SYSTEMATIC REVIEW AND META-ANALYSIS

DOI: http://dx.doi.org/10.15403/jgld-181

Association between Smoking and Risk of Primary Biliary Cholangitis: A Systematic Review and Meta-Analysis

Karn Wijarnpreecha[1], Monia Werlang[1], Panadeekarn Panjawatanan[2], Paul T. Kroner[1], Omar Y. Mousa[3], Surakit Pungpapong[1], Frank J. Lukens[1], Denise M. Harnois[1], Patompong Ungprasert[4]

1) Division of Gastroenterology and Hepatology, Mayo Clinic College of Medicine, Mayo Clinic, Jacksonville, Florida, USA
2) Department of Medicine, Bassett Medical Center, Cooperstown, New York, USA
3) Division of Gastroenterology and Hepatology, Mayo Clinic College of Medicine, Mayo Clinic, Rochester, Minnesota, USA
4) Clinical Epidemiology Unit, Department of Research and Development, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand

Address for correspondence:
Patompong Ungprasert, MD, MS
2 Wanglang Road, Bangkoknoi, Bangkok, Thailand 10700
p.ungprasert@gmail.com

Received: 03.04.2019
Accepted: 22.05.2019

ABSTRACT

Background & Aims: Studies have suggested that smokers may have a higher risk of primary biliary cholangitis (PBC) although the results have been inconsistent. This systematic review and meta-analysis aim to better characterize the risk of PBC among smokers by identifying all relevant studies and summarizing their results together.

Methods: A comprehensive literature review was conducted using Embase and Pubmed/MEDLINE databases from inception to September 2018 to identify all studies which compared the risk of PBC among current, ever and former smokers to non-smokers. Effect estimates from each study were extracted and combined together using the random-effect, generic inverse variance method of DerSimonian and Laird.

Results: Nine case-control studies with 21,577 participants met the eligibility criteria and were included in the meta-analysis. The risk of PBC among ever smokers was significantly higher than non-smokers with the pooled odds ratio (OR) of 1.31 (95% CI, 1.03-1.67; I^2 89%). Subgroup analysis found that the risk was higher in both former smokers (pooled OR 1.36; 95% CI, 1.01-1.84; I^2 75%) and current smokers (pooled OR 1.18; 95% CI, 0.94-1.50; I^2 79%), although the latter did not reach statistical significance. Immunomodulatory and cytotoxic effect of cigarettes were the possible mechanisms behind this increased risk.

Conclusions: A significantly increased risk of PBC among individuals who ever smoked was observed in this study, adding to the already long list of harmful health consequences of smoking.

Key words: primary biliary cholangitis – biliary cirrhosis – smoking – cigarettes – meta-analysis.

Abbreviations: PBC: primary biliary cholangitis.

INTRODUCTION

Primary biliary cholangitis (PBC) is a chronic autoimmune cholestatic liver disease characterized by the presence of anti-mitochondrial antibody and destruction of the intrahepatic bile ducts [1]. The reported prevalence of PBC was approximately 19 to 400 cases per 1,000,000 persons in Western countries [2, 3]. The exact cause of PBC is not known but is believed to be a complex interaction between genetic and environmental factors [4, 5]. Interestingly, PBC is often found in association with certain autoimmune disorders, such as inflammatory bowel disease and autoimmune thyroid disease [4].

Cigarette smoking is one of the leading causes of preventable death worldwide as a result of the increased risk of cardiovascular and pulmonary diseases and malignancy [6, 7]. In fact, even among smokers who have already developed cardiovascular disease, smoking cessation can reduce the risk of mortality by 36% compared with smokers who continued to smoke [8]. Smoking may also increase the risk of PBC as suggested by multiple epidemiologic studies, although the results were inconsistent [4, 9-16]. This systematic review and meta-analysis was conducted with the aim to better characterize the risk of PBC among smokers by identifying all relevant studies and summarizing their results together.

