

Aspirin use is associated with a reduced risk of cholangiocarcinoma: a systematic review and meta-analysis

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Background: Aspirin has been revealed to probably decrease the risk of cholangiocarcinoma (CCC), which, nevertheless, is of controversy. To this end, a systematic review and meta-analysis was performed to investigate the above-described association.

Methods: We thoroughly searched PubMed, EMBASE, and ISI Web of Science for relevant studies published prior to October 2017, followed by random-effects model for calculation of pooled ORs and corresponding 95% CIs. Additionally, subgroup and sensitivity analyses were carried out to confirm whether the outcomes were stable.

Results: Nine articles, consisting of 12,535 CCC patients and 92,97,450 healthy controls, were enrolled in this study. We demonstrated a significantly decreased risk of CCC in those using aspirin, with studies being heterogeneous ($OR=0.69$; $CI=0.43-0.94$; $I^2=97.4\%$). Moreover, this relationship was detected only in case-control studies ($OR=0.65$; $95\% CI=0.38-0.93$), rather than cohort studies ($OR=0.94$; $95\% CI=0.70-1.27$). Besides, in separated analysis of intrahepatic CCC and extrahepatic CCC, aspirin was more strongly correlated with a declined risk of intrahepatic CCC ($OR=0.33$, $95\% CI=0.26-0.39$; $I^2=93.6\%$) than the risk of extrahepatic CCC ($OR=0.56$, $95\% CI=0.41-0.73$; $I^2=0\%$).

Conclusion: Collectively, the aspirin administration was correlated with a significant 31% decreased risk of CCC, particularly in the intrahepatic CCC.

Keywords: aspirin, cholangiocarcinoma, biliary tract neoplasms, meta-analysis

Introduction

Cholangiocarcinoma (CCC) is a type of malignancy derived from the bile duct epithelium, which was first described by Durand-Fardel in 1840.¹ These tumors can be categorized into intrahepatic (ICC), extrahepatic (ECC), and hilar cholangiocarcinoma according to tumor location.² Hilar cholangiocarcinoma is usually considered as ECC.³ CCC ranks the second among all primary hepatic carcinoma (HCC) in terms of incidence, accounting for 10%–25% of malignant HCCs and 3% of all gastrointestinal neoplasms.^{4,5} In addition, the incidence of CCC has continued to increase in recent years. Interestingly, there are certain differences of the epidemiological features between ICC and ECC. To be specific, there has been an increased incidence of ICC, while a decreased incidence of ECC in certain countries, including the UK and the USA.⁶ In the USA, the age-adjusted incidence rate of ICC has risen by 165% in the last two decades, whereas that of ECC has declined by 14%.⁷ In addition, CCC patients harbor a particularly poor prognosis. The overall 1-, 3-, and 5-year relative survival rates have been demonstrated to be 25.0%, 9.7%, and 6.8%, respectively, nearly without any changes in recent decades.⁸ The causes of CCC are still not well defined, with only several

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risk factors being identified, including parasitic infections, bile duct cysts, hepatolithiasis as well as primary sclerosing cholangitis.⁹ Recent studies have reported that some factors may increase CCC risk, including cirrhosis, hepatitis B or C, diabetes mellitus, gallstones, alcohol, and smoking.^{10–15} These risk factors have a common feature, which may be involved in the pathogenesis of CCC through a chronic biliary tract inflammatory process. Bile duct inflammation is a recognized cause of duct carcinogenesis.¹¹ Recently, a certain study has reported that aspirin, an inhibitor of COX-2, might suppress cancer progression by suppressing inflammatory processes.¹⁶ Moreover, aspirin has been demonstrated to probably decrease CCC risk. Nevertheless, the results are conflicting. Accordingly, this meta-analysis was conducted for a better evaluation of the relationship between aspirin use and CCC risk.

Methods

The present research was carried out in line with PRISMA Statement¹⁷ and the guidelines for Meta-analysis Of Observational Studies in Epidemiology (MOOSE).¹⁸

Data sources and search strategy

PubMed, EMBASE, and Web of Science databases were thoroughly searched for relevant published studies using the following keywords: (“aspirin” OR “non-steroidal anti-inflammatory drugs” OR “NSAIDs” OR “salicylate” OR “cyclooxygenase-2 inhibitors” OR “COX-2 inhibitors”) and (“biliary tract neoplasms” OR “cholangiocarcinoma” OR “bile duct cancer” OR “biliary tract cancer”). Neither language nor date of publication was restricted.

