, years
Prospective cohort/nested case control						
Lindkvist	2008	179/33346	Diagnosis registries	Former Current <20 cig/d 20-30 cig/d >30 cig/d	1.09 (0.66-1.80) 2.14 (1.48-3.09) 1.84(1.19-2.85) 3.19(2.03-5.00) 2.87(1.57-5.24)	11,3
Tolstrup	2009	235/17905	Discharge register	Former <15 cig/d 15-24 cig/d 25 + cig/d	2.3 (1.3-4.1) 2.0 (1.1-3.6) 2.8 (1.5-5.0) 3.8 (1.9-7.5)	20,2
Bexelius	2009	265/2000	1 + 2 or 1 + 3	Former Current	1.2 (0.85-1.68) 1.41 (1.04-1.91)	3,8
Sadr-Azodi	2012	541/84,667	Discharge register	Former Current <20 pk-y 20 + pk-y	1.19 (0.97-1.46) 1.33 (1.07-1.66) 1.11 (0.80-1.54) 1.53 (1.17-2.01)	12
Case-control						
Talamini	1996	67/265	1 + 2	1-10 cig/d 11-20 cig/d >21 cig/d	1.44(0.41-5.00) 3.63(1.53-8.58) 6.44(2.73-15.2)	-
Eland	2006	724/1791	1 + 2 or 1 + 3	1-10 cig/d 11-20 cig/d >21 cig/d	0.9 (0.7-1.3) 1.7 (1.3-2.2) 2.0 (1.1-3.4)	-
DiMagno	2013	211/348	1 + 2 or 1 + 3	Former Current	0.87(0.70-1.07) 0.4(0.2-0.8)	-
Yang	2014	45/23294	1 + 2 or 1 + 3	Ever	2.66(1.48e4.78)	-

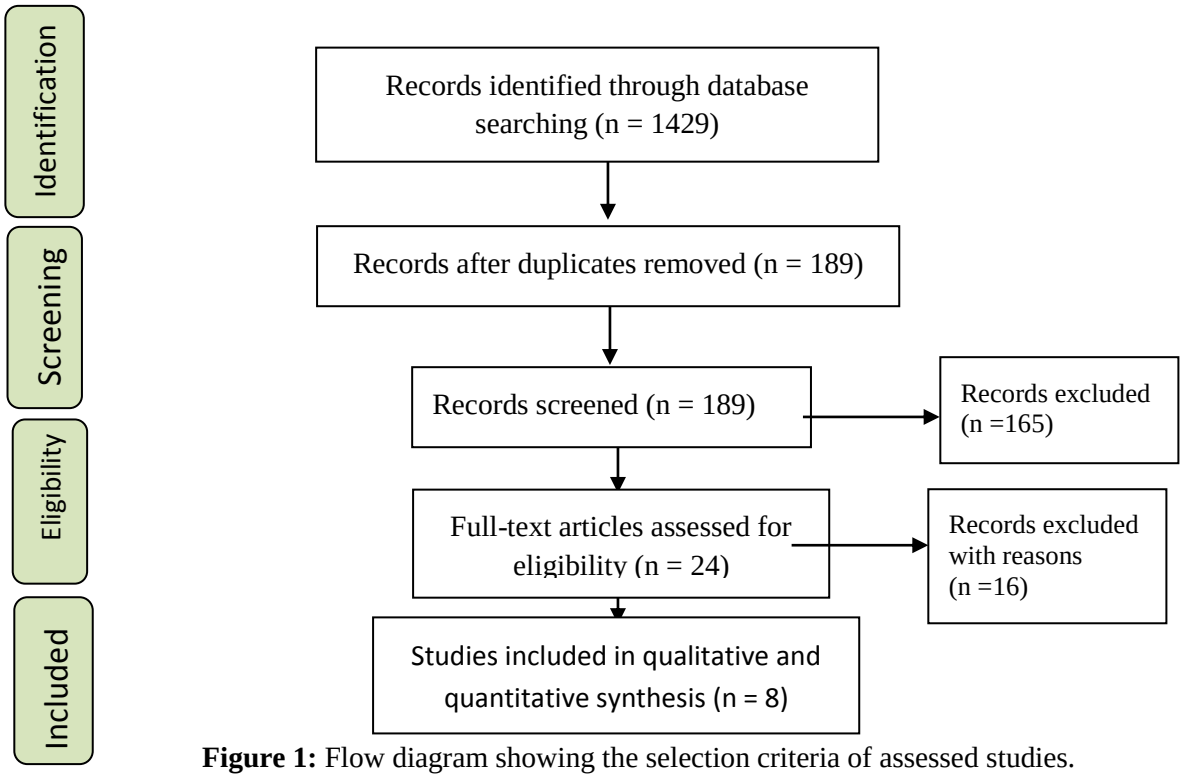

Figure 1: Flow diagram showing the selection criteria of assessed studies.