METHODS

Information sources and search strategy

A systematic literature search was conducted using the Embase and Pubmed / MEDLINE databases from inception to September

2018 to identify all original studies that reported the relationship between smoking and PBC. The systematic literature review was independently conducted by three investigators (K.W., P.P., and P.U.) using the search strategy that included the terms for "primary biliary cholangitis", "primary biliary cirrhosis", "smoking" and "cigarettes". A manual search for additional potentially relevant studies using the references of the included studies and selected review articles was also performed. No language limitation was applied. This study was conducted in accordance to the PRISMA (Preferred reporting Items for Systematic Reviews and Meta-Analysis) (see Supplementary TableI). EndNote X7 (Clarivate Analytics, Pennsylvania, United States) was used for study retrieval.

Selection criteria

Eligible studies must be case-control or cohort studies that compared the risk of PBC among current smokers, ever smokers and former smokers versus non-smokers. Eligible cohort studies must start with recruitment of smokers and non-smokers (without history of PBC at enrollment) and follow them until the occurrence of PBC or the end of the study. Eligible case-control studies must recruit cases with PBC and controls without PBC and ask for their smoking status (current, former and never). Eligible studies must provide the effect estimates (odds ratios, OR, relative risks, RR, hazard ratios, HR or standardized incidence ratio, SIR) with 95% confidence intervals (CI) or sufficient raw data to calculate those effect estimates. Inclusion was not restricted by study size. When more than one study using the same database / cohort was available, only the study with the most comprehensive data / analyses was included.

Retrieved articles were independently reviewed for their eligibility by the same three investigators. Discrepancy was resolved by conference with all investigators. The Newcastle-Ottawa quality assessment scale was used to appraise the quality of the included studies in three areas, including identification and recruitment of participants, the comparability between the two groups and the ascertainment of the outcome of interest for the cohort study and the exposure of interest for the case-control study [17]. Kappa statistics were used for the evaluation of inter-rater agreement on the Newcastle-Ottawa scale.

Data abstraction

A structured data collection form was used to extract the following data from each study: title of the study, publication year, name of the first author, calendar year(s) when the study was conducted, country or countries where the study was conducted, number of subjects, demographic data of subjects, methods used to identify and verify diagnosis of PBC as well as smoking status, adjusted effect estimates with 95% CI and covariates that were adjusted in the multivariable analysis.

To ensure the accuracy, this data extraction process was independently performed by two investigators (K.W. and P.P.). Case record forms were cross-checked by the senior investigator (P.U.). Any data discrepancy was resolved by referring back to the original articles.

Statistical analysis

Data analysis was performed using the Review Manager 5.3 software from the Cochrane Collaboration (London, United Kingdom). Adjusted point estimates for the association between smoking status and PBC from each study were extracted and combined using the generic inverse variance method of DerSimonian and Laird, which assigned the weight of each study in the pooled analysis inversely to its variance [18].

In light of the high likelihood of between study variance because of the difference in background populations, a random-effect model was used. Cochran's Q test and I^2 statistic were used to determine the between-study heterogeneity. This I^2 statistic quantifies the proportion of total variation across studies, which is due to true heterogeneity rather than chance. A value of I^2 of 0-25% represents insignificant heterogeneity, 26-50% represents low heterogeneity, 51-75% represents moderate heterogeneity and more than 75% represents high heterogeneity [19]. We used a funnel plot and the Egger's regression test for the assessment of the presence of publication bias. We performed Egger's regression test using Comprehensive Meta-analysis 3.0 software (Englewood, New Jersey, United States) [20].