Inclusion criteria

Eligible studies were included if they met the following criteria: study design (case control or cohort); aspirin as the exposure factor and CCC or bile duct cancer or biliary tract cancer as the outcome; accessible OR/risk ratio (RR) values and corresponding 95% CIs or adequate data for calculation. In the case of the same data reported by two studies, the study with a larger sample was selected.

Data extraction and quality evaluation

The extraction of necessary data was independently conducted by two investigators (WX and JB) from the selected studies following standardized protocol. The following data were extracted from every article: name of first author, year of publication, country, study design (case-control or cohort), period of follow-up, number of subjects, adjusted confounding variables, sources of controls, and OR/RR values and 95% CIs.

The study quality was assessed by the Newcastle–Ottawa Scale (NOS),¹⁹ and quality categories were assigned in line with the scores of every research. The maximal score was 9 points. To be specific, NOS scores of <4, 4–6, and 7–9 suggested low-, medium-, and high-quality studies, respectively.²⁰ All discrepancies were handled by consensus.

Statistical analysis

The association between CCC risk and aspirin use was assessed by OR/RR values and corresponding 95% CIs, followed by quantification by random-effects model, which was proposed by DerSimonian and Laird.²¹ HRs were considered as equivalent to RRs.

The I^2 statistic was employed for quantification of heterogeneity between studies, where I^2 values of 25%, 50%, and 75% indicated low, medium, and high heterogeneity, respectively.²² A P -value <0.1 implicated the presence of heterogeneity. Meta-regression was used to evaluate the extent to which heterogeneity between the results was related to study design, geographical locations, and confounders adjusted for smoking status, alcohol use, and cholangitis. Funnel plots and Begg's²³ and Egger's²⁴ tests were employed to assess publication bias, where a P -value <0.05 or funnel plot asymmetry was indicative of bias.²⁵

Subgroup analyses were further conducted according to study design, geographic regions, tumor subtype, and whether smoking, alcohol consumption, or cholangitis were adjusted. Moreover, the stability of the outcomes was assessed by sensitivity analysis via sequential omission of one by one, which was conducted by altering the pooling model (fixed-effects model or random-effects model) and eliminating researches with NOS sources under 7 as well.²⁶

STATA version 12.0 (Stata) was employed for statistical analysis.

Results

Study selection and study features

The selection process is shown in Figure 1. In total, 605 studies were initially selected (118, 276, and 211 from PubMed, EMBASE, and Web of Science, respectively), while, 189 researches were repeated. Another 338 researches were eliminated after reviewing title and abstract. After further elimination of another five studies in consideration of inadequate information,^{27–31} nine eligible observational researches were ultimately enrolled in this meta-analysis.^{32–40}

The major features of nine enrolled researches are summarized in Table 1.^{32–40} Among them, four, three, and two studies were conducted in the USA, the UK, and China,