As shown in Table. 2, compared to never smokers, the summary risk estimates were 1.49 (95% CI = 1.29-1.78) for ever smokers based on 8 studies, 1.69 (95% CI = 1.42-2.21) for current smokers based on 7 studies. There was evidence of significant heterogeneity among the studies of ever smokers (Pheterogeneity < 0.001, I^2 = 75.2%), of current smokers (Pheterogeneity < 0.001, I2 = 77.4%), but not studies of former smokers (Pheterogeneity = 0.051, I^2= 47.8%).

Current smokers had a significantly higher risk of AP development than former smokers (P for difference = 0.001).

Table 2: Risk of AP development for ever smokers versus never smokers

Study	Relative Risk	(95%, CI)
Lindkvist, former	1,09	(0.66, 1.80)
Lindkvist, curr	2,14	(1.48, 3.09)
Tolstrup, former	2,3	(1.30, 4.10)
Tolstrup, curr	2,69	(1.88, 3.86)
Bexelius, former	1,2	(0.85, 1.68)
Bexelius, curr	1,41	(1.04, 1.91)
Sadr-Azodi, form	1,19	(0.97, 1.46)
Sadr-Azodi, curr	1,33	(1.07, 1.66)
Talamini, curr	3,84	(2.22, 6.63)
Eland, curr	1,37	(1.13, 1.65)
DiMagno,curr	0,4	(0.20, 0.80)
DiMagno,former	0,87	(0.70, 1.07)
Yang,ever	2,66	(1.48, 4.78)

Table 3: Risk of AP development for former smokers versus never smokers

Study	Relative Risk	(95%, CI)
Cohort		
Lindkvist	2,14	(1.48, 3.09)
Tolstrup	2,69	(1.88, 3.86)
Bexelius	1,41	(1.04, 1.91)
Sadr-Azodi	1,33	(1.07, 1.66)
Case-control		
Talamini	3,84	(2.22, 6.63)
Eland	1,37	(1.13, 1.65)
DiMagno	0,4	(0.20, 0.80)

There was no indication of publication bias according to either the Egger's test (P = 0.892 for ever, P = 0.391 for current, and P = 0.247 for former smokers, respectively) or the Begg's tests for each of the three smoking categories (P = 0.322 for ever, P = 0.250 for current, and P = 0.257 for former smokers, respectively)

We then conducted subgroup meta-analyses by geographical area, study design, number of cases, methods of assessing cases, duration of follow-up, and confounders. A stratified analysis agreeing with study design showed significant risk relations in the cohort/nested case control studies for each of the three smoking categories, while the summary RR was significant in case control studies for only ever-smokers. The approaches of evaluating cases

did not significantly alter the risk association. Alcohol abuse and BMI (obesity) are significant risk factors for the development of AP. When limiting the analysis to studies that were controlled for alcohol consumption or BMI (obesity), the summary RR evaluations were still significant for each of the 3 smoking categories. Besides, a stratified analysis for the methods of measuring alcohol use (as a dichotomous variable, or other approaches, comprising continuous variables, classification, a scoring system, etc.) presented somewhat higher risk estimates when the measure of alcohol use was a dichotomous variable.

We then performed a sensitivity analysis by ignoring one study at a time and calculated the pooled RR for the remaining studies, and found that there were no changes in the direction of the effect when any one study was excluded (data not shown). Meta-regression analysis showed that none was a significant factor for the high heterogeneity among studies of ever or current smokers.

Table 4: Risk of AP development for dose response analysis of per 10 cigarettes per day increase in current smokers.

Study	Relative Risk	(95%, CI)
Talamini	1,67	(1.37, 2.04)
Eland	1,27	(1.14, 1.42)
Lindkvist	1,47	(1.29, 1.68)

Three studies [8, 9, 12] were included in a dose response analysis, which found that current smokers had a 40% (95% CI, 30%-51%) increased risk of AP for every additional 10 cigarettes per day in comparison with never smokers (Table. 4).