RESULTS

Two hundred and eighty-three potentially eligible articles were identified using the described search strategy (99 articles from Medline and 184 articles from EMBASE). After the exclusion of 98 duplicated articles, 185 articles underwent a title and abstract review. A total of 165 articles were excluded at this stage since they clearly did not fulfill the eligibility criteria based on the type of article, study design, population and measured outcomes, leaving 20 articles for a full-text review. Eight of them were excluded after the full-length review, as they did not report the outcome of interest. Three articles were excluded because they were descriptive studies without comparators. Finally, nine case-control studies [4, 9-16] with 21,577 participants were included in the meta-analysis. The literature review and selection process are demonstrated in Fig. 1. The characteristics and quality assessment of the studies are presented in Table I. It should be noted that the inter-rater agreement for the quality assessment using the Newcastle-Ottawa scale was high with the kappa statistics of 0.68.

Risk of primary biliary cholangitis among ever smokers, former smokers and current smokers

Overall, the pooled analysis demonstrated an increased risk of PBC among ever smokers compared with non-smokers with the pooled OR of 1.31 (95% CI, 1.03-1.67). Statistical heterogeneity was high with I^2 of 89%. Subgroup analysis found the increased risk of PBC in both former smokers and current smokers, although a statistical significance was not reached by the latter (pooled OR 1.36; 95% CI, 1.01-1.84; I^2 of 75% and pooled OR 1.18; 95% CI, 0.94-1.50; I^2 of 79%, respectively). The forest plots of the meta-analyses of the risk of PBC among ever smokers, former smokers and current smokers are shown in Figs. 2, 3 and 4, respectively.

Sensitivity analysis

To further explore the high between-study heterogeneity of the main analysis of ever smokers versus non-smokers, a

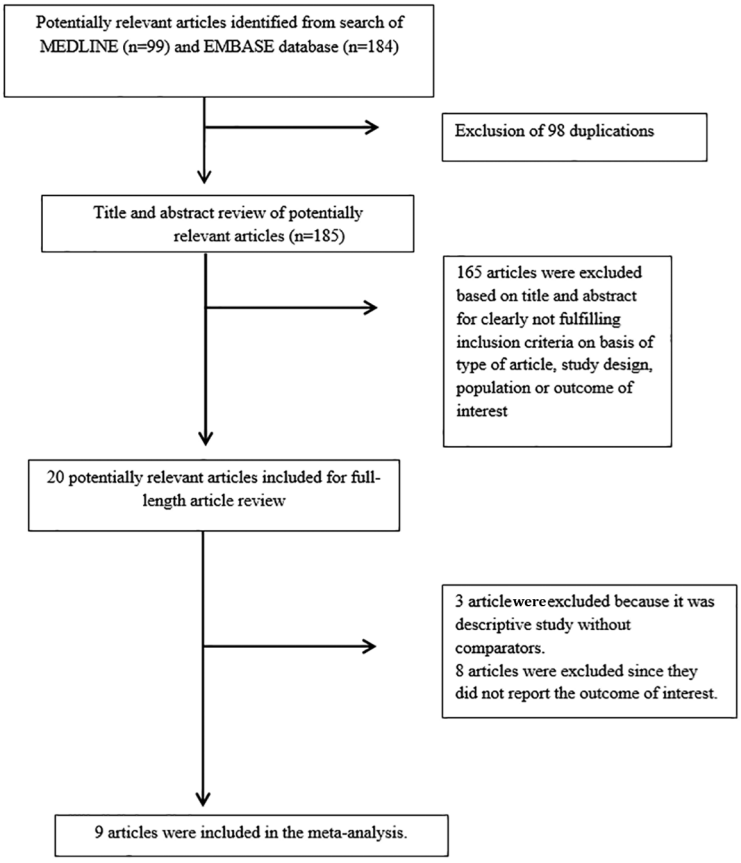

Fig. 1. Literature review process

sensitivity analysis based on quality of the included studies was performed. This sensitivity analysis excluded two studies [12, 16] with obvious methodological drawback from the full analysis. The study by Varyani et al. [16] was excluded because it was the only study that diagnosed PBC based on diagnostic codes alone without further case verification which would result in a limited accuracy of case identification. The study by Lammert et al. [12] was excluded because it was the only study that did not match their controls to cases by age and sex. Therefore, it was likely that the result of this study

