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Original article

Meta-analysis: Tobacco smoking may enhance the risk of acute pancreatitis

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ABSTRACT

Background and aim: Questions remain unclear about the association of smoking status and the development of acute pancreatitis (AP). We performed a meta-analysis of observational studies explore this association.

Methods: A computerized literature search was performed in MEDLINE and EMBASE through November 30, 2014. We also searched the reference lists of pertinent articles. We used a random-effects model to calculate the summary relative risks (SRRs) and their corresponding 95% confidence intervals (CIs).

Results: A total of 3690 incident cases of AP included 12 observational studies (6 case–control and 6 prospective cohort/nested case–control studies) were identified. Compared with never smokers, the summary RR estimates were 1.54 (95% CI, 1.31–1.80) for ever smokers, 1.71 (95% CI, 1.37–2.14) for current smokers, and 1.21 (95% CI, 1.02–1.43) 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%–51%) increased risk of AP for every additional 10 cigarettes per day.

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

Introduction

The incidence of acute pancreatitis (AP) has increased worldwide in recent decades [1–3]. Most episodes of AP are self-limiting and mild, requiring only a short hospitalization [4]; however, approximately 20% of AP patients will progress to a life-threatening condition with local and extra-pancreatic complications characterized by the early development of multi-organ failure [5,6].

In the general population, 80–90% of AP cases occur as a result of either gallstone disease or alcohol abuse [7,8]. Several other risk factors also have been proposed, including high levels of triglycerides [9], hypercalcemia, a high body mass index (BMI) or obesity, drugs, and diabetes mellitus (DM) [10,11]. The role of smoking in the risk of pancreatic cancer and chronic pancreatitis has been clarified [12,13], however, its role in the risk of AP has not been established. Some previous studies that have investigated the association between smoking status and risk of AP have yielded inconsistent results [14–25]. When we were preparing this manuscript, a meta-analysis on the same topic was published, which included only five studies [26]. On reviewing the references, we found that seven studies were not included in that meta-analysis, which reported AP related to alcohol use [14], antihypertensive medications [16,25], multiple etiological factors [24], endoscopic retrograde cholangiopancreatography pancreatitis (ERCP) [23], or reported only of persons who had ever smoked ("ever-smokers") [20,27]. In addition, that meta-analysis did not report dose–response relationships or determine whether the etiologic classification of AP (gallstone, alcohol use, drugs, ERCP, etc) influences the association between smoking and the development of AP.

Therefore, the purpose of the present study was to examine the important epidemiological observations linking tobacco smoking to AP development.

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Materials and methods

This meta-analysis was carried out following the meta-analysis of observational studies in epidemiology (MOOSE) guidelines [28].

Data searches and study selection

Two independent investigators (S.X.B. and H.X.Q.) carried out a computerized literature search in MEDLINE (from January 1, 1966) and EMBASE (from January 1, 1974), up to 30 November, 2014. We searched the relevant studies with the following key words: 1) AP, and 2) cigarette OR tobacco OR smoke OR smoking. 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.

Studies were included in case that they met all of the following criteria: [1] based on an observational design; [2] the outcome of interest was AP; [3] the exposure of interest was tobacco smoking; and [4] 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 a study appeared in more than one article, only the most recent study was included. Two authors (S.X.B. and H.X.Q.) independently evaluated all potentially relevant articles from the databases.

Data extraction

Data were abstracted independently by 2 reviewers (S.X.B. and H.X.Q.) using a standardized data collection form to increase the uniformity and to reduce reporting bias. In the case of discrepancy, a consensus decision was made with the help of the senior author (Z.R.F.). The following data were extracted from the 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.

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 [29]. 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.

Publication bias was assessed using funnel plots and the further Begg's adjusted rank correlation test and Egger's regression asymmetry test [30,31]. Statistical heterogeneity among studies was evaluated using the Q and I^2 statistics [32]. For the Q statistic, a P value of less than 0.10 was considered representative of significant heterogeneity. For I^2, values of 25%, 50%, and 75% were assigned to low, moderate, and high heterogeneity, respectively [33]. We evaluated the role of several potential sources of heterogeneity by subgroup and meta-regression analyses according to study design (case–control vs. cohort/nested case–control study), geographical locations (USA, Europe and Asia), and the adjusted confounders: alcohol abuse, BMI (or obesity). We conducted sensitivity analysis to estimate the influence of each individual study on the summary results by repeating the random-effects meta-analysis after omitting 1 study at a time.

In the dose–response analysis, we considered cigarettes per day as explanatory variables, because only 2 studies reported risk estimations for pack-year [34,35]. We performed a dose–response meta-analysis using generalized least-squares trend estimation (GLST) analysis developed by Greenland and Orsini [36,37]. This method requires that the number of cases and person-time for at least 3 quantitative exposure categories are known. When this information was unavailable, we estimated the dose–response slopes using variance-weighted least squares (vwls) regression analysis. This method also requires medians for categories of exposure level. Because in many studies continuous exposures were reported as categorical data with a range, we assigned the midpoint of the range as the average exposure. For the highest open categories, we considered 60 cigarettes per day as the maximum [38]. When the lowest category was open-ended, the lowest boundary was considered as zero.

Results

Search results and study characteristics

The detailed search steps are described in Fig. 1. Briefly, from the initial literature search, we identified and screened 1709 articles. Thirty-five articles were considered to be of interest and their full text was retrieved. Twenty-seven of these 35 articles were subsequently excluded for different reasons. References were also reviewed, and four additional relevant studies were identified. Thus, a total of 12 articles (6 case–control and 6 cohort/nested case–control studies) were used in this meta-analysis (Table 1).

These 12 studies were published between 1996 and 2014, including a total of 3690 incident cases of AP. The continents or countries in which the studies were conducted were as follows: China (n = 1), the United States (n = 2), and Europe (n = 9). 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 seven studies [14–17,23,25,27]. In the remaining five studies, the ascertainment of AP was based on medical claims or diagnostic codes.

Quantitative data synthesis

As shown in Fig. 2A–C, compared to never smokers, the summary risk estimates were 1.54 (95% CI = 1.31–1.80) for ever-smokers based on 12 studies, 1.71 (95% CI = 1.37–2.14) for current smokers based on 10 studies, and 1.21 (95% CI = 1.02–1.43) for former smokers based on seven studies. There was evidence of significant heterogeneity among the studies of ever smokers ($P_{heterogeneity}$ < 0.001, I^2 = 77.4%), of current smokers ($P_{heterogeneity}$ < 0.001, I^2 = 79.6%), but not studies of former smokers ($P_{heterogeneity}$ = 0.047, I^2 = 49.0%). Current smokers had a significantly higher risk of AP development than former smokers (P for difference = 0.001).

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