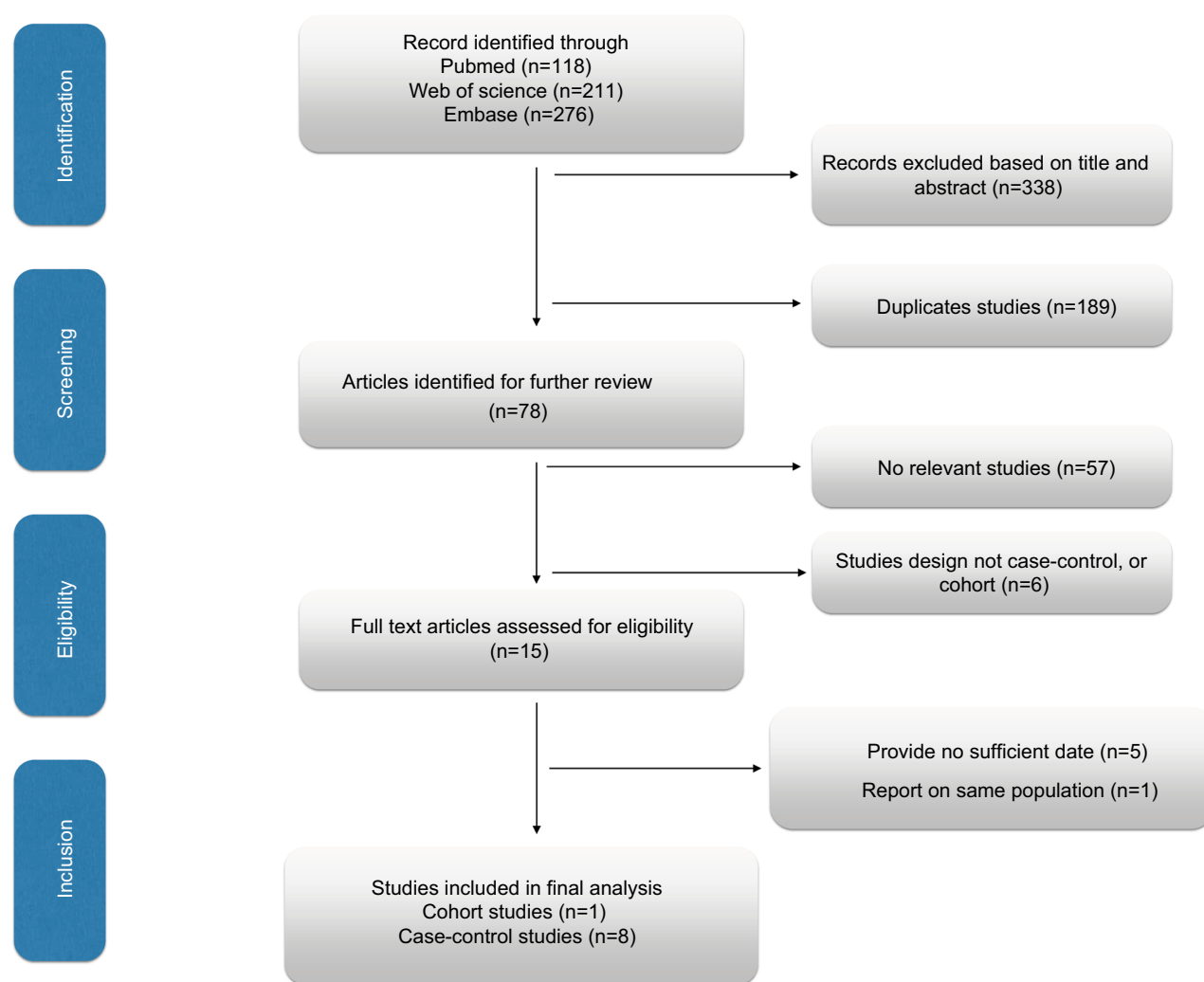


Figure 1 The process of study selection for the meta-analysis.

respectively, all of which, were observational ones. Eight of these studies were case-control design, while the remaining one was cohort design. A total of 12,535 CCC subjects and 92,97,450 healthy controls were included to examine the role of aspirin on CCC risk in this meta-analysis, ranging from 1977 to 2016. The NOS scores of all selected researches varied from 5 to 9, with seven high-quality researches and two of medium quality (Table 2).

Overall results

Of the nine researches, a significantly lower CCC risk was observed in those taking aspirin in three studies, while in the remaining six studies, there was no such correlation between the two. The pooled estimate was significant ($OR=0.69$; 95% $CI=0.43-0.94$), with studies being significantly heterogeneous ($I^2=97.4\%$; $P=0.001$; Figure 2). Compared with non-

use, aspirin administration was correlated with a significant 31% declined CCC risk. Nevertheless, the above correlation was detected only in case-control studies ($OR=0.65$; 95% $CI=0.38-0.93$), but not in cohort studies ($OR=0.94$; 95% $CI=0.70-1.27$; Table 3).