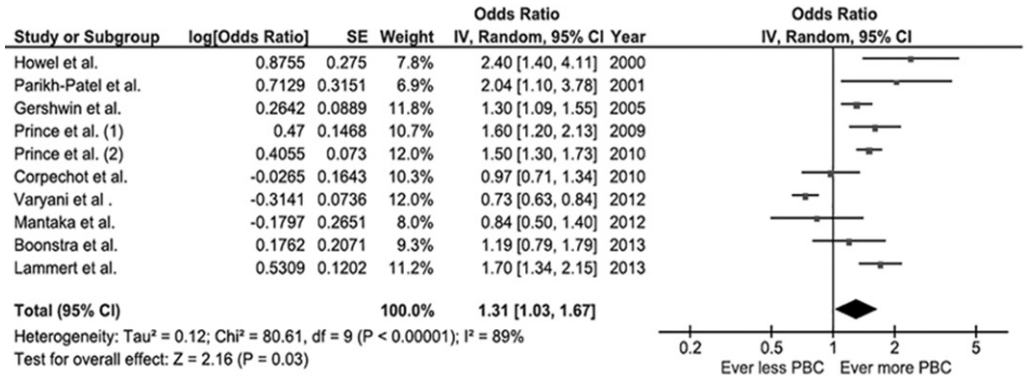

Fig. 2. Forest plot of the meta-analysis evaluating the risk of primary biliary cholangitis among ever smokers compared with non-smokers.

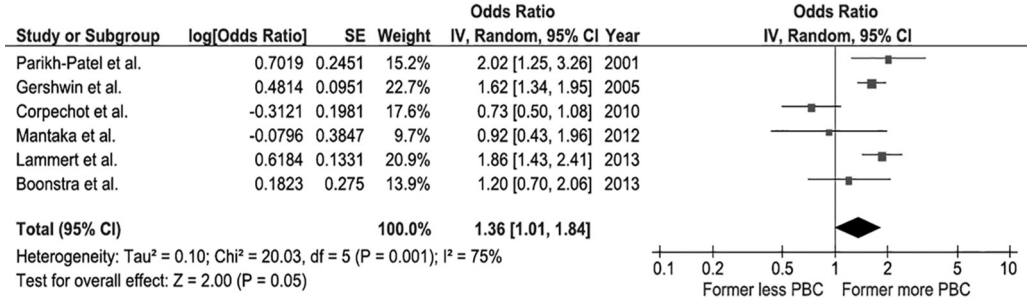

Fig. 3. Forest plot of the meta-analysis evaluating the risk of primary biliary cholangitis among former smokers compared with non-smokers.

