SYSTEMATIC REVIEW AND META-ANALYSIS

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# Statins and Risk of Cholangiocarcinoma: A Systematic Review and Meta-analysis

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## ABSTRACT

**Background & Aims**: The use of statins has been shown to be associated with a decreased risk of cholangiocarcinoma (CCA) in many studies although the results have been inconsistent. We conducted this systematic review and meta-analysis to further investigate this possible association by identifying all relevant studies and combining their results together.

**Methods**: A comprehensive literature review was conducted utilizing the MEDLINE and EMBASE databases through March 2020 to identify all studies that compared the risk of CCA among individuals who use statins with individuals who do not use statins. Effect estimates from each study were extracted and combined using the random-effect, generic inverse variance method of DerSimonian and Laird.

**Results**: A total of seven studies with 6,251,187 participants fulfilled the eligibility criteria and were included in this meta-analysis. The pooled analysis found a significantly decreased risk of CCA among individuals who use statins compared with individuals who do not use statins with the pooled odds ratio of 0.68 (95% CI: 0.52-0.89; $I^2$ 96%).

**Conclusions**: The current systematic review and meta-analysis found a significant association between the use of statins and a decreased risk of CCA.

**Key words:** statins – bile duct cancer – biliary tract cancer – cholangiocarcinoma – meta-analysis.

**Abbreviations**: CCA: cholangiocarcinoma; CI: confidence interval; ECC: extrahepatic cholangiocarcinoma; HMG-CoA: 3-hydroxy-3-methylglutaryl coenzyme A; ICC: intrahepatic cholangiocarcinoma; OR: odds ratio; Rac1: Ras-related C3 botulinum toxin substrate 1; RR: relative risk.

## INTRODUCTION

Cholangiocarcinoma (CCA) are a heterogeneous group of biliary epithelial tumors, which are classified anatomically as intrahepatic cholangiocarcinoma (ICC) or extrahepatic cholangiocarcinoma (ECC) [1]. Data suggests that ICC and ECC are biologically different cancers, with differences in incidence, risk factors, and mortality [2]. The incidence of ICC is increasing in the United States and around the world [3-5]. The incidence of ECC, on the other hand, has remained stable [6]. The overall mortality associated with CCA in the United States has increased by 36% between 1999 and 2014 [6]. The survival rate for CCA is low as patients are often diagnosed at a later stage and thus, effective treatments are lacking [7-9]. Given the poor prognosis associated with the diagnosis of CCA, preventative strategies are of paramount significance.

The determinants of CCA risk are largely undefined but recently more attention is being paid to the role of lipid metabolism and metabolic syndrome on the risk of CCA. Some studies have shown a link between disorders of lipid regulation and metabolic syndrome and an increased risk of biliary tract cancers [10-12]. Statins, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, have been theorized to exert beneficial anti-cancer effects in CCA, but the presumed chemopreventive effect of statins remains controversial [13-19]. The aim of this systematic review and meta-analysis was to assess whether statin use is associated with a reduced risk of CCA.

## METHODS

A systematic literature search of the Ovid MEDLINE and EMBASE databases was carried out from inception to March 16, 2020 to identify all original studies that compared the risk of CCA between individuals who use statins and those who do not use statins. Three investigators (K.W., H.G., and P.U.) independently screened and reviewed the literature using the search strategy that included the terms for "cholangiocarcinoma", "bile duct cancer", "biliary tract cancer", "bile duct carcinoma", "hydroxymethylglutaryl coenzyme a reductase inhibitor", "atorvastatin", "lovastatin", "fluvastatin", "mevinolin", "pravastatin", "rosuvastatin", "simvastatin" and "pitavastatin" as described in the Supplementary file 1. No limitations on language, publication status or publication date were applied. References cited in selected articles were reviewed for additional eligible studies. We reported this systematic review and meta-analysis in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guideline [20], which is provided as the Supplementary file 2.