Subgroup and sensitivity analyses

The outcomes of subgroup and sensitivity analyses are displayed in Table 3. In the separated analyses of ICC and ECC, we found that aspirin was more strongly correlated with a declined risk of ICC ($OR=0.33$; 95% $CI=0.26-0.39$; $I^2=93.6\%$) than that of ECC ($OR=0.56$; 95% $CI=0.41-0.73$; $I^2=0\%$). Sensitivity analysis indicated that after elimination of studies with NOS sources <7 , aspirin use was stably related to CCC risk (Table 3). Moreover, the overall outcomes of the correlation between aspirin and CCC were stable in changing

Table 1 The main characteristics of the included studies

| Study/ Years of publication | Country | No. case/ person-years | Follow- up | Sources of controls | Subtype of cancer | Study design | Adjusted factors | Adjusted OR/RR (95% CI) |
|-------------------------------------|---------|---------------------------|---------------|---------------------------|-------------------------|------------------|--|---|
| Choi et al 2016 ³⁴ | USA | 2,395/4,679 | 2000– 2014 | Hospital | ICC ECC | Case- control | Age, sex, race, obesity, hypertension, diabetes, CVA, coronary artery disease, peripheral vascular disease, atrial fibrillation, nonalcoholic fatty liver disease/nonalcoholic steatohepatitis, PSC, cirrhosis, IBD, and smoking status | ICC :0.35 (0.29, 0.42) ECC:0.32 (0.27, 0.40) |
| Petrick et al 2015 ³⁹ | USA | 200/1,17,20,561 | 2001– 2013 | Population | ICC | Cohort | Sex, age (continuous), race (white, black, Asian/Pacific Islander, American Indian/Alaskan Native, other), cohort (AARP, AHS, USRT, PLCO, HPFS, CPSII, IWHS, BWHS, WHI, NHS), BMI (continuous), smoking status (nonsmoker, former smoker, current smoker), alcohol | 0.94 (0.70, 1.27) |
| Liu et al 2005 ³⁶ | China | 191/959 | 1997– 2001 | Population | ECC | Case- control | Age, sex, education, and biliary stone status | 0.48 (0.19, 1.19) |
| Burr et al 2014 ³³ | UK | 81/275 | 2004– 2010 | Population | CCC | Case- control | Age at diagnosis and gender, smoking and type2 diabetes | 0.45 (0.22, 0.92) |
| Grainge et al 2009 ³⁵ | UK | 286/3,913 | 1987– 2002 | Population | CCC | Case- control | Cigarette smoking, alcohol consumption, and BMI | 1.00 (0.80, 1.26) |
| Coogan et al 2000 ⁴⁰ | USA | 125/5,952 | 1977– 1998 | Hospital | ECC | Case- control | Age, sex, interview year, center, race, religion, cigarettes, family history of digestive cancer, education, and alcohol consumption | 0.5 (0.31, 1.1) |
| Peng et al 2015 ³⁷ | China | 720/840 | 2002– 2011 | Population | CCC | Case- control | NR | 1.13 (0.45, 1.67) |
| Altai et al 2017 ³⁸ | USA | 8,460/81,08,530 | 1999– 2016 | Hospital | CCC | Case- control | Age, gender, ethnicity, primary sclerosing cholangitis, inflammatory bowel disease, cirrhosis, smoking | 0.86 (0.82, 0.90) |
| Talboys et al 2011 ³² | UK | 77/251 | 2004– 2010 | Population | CCC | Case- control | Age and gender | 0.55 (0.28, 1.07) |

Abbreviations: AARP, American Association of Retired Persons; AHS, Agriculture Health Study; BCDDP, The Breast Cancer Detection Demonstration Project; BMI, body mass index; BWHS, Black Women's Health Study; CCC, cholangiocarcinoma; CPSII, Cancer Prevention Study II; CVA, cerebrovascular accident; ECC, extrahepatic cholangiocarcinoma; HPFS, Health Professionals Follow-up Study; IBD, inflammatory bowel disease; ICC, intrahepatic cholangiocarcinoma; NHS, Nurses' Health Study; NR, none reported; PLCO, Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; PSC, primary sclerosing cholangitis; RR, relative risk; WHI, Women's Health Initiative; USRT, United State Radiologic Technologist Study.

the pooling model (fixed-effects model: OR=0.64; 95% CI=0.61–0.67 and random-effects model: OR=0.69; 95% CI=0.43–0.94; Table 3). In sequential omission of research one by one for evaluation of the outcomes stability, the pooled risk estimate was not affected by any study (Figure 3). Meta-regression analyses were also performed to examine the potential source of heterogeneity, which, however, did not indicate that the study design ($P=0.980$), geographical locations ($P=0.965$), or confounders adjusted for smoking status ($P=0.914$), alcohol use ($P=0.759$), or cholangitis ($P=0.745$) was a source of heterogeneity.