Table I. Main characteristics of the studies included in this meta-analysis

Study	Howel et al. [11]	Parikh-Patel et al. [14]	Gershwin et al. [4]	Prince et al. [15]	Corpechot et al. [10]
Country/Year	UK/2000	USA/2001	USA/2005	UK/2009	France/2010
Total number of participants	322 (100 patients with PBC and 222 subjects without PBC)	342 (201 patients with PBC and 141 subjects without PBC)	2,073 (1,032 patients with PBC and 1,041 subjects without PBC)	5,014 (2,576 patients with PBC and 2,438 subjects without PBC)	731 (222 patients with PBC and 509 subjects without PBC)
Participants	Cases: patients with PBC aged 18 years and older who were first given the diagnosis between January 1, 1993 and October 31, 1995 and identified from a population-based register that covered 6 districts in the UK. Controls: individuals without PBC identified from the Family health service authority registers of the same regions with sex and age-matched to cases	Cases: Cases were patients with PBC identified from internet support group for PBC Controls: individuals without PBC who were friends of cases with PBC (names and addresses of controls were provided to investigators by cases) with sex and age-matched to cases	Cases: patients with PBC seen by hepatologists from one of the study 23 centers across the US between November 1999 and June 2004. Controls: individuals without PBC selected by random-digit-dialing method with sex, age, ethnicity and geographic area-matched to cases	Cases: patients with PBC were identified from 2 sources (1) the survey of consultant gastroenterologists and hepatologists in the northeast England from 1997 to 2003 and (2) member list of the UK PBC foundation (cases with residency in the northeast area were excluded to avoid double counting) Controls: individuals without PBC randomly selected from electoral roll datasets with sex and age-matched to cases	Cases: patients with PBC were identified from the database of the Saint-Antoine hospital, Paris, France. Controls: individuals without PBC randomly selected from the Ipsos access panels with sex, age, and geographic area-matched to cases
Determination of smoking status	self-reported using health questionnaire	self-reported using health questionnaire	self-reported using health questionnaire	self-reported using health questionnaire	self-reported using health questionnaire
Diagnosis of PBC	At least 2 of the following criteria: (1) presence of AMA (≥1:40), (2) abnormal LFT (bilirubin, AST, and ALP), (3) compatible liver histology.	self-reported; half of them were also verified by the presence of AMA plus either cholestatic pattern of serum biochemical tests or compatible liver histology	Presence of AMA plus either cholestatic pattern of serum biochemical tests or compatible liver histology. In the case of negative AMA, diagnosis can still be made with positive ANA or ASMA and presence of both cholestatic pattern biochemical tests and compatible liver histology.	At least 2 of the following criteria: (1) persistently cholestatic LFT over 3 months, (2) presence of AMA (≥1:40 or greater twice or more), (3) compatible liver histology	Presence of biochemical evidence of prolonged cholestasis, presence of AMA, and compatible liver histology
Percentage of females	Cases: N/A Controls: N/A	Controls: N/A Cases: N/A	Cases: 93 Controls: 92	Cases: 93 Controls: N/A	Cases: 89 Controls: 85
Average age of participants in years	Cases: N/A Controls: N/A	Cases: 53 Controls: 54	Cases: 58 Controls: 58	Cases: N/A Controls: N/A	Cases: 60 Controls: 59
Confounder adjusted in multivariate analysis	None	Other autoimmune disease, history of tonsillectomy and history of abdominal surgery	None	Age, alcohol intake, hair dye, appendectomy, tonsillectomy, thyroid disease, celiac disease, UTI, shingles and obstetric pruritus	None
Quality assessment (Newcastle-Ottawa scale)	Selection: 4 Comparability: 1 Outcome: 2	Selection: 4 Comparability: 1 Outcome: 2	Selection: 4 Comparability: 2 Outcome: 3	Selection: 3 Comparability: 1 Outcome: 2	Selection: 4 Comparability: 2 Outcome: 2

Study	Varyani et al. [16]	Mantaka et al. [13]	Lammert et al. [12]	Boonstra et al. [9]
Country	UK/2012	Greece/2012	USA/2013	The Netherlands/2013
Total number of participants	11,105 (1,009 patients with PBC and 10,096 subjects without PBC)	260 (111 patients with PBC and 149 subjects without PBC)	1,138 (522 patients with PBC and 616 patients without PBC)	592 (464 patients with PBC and 128 patients without PBC)

Table I (continued)