To be eligible for this meta-analysis, studies had to compare the risk of CCA among individuals who use statins versus individuals who do not use statins. The study design could be either a cohort study, a case-control study, or a cross-sectional study. Eligible cohort studies had to include two groups of participants, individuals who use statins and those who do not use statins and follow them for CCA incidence. The relative risk (RR) comparing the incidence of CCA between the two groups along with 95% confidence interval (CI) had to be provided. Eligible case-control studies had to include cases with CCA and controls without CCA and explore their prior history of statin use. Odds ratio (OR) comparing the prevalence of CCA between the two groups along with 95%CI had to be provided. Eligible cross-sectional studies had to recruit participants and explore whether they had CCA and statin use at the same time. OR of this association along with 95%CI had to be provided. Inclusion was not limited by study size. When more than one article utilizing the same database/cohort was available, only one study with the most comprehensive data/analyses was included.

Retrieved articles were reviewed for their eligibility independently by the same three investigators (K.W., H.G. and P.U.) with disagreements resolved by consensus. The Newcastle-Ottawa quality assessment scale was used to appraise the quality of cohort and case-control studies [21].

The investigators used a structured information collection form to extract the following data from each study: title of the study, name of the first author, publication year, year of study, study design, country where the study was conducted, number of participants, baseline characteristics of participants, methods used to identify and confirm the diagnosis of CCA, definition of statin exposure, adjusted effect estimates with 95% CI and covariates that were adjusted in the multivariate analysis.

To ensure the accuracy, this data extraction process was independently performed by two investigators (K.W. and H.G.) and was reviewed by the senior investigator (P.U.).

Data analysis was performed using the Cochrane Collaboration's Review Manager 5.3 software (London, United Kingdom). Adjusted point estimates from each study were consolidated by the generic inverse variance method of DerSimonian and Laird, which assigned the weight of each study for the pooled analysis based on the magnitude of its variance [22]. A random-effect model was chosen over the fixed-effect model because the basic assumption of the fixed-effect model that all studies should yield the same result is universally not true for observational studies. The RR of the cohort study was used as an estimate of OR to calculate pooled OR along with the OR of the case-control and cross-sectional study. Cochran's Q test and $I^2$ statistic were used to quantify the between-study heterogeneity. 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 [23]. A funnel plot was used for the assessment for the presence of publication bias.

## RESULTS

A total of 191 potentially eligible articles were identified using the described search strategy (75 from MEDLINE and 116 from EMBASE). After the exclusion of 72 duplicate articles, titles and abstracts of 119 unique articles were reviewed. One hundred and four articles were excluded at this stage since they were case reports, case series, correspondence, review articles, in vitro studies, animal studies or interventional studies, leaving 15 articles for full-text review. Eight were excluded after the full-length review because they did not report the outcome of interest. Finally, a total of seven studies [13-19] (two cohort studies [13, 16] and five case-control studies [14, 15, 17-19] with 6,251,187 participants were included in the meta-analysis. The literature retrieval, review and selection process are demonstrated in Fig. 1. The characteristics and quality appraisal of the included studies are presented in Table I. Inter-rater agreement for the quality assessment using the Newcastle-Ottawa scale was high with the kappa statistic of 0.85.

The pooled analysis found a significantly decreased risk of CCA among individuals who use statins versus those who do not use statins with the pooled OR 0.68 (95% CI, 0.52-0.89; $I^2$ 96%) as shown in Fig. 2. Statistical heterogeneity was high with $I^2$ of 96%. A funnel plot was constructed for the analysis of publication bias. The funnel plot was symmetric and, thus, was not suggestive of publication bias (Fig. 3).

## DISCUSSION

In this systematic review and meta-analysis, we observed a statistically significant association between statins use and the decreased risk of CCA. The statins impact the conversion of HMG-CoA to mevalonate, which in turn reduces the production of hepatic cholesterol. The pleiotropic effects of statins, including the potential cancer chemoprevention effect, are thought to be due to the inhibition of the synthesis of a variety of other metabolites, particularly isoprenoids, in addition to the inhibition of cholesterol biosynthesis [24, 25].