Publication bias

The funnel plot failed to demonstrate any substantial asymmetry, neither did Begg's ($P=0.468$) nor Egger's tests reveal any substantial publication bias ($P>0.05$; Figure 4).

Discussion

Aspirin has been widely applied in prevention and treatment of diverse cerebrovascular disorders, such as myocardial infarction and stroke. At present, great attention has been paid to other potential benefits of aspirin globally. For instance, aspirin has been suggested to reduce the risk of certain types

Table 2 Scores of the Newcastle–Ottawa scale for included studies

| Case-control study | | | | | | | | | | |
|-------------------------------------|---|---|------------------------------|---|---|------------------------------|--|---------------------------|----------------|--|
| Study/ Years of publication | Fully defined cases | Representative cases | Selection of controls | Definition of controls | Controlling the important factors or confounding factors | Determination of exposure | Same method of determination for cases and control | Nonresponse rate | Total score | |
| Choi et al 2016 ³⁴ | * | * | * | * | ** | * | * | | 8 | |
| Liu et al 2005 ³⁶ | * | * | * | | ** | * | * | | 7 | |
| Burr et al 2014 ³³ | * | * | | * | ** | * | * | * | 8 | |
| Grainge et al 2009 ³⁵ | * | * | | * | * | * | * | * | 7 | |
| Coogan et al 2000 ⁴⁰ | * | * | * | * | * | * | * | | 7 | |
| Peng et al 2015 ³⁷ | * | * | * | | ** | | * | * | 7 | |
| Altafi et al 2017 ³⁸ | * | * | * | | ** | | * | | 6 | |
| Talboys et al 2011 ³² | * | | | * | * | * | | * | 5 | |
| Cohort study | | | | | | | | | | |
| Study/ years of Publication | Representativeness of exposed cohort | Selection of the non- exposed cohort | Determination of exposure | Outcome not present at study start | Controlling the important factors or confounding factors | Assessment of outcome | Follow-up long enough for outcome to occur | Integrity of follow up | Total score | |
| Petrick et al 2015 ³⁹ | * | * | | * | ** | * | * | * | 8 | |

Note: The asterisks represent a score (number of stars).