Participants	Cases: patients with PBC identified from the GPRD database which included over 50 million patient years of data from primary care physicians across the UK from 1987 to 2008 Controls: individuals without PBC randomly selected from the same database with sex and age-matched to cases	Cases: patients with PBC seen at the Department of Gastroenterology and Hepatology of the University Hospital of Heraklion, Crete Greece, from March to October, 2007 Controls: individuals without PBC who were recruited from the same hospital with sex, age and residence-matched to cases	Cases: patients with PBC identified from the MCPGE Registry which included PBC patients who followed at Mayo Clinic and other hospitals across the US Controls: individuals without PBC who were recruited from general internal medicine clinic of the Mayo Clinic	Cases: patients with PBC identified from the databases of 44 hospitals which covered 50% of the population of the Netherlands from 2008 to 2011 Controls: individuals without PBC who were recruited from outpatient clinic of 4 participating hospitals with sex and age-matched to cases
Determination of smoking status	retrieved from the database	self-reported using direct interview	self-reported using health questionnaire	self-reported using health questionnaire
Diagnosis of PBC	Presence of diagnostic codes of PBC in the database	Compatible clinical presentation, liver histology and biochemical parameters	Biochemical cholestasis for more than 6 months and compatible liver histology with or without the presence of AMA	Combination of compatible clinical presentation, elevation of liver ALP for at least 6 months and presence of AMA (≥1:40)
Percentage of females	Cases: 88 Controls: 88	Cases: 85 Controls: 85	Cases: 91 Controls: 75	Cases: 90 Controls: 84
Average age of participants in years	Cases: 63 Controls: 63	Cases: 65 Controls: 65	Cases: N/A Controls: N/A	Cases: 63 Controls: 61
Confounder adjusted in multivariate analysis	None	None	None	None
Quality assessment (Newcastle-Ottawa scale)	Selection: 4 Comparability: 1 Outcome: 2	Selection: 3 Comparability: 2 Outcome: 3	Selection: 3 Comparability: 1 Outcome: 2	Selection: 4 Comparability: 1 Outcome: 2

Abbreviations: ALP: alkaline phosphatase; AMA: antimitochondrial antibody; ANA: antinuclear antibody; ASMA; anti-smooth muscle antibody, AST: aspartate transaminase; GGT: gamma glutamyltranspeptidase; GPRD: the United Kingdom General Practice Research Database; LFT: liver function test; MCPGE: Mayo Clinic PBC Genetic Epidemiology; PBC: primary biliary cholangitis; UTI: urinary tract infection.

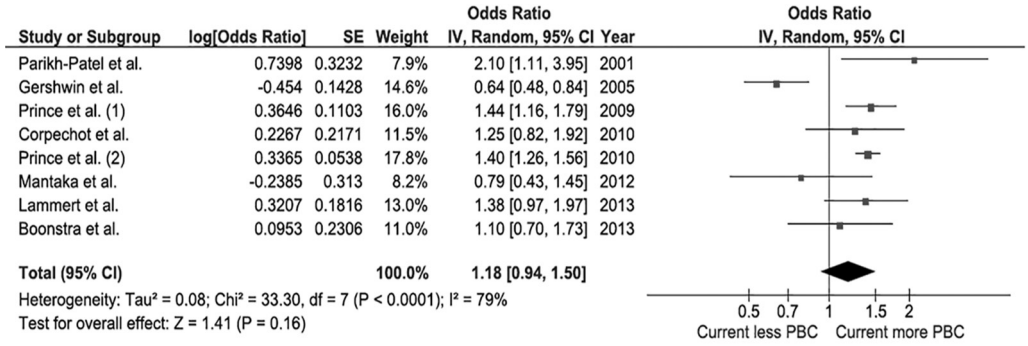

Fig. 4. Forest plot of the meta-analysis evaluating the risk of primary biliary cholangitis among current smokers compared with non-smokers.

was confounded by difference in baseline demographic data. Exclusion of these two studies from the full analysis did not significantly alter the pooled result (pooled OR 1.37; 95% CI, 1.16 – 1.62) and decreased between-study heterogeneity to moderate level (I^2 59%).

Evaluation for publication bias

The meta-analysis of the risk of PBC among ever smokers was used for the evaluation for publication bias as it was the meta-analysis with the highest number of included studies. The graph was symmetric and was not suggestive of publication bias (Fig. 5). In addition, publication bias was not detected by Egger's regression test with p-value of 0.44.

DISCUSSION

The current study is the first systematic review and meta-analysis that comprehensively investigated the relationship between PBC and smoking and found an approximately 30% increased risk of PBC among individuals who ever smoked. There are some plausible explanations for this observation.