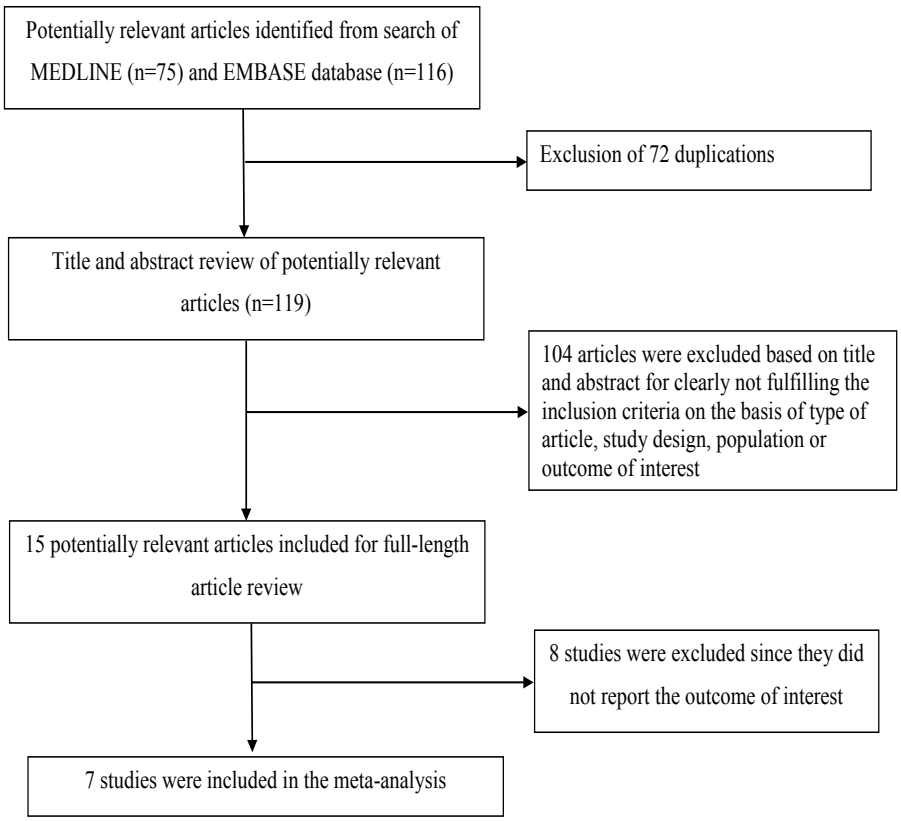


**Fig. 1**. Literature review process

Geranylgeranyl pyrophosphate and farnesyl pyrophosphate, isoprenoid intermediates, normally bind to Ras and Rho proteins, which play important roles in the cellular pathways of cancer progression. Statins reduce the isoprenylation of these proteins, which would decrease their ability to interact with effector molecules [26, 27]. In addition, Rho proteins are necessary for vascular endothelial growth factor activation and its downstream effects [28, 29]. All of this may eventually lead to the inhibition of tumor cell growth due to cell cycle arrest, inhibition of angiogenesis and induction of apoptosis.

There are also preclinical studies that specifically look at the effect of statins on CCA. Simvastatin was found to suppress cell proliferation by induction of G1 phase cell cycle arrest and apoptosis via caspase-3 activation, down-regulation of B-cell lymphoma 2 (Bcl-2) protein expression and increased Bcl-2-like protein 4 (Bax) expression in bile duct cancer cells [30]. Statins were also found to be associated with suppression of insulin-like growth factor-1 receptor expression, which is involved in carcinogenesis [30, 31]. In another preclinical study looking at the effect of statins on human CCA cells lines, they found that statins lead to apoptosis through the release of caspase-3 and cytochrome c [32]. Statins were also shown to be associated with the inhibition of migration of CCA cell [32]. Miller et al. [33] found that simvastatin is associated with the disruption of Ras-related C3 botulinum toxin substrate 1 (Rac1) co-localization in lipid rafts and down regulation of Rac1 activity. Rac1 is involved in multiple signaling pathways that control cytoskeletal reorganization, transcription and cell proliferation [33].