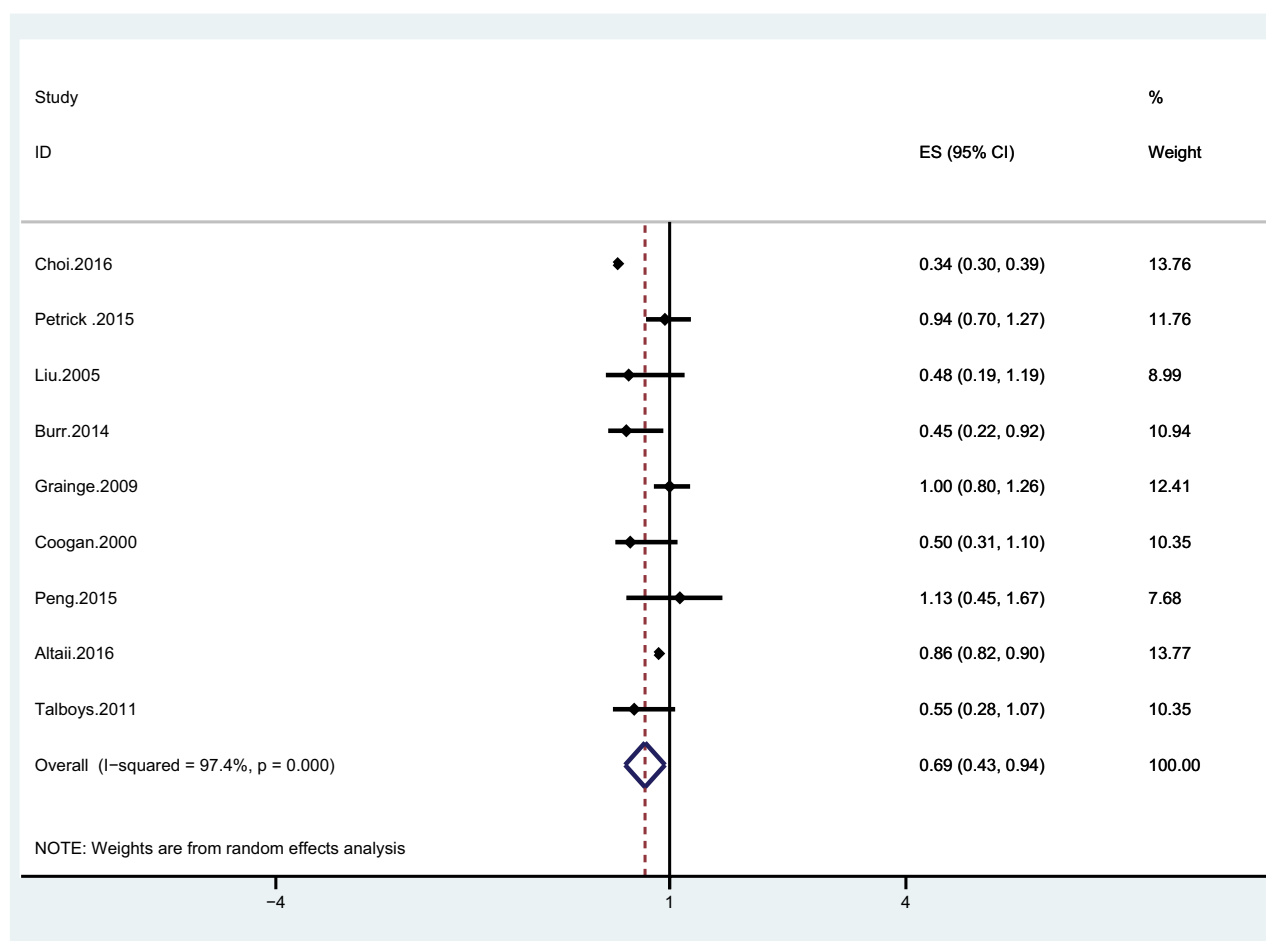


Figure 2 Forest plot showing the relationship between aspirin and the risk of cholangiocarcinoma.

Notes: Points represent the risk estimates for each individual study. Horizontal lines represent 95% CIs, and diamonds represent the summary risk estimates with 95% CIs. **Abbreviation:** ES, effect size.

of malignancies, including colorectum, stomach, esophagus, breast, ovary, and lung.^{41–45} As far as we know, this is the first comprehensive meta-analysis exploring the association of aspirin use with CCC risk. We collected nine researches to explore the role of aspirin on CCC risk, which demonstrated that aspirin administration was related to a significant 31% decreased risk of CCC, especially in ICC.

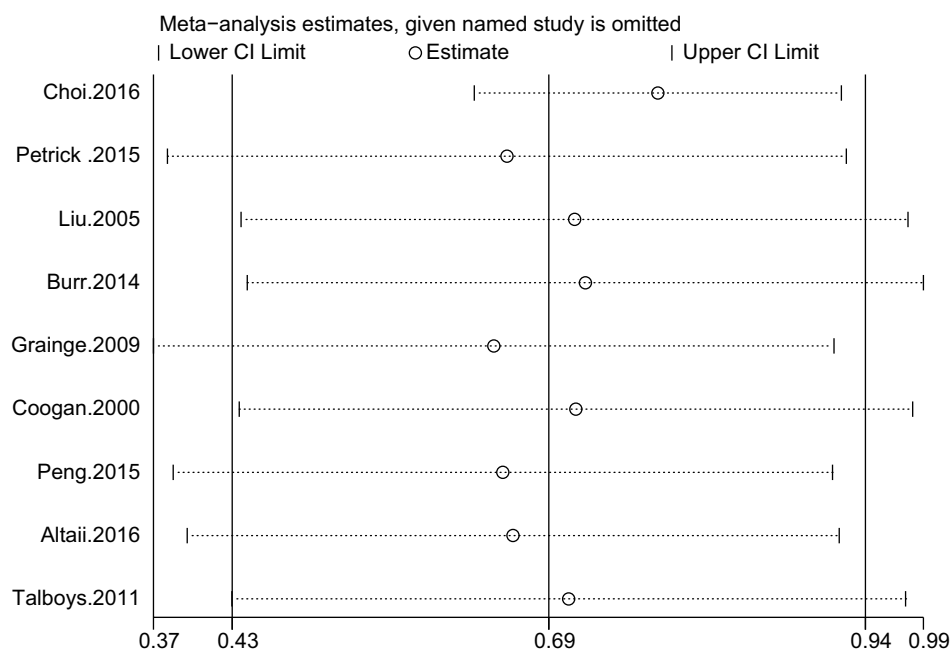
Our finding of a decreased risk of CCC in patients taking aspirin has multiple possible explanations. Firstly, a previous study reported that overexpression of COX-2 might be a critical characteristic human CCC,⁴⁶ indicating COX-2 as potentially important targets relevant to chemoprevention or adjunct therapy of CCC.^{47,48} Thus, inhibition of COX-2 by aspirin may prevent CCC development through inhibition of inflammatory processes. Secondly, bile duct inflammation is a recognized cause of bile duct carcinogenesis.¹¹ Therefore, suppression of COX-2 by aspirin might also inhibit CCC progression by suppressing inflammatory processes.¹⁶