DISCUSSION

The current meta-analysis extends our understanding of the effect of smoking on the pancreas and supports the evidence of the association between cigarette smoking and the risk for AP development, which is independent of BMI (obesity) and alcohol use. The likelihood of developing AP was proportional to the amount of tobacco use, suggesting that smoking exerts a dose-related effect on initiating acute pancreatic injury. Furthermore, smoking was found to be a potential risk factor for alcohol use, idiopathic factors and drug-related AP, but not for gallstone-related AP or PEP. In this meta-analysis, a small, but significantly higher risk was observed for former smokers than that for current smokers, suggesting that the effects of smoking on the pancreatic injury persist irreversibly at least for many years, even after cessation. For example, a follow-up study of 84,667 Swedish women and men found that two decades of smoking cessation were required to reduce the risk of non-gallstone-related pancreatitis to the level comparable to never smokers [14]. The suggestion between smoking status, and AP was further investigated in separate strata of different etiologies. We found that this association was not statistically significant in gallstone-related acute pancreatitis or PEP for each of the three smoking categories, whereas the summary RR was significantly increased in alcohol use, idiopathic factors, and antihypertensive medication-related acute pancreatitis, especially for alcohol associated AP. The different risk associations are expected from a pathogenetic point of view. It is thought that alcohol use, which interacts with nicotine, can promote stronger cholecystokinin-stimulated zymogen conversion and activation, thus inducing acute pancreatitis [18, 19].

Alcohol improves the inflammatory effect of smoking on the pancreas of rats, resulting in more pronounced ischemia and leucocyte sequestration [14]. The significance of smoking, thus, would be greater in alcoholic AP than in that of gallstone-related AP. On the other hand, smoking can lead to the accumulation of potentially harmful pancreatic proteases, which play a deteriorating role in the initial phase of AP [12]. Remarkably, based on one study [10], we found that current smoking is potentially protective against PEP, which contrasts with a latest report that active smoking is an independent interpreter of PEP [20]. Though, that study was underpowered (n = 36 cases of PEP) and the investigators omitted established PEP variables (moderate/ difficult cannulation, suspected sphincter of Oddi dysfunction [SOD], etc) from the analysis. Three hypothesized roles of nicotine have been recommended: an anti-inflammatory role [21], relaxation of the sphincter of Oddi [22], and reducing secretagogue-evoked necrosis in discrete pancreatic acinar cells [21], all of which might decrease PEP risk.

The nearness of a dose reaction relationship is thought to be a noteworthy paradigm for assurance of the causality of an affiliation. In this manner, we incorporated these factors in our meta-examination regardless of a few confinements, for example, the distinctions in the arrangement of presentation in the individual investigations. Curiously, there is by all accounts an immediate

connection between higher quantities of cigarettes smoked every day and an expanded danger of creating AP. Inside and out, these discoveries demonstrate inward consistency and bolster the legitimacy of our discoveries. The instrument that would clarify the lifted danger of AP in smokers is misty, albeit a few examinations have shown the conceivable impacts of nicotine on the pancreas. It has been accounted for that tobacco smoking can prompt the restraint of pancreatic emissions and expanded spillage of pancreatic zymogens into the circulatory system, both of which can actuate the improvement of AP [23]. Studies utilizing rodent models to research the impact of smoking on the pancreas have discovered expanded incendiary action and pancreatic catalyst union and gathering inside the pancreas [24].

There likewise might be an unevenness between generation of stomach related chemicals, for example, trypsinogen, and inhibitory antiprotease, for example, the pancreatic trypsin inhibitor, which has been seen in the rodent model of liquor incited pancreatitis [25]. Likewise, expanded articulation of stomach related compound qualities and lessened blood stream inside the pancreas have been seen in rats after presentation to tobacco smoke [14,25].

Lastly, as we did not endeavour to uncover unpublished studies and did not comprise studies with insufficient information to estimate a summary risk estimate, the likelihood of publication bias is inevitable. Truly, significant evidence of publication bias was observed rendering to the Begg's test, even though it was not evident rendering to the Egger's test.

CONCLUSION

This meta-analysis indicated that there is an increased risk of AP development in smokers. Nevertheless, the likelihood that the suggestion might be as a result of misclassification bias or confounding cannot be fully ruled out. Additional studies are necessary to determine the likely biological mechanism behind the association between smoking and acute pancreatitis.

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