First, cigarettes contain multiple cytotoxic and antigenic components that have detrimental effects on human body [21]. In fact, there is a report of a cluster of cases of PBC near a toxic waste site that produced chlorinated hydrocarbons-contaminated air. These chlorinated hydrocarbons, such as benzene, are also found in cigarettes [22].

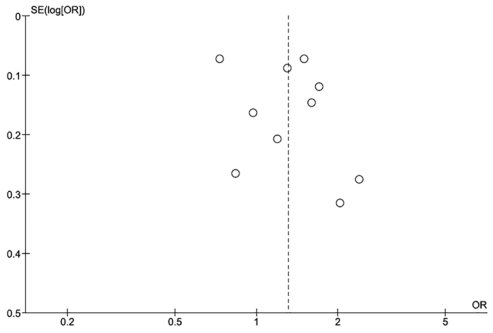

Fig. 5. Funnel plot of the meta-analysis evaluating the risk of primary biliary cholangitis among ever smokers compared with non-smokers.

Second, smoking is known to increase pro-inflammatory interleukins (such as IL-1, IL-6 and IL-8) and tumor necrosis factor alpha, which could disrupt the homeostasis of T cells, resulting in abnormal Th1 adaptive immune response [23-26]. This may have an implication in the pathogenesis of PBC, as Th1 cells are the predominant type of lymphoid aggregates seen in the liver of patients with this disease [27, 28].

It should be noted that subgroup analysis of this systematic review and meta-analysis found that the significantly increased risk of PBC was observed in former smokers but not in current smokers. It is difficult to find a biological mechanism to explain as to why smoking cessation would heighten the risk. The more likely explanation is that smokers who develop serious health consequences are more likely to quit smoking [29, 30], resulting in a lower number of current smokers and higher number of former smokers among cases with PBC.

Although the quality of the studies included in the current analysis was high as reflected by the high Newcastle-Ottawa scores and the literature review process was comprehensive, there are some limitations that should be acknowledged.

First, statistical heterogeneity was high in the meta-analysis. We believe that variation in quality of the included studies was one of the factors for the high between-study heterogeneity as sensitivity analysis excluding studies with obvious methodological drawback can reduce the heterogeneity to a moderate level. Second, all of the included studies were conducted in Western countries. Therefore, generalizability of the results to other populations is limited. Third, most studies included in this meta-analysis did not adjust their effect estimates for potential confounders. Therefore, it is also possible that the observed relationship is not causal and is a function of confounding effect.

CONCLUSION

The current study found a significantly increased risk of PBC among individuals who ever smoked, adding to the already long list of potential harmful health consequences of smoking.

Conflict of interest: None to declare.

Authors' contributions: K.W.: study concept and design, acquisition and analysis of data and drafting of the manuscript. M.W.: study concept and design, acquisition and analysis of data, and critical revision of the manuscript. P.P.: acquisition of data, analysis, of data and drafting manuscript. P.T.K., O.M.Y.: interpretation of data and critical revision of the manuscript. S.P., F.L.: study concept, critical revision of the manuscript, and study supervision. D.M.H., P.U. study concept and design, interpretation of data, drafting of the manuscript, critical revision of the manuscript, and study supervision.

Acknowledgement: We thank Melissa Scribani, a professional statistician at Bassett Medical Center in Cooperstown, New York, for her assistance with the review of statistical techniques used in this manuscript.

Supplementary material: To access the supplementary material visit the online version of the *J Gastrointestin Liver Dis* at http://dx.doi.org/10.15403/jgld-181

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	3-4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	3-4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	3-4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	3-4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4-5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4-5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4-5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Table 1
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5-6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5-6

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5-6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	5-6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Table 1
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Figure 2, 3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	6-7
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	6-7
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	6-7
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	7-8
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	8
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	8
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	9

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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