The advantages of the study are as follows. To begin with, this is the first meta-analysis consisting of a large sample (12,535 CCC subjects and 92,97,450 healthy controls) in investigation of the role of aspirin in CCC risk, which might supply certain insight into the correlation of aspirin with CCC risk, and might be attractive in terms of CCC research. Moreover, further investigation concerning the mechanism of relationship of aspirin and CCC might give rise to novel therapeutic targets. Secondly, we further carried out subgroup and sensitivity analyses to identify the possible factors influencing the outcomes, which renders reliability of the present findings. Thirdly, the PubMed, EMBASE as well as Web of Science databases were comprehensively searched to collect possible researches in determining the factors affecting CCC risk. This systematic and comprehensive approach strengthened our findings. Additionally, the majority of enrolled researches harbored high quality in this meta-analysis. The above-described characteristics make our conclusions more reliable.

Table 3 Subgroup and sensitivity analyses of the effect of aspirin and the risk of cholangiocarcinoma

| Subgroup | No. of studies | RR (95% CI) | I ² value(%) | P-value |
|--|----------------|-------------------|-------------------------|---------|
| All studies | 9 | 0.69 (0.43, 0.94) | 97.4 | 0.001 |
| Subtype of cancer | | | | |
| ECC | 2 | 0.56 (0.41, 0.73) | 93.60 | 0.001 |
| ICC | 3 | 0.33 (0.26, 0.39) | | 0.565 |
| Geographic areas | | | | |
| West | 7 | 0.67 (0.39, 0.95) | 98 | 0.001 |
| East | 2 | 0.78 (0.43, 1.42) | 61.7 | 0.106 |
| Study design | | | | |
| Cohort study | 1 | 0.94 (0.70, 1.27) | – | – |
| Case-control study | 8 | 0.65 (0.38, 0.93) | 97.7 | 0.001 |
| Adjustment for confounders | | | | |
| Cholangitis | | | | |
| Yes | 2 | 0.60 (0.09, 1.11) | 99.7 | 0.001 |
| No | 7 | 0.73 (0.52, 0.94) | 57.2 | 0.029 |
| Smoking | | | | |
| Yes | 5 | 0.72 (0.39, 1.04) | 98.7 | 0.001 |
| No | 4 | 0.61 (0.36, 0.85) | 12.5 | 0.330 |
| Alcohol intake | | | | |
| Yes | 3 | 0.85 (0.59, 1.12) | 57.8 | 0.094 |
| No | 6 | 0.61 (0.29, 0.93) | 98.3 | 0.001 |
| Sensitive analyses | | | | |
| High-quality studies | 7 | 0.62 (0.32, 0.92) | 89.2 | 0.001 |
| Fixed-effects vs random-effects model method | | | | |
| Fixed-effects model | 9 | 0.64 (0.61, 0.67) | 97.4 | 0.001 |
| Random-effects model | 9 | 0.69 (0.43, 0.94) | 97.4 | 0.001 |

Abbreviations: ECC, extrahepatic cholangiocarcinoma; ICC, intrahepatic cholangiocarcinoma; RR, relative risk.

**Figure 3** Sensitivity analysis of the association between aspirin and the risk of cholangiocarcinoma.

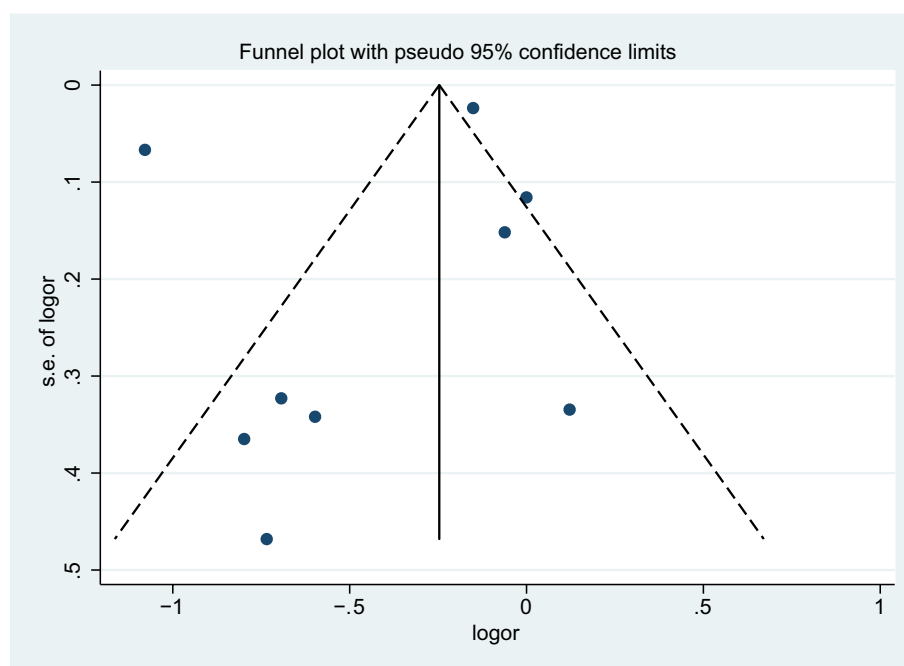


Figure 4 Funnel plot of studies included in the meta-analysis of the relationships between aspirin and the risk of cholangiocarcinoma.

Abbreviations: logor, logodds ratio; s.e., standard error.

There exist certain shortcomings in the study. To begin with, the majority of the enrolled researches were case-control ones, thereby possibly leading to the generation of recall as well as selection biases. Besides, the current outcomes are subject to diagnostic bias. Those taking aspirin are prone to receive physical examination more frequently, which might result in more diagnoses than controls in general. Secondly, we did not search for unpublished studies or for original data. Besides, we did not take into account the possible interactions with other drugs due to a lack of relative data. Aspirin administration is often associated with other drugs use, such as statin and angiotensin converting enzyme inhibitors, which could have concealed a possible relationship with aspirin.⁴⁹ Thirdly, we only investigated a correlation, which might be affected by confounding bias. The followings are well-defined risk factors for CCC, including parasitic infections, bile duct cysts, hepatolithiasis as well as primary sclerosing cholangitis,⁹ which, however, have been adjusted in a few studies. Fourthly, we failed to conduct a meta-analysis concerning the roles of different duration or doses of aspirin due to the restricted number of enrolled researches. Nevertheless, three studies reported results on the impact of both the dose of aspirin and the duration of aspirin treatment. Two studies^{34,36} indicated that the impact of aspirin was dose dependent, with strong effect estimates in patients with >3 years of aspirin

use in comparison with those harboring shorter use duration. Additionally, Choi et al³⁴ reveal that lower dose of aspirin (81–162 mg/day) may be more beneficial for CCC, than high dose aspirins (>325 mg/day). Petrick et al,³⁹ however, failed to discover a significantly different effect of aspirin when used for >163 mg or less. Finally, studies enrolled were significantly heterogeneous due to the differences in the study design, methods of measuring exposure, quality scores, and demographic characteristics inconsistency. In spite of inability to guarantee the source of heterogeneity, several sensitivity as well as subgroup analyses have been conducted to handle this issue.

In summary, our study indicated that aspirin administration was related to a significantly decreased CCC risk compared with those who never use aspirin. In the separate analysis of ICC and ECC, aspirin was suggested to be more strongly correlated with a decreased risk of ICC than that of ECC. More prospective and basic researches are warranted to confirm the correlation of aspirin with CCC risk as well as the potential mechanisms.

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Author contributions

JPX conceived the study and wrote the manuscript. JPX and HCH searched database, reviewed studies, and selected date. WYX, YB, and JB performed statistical analyses. YYX, HTZ, and XL critically revised the article for essential intellectual content and administrative support. All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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