A few strengths of the current study should be noted. First, the systematic review technique allowed us to combine data from all available studies, including two large cohort studies [13, 16]. Second, all included studies were adjusted for basic confounders (age and gender) and some studies also were adjusted for additional confounders, such as body mass index, comorbidity, medication, smoking and alcohol consumption. Thus, at least some of the potential confounders were accounted for in the pooled analysis.

Although the quality of included studies was satisfactory, we acknowledge several limitations of our meta-analysis. First, there was a high heterogeneity between the studies, which is potentially due to differences in study population (some studies only included patients with hyperlipidemia [18, 19]), study designs, definition of statins exposure and definition of CCA, given some studies focused on ICC while others focused on ECC. The variation in the definition of statins exposure is of particular concern as some studies defined it very loosely as any use of statins. This could lead to a very limited amount of statins exposure that may not be enough to exert a protective effect against the development of CCA. Secondly, this is a pooled analysis of observational studies. Therefore, it is still possible that the observed association is a function of confounders rather than a true association. One particular concern is confounding by indication as most of statin users carry a diagnosis of dyslipidemia. Third, this study evaluated the effect of statins as a single medication group. Future studies are needed to clarify the type of statins, dosage and duration that may exert this potential benefit.

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

| Study, reference | Chaiteerakij et al. [19] | Peng et al. [15] | Liu et al. [17] | Menon et al. [13] | Marcano-Bonilla et al. [14] | Tran et al. [16] | Lavu et al. [18] |
|---|---|---|---|---|---|---|---|
| Country | USA | Taiwan | UK | UK | Sweden | UK | USA |
| Study design | Case-control | Case-control | Case-control | Case-control | Cohort | Cohort | Case control |
| Year | 2013 | 2015 | 2018 | 2019 | 2018 | 2020 | 2020 |
| Total number of participants | 421 (165 cases and 256 controls) | 6,348 (3,174 cases and 3,174 controls) | 10,000 (1,678 cases and 8,322 controls) | 903 (301 cases and 602 controls) | 5,760,482 | 471,851 | 1,182 (394 cases and 788 controls) |
| Recruitment of participants | Cases: Cases were hyperlipidemic patients with ICC seen at Mayo Clinic, Rochester between January 2000 and May 2010.<br><br>Controls: Controls were hyperlipidemic individuals without CCA who were randomly identified from the Mayo Clinic Biobank databases. They were matched to the cases by age, gender, ethnicity and residence. | Cases: Cases were patients aged over 20 years who were newly diagnosed with CCA between 2002 and 2011. Cases were identified from the Registry of Catastrophic Illnesses Patient Database.<br><br>Controls: Controls were individuals without CCA who were randomly identified from the Longitudinal Health Insurance Database 2000.<br><br>Both databases are derived from the National Health Insurance Research Database which covers 99% of residents of Taiwan. | Cases: Cases were patients aged over 20 years who were newly diagnosed with CCA between 1990 and 2017. Cases were identified from the UK Clinical Practice Research Datalink which contained information of about 13 million patients across the UK.<br><br>Controls: Controls were individuals without CCA who were randomly identified from the same database. Five controls were identified for one case. They were matched on sex, year of birth, diagnosis year, number of years in the general practice and in the database prior to diagnosis/ selection date. | Cases: Cases were patients aged over 20 years who were newly diagnosed with CCA. Cases were identified from The Health Improvement Network database between 1980 and 2015.<br><br>Controls: randomly subjects identified from the Health Improvement Network database matched by age, practice, and gender, with at least 1 year of follow up on the database. | Participants were identified from the Swedish Prescribed Drug Registry cohort which contained information of all prescriptions in Sweden. Follow-up was from July 1st, 2005 until December 31st, 2012. | Participants were identified from the UK Biobank database which recruited participants aged 40-69 years from England, Scotland and Wales from 2006 to 2010. Follow-up was until September 30th, 2014 (median follow-up duration was 4.6 years). | Cases were hyperlipidemic patients with ECC seen at Mayo Clinic, Rochester between January 2005 and May 2015.<br><br>Controls were hyperlipidemic individuals without CCA who were randomly identified from the Mayo Clinic Biobank databases. They were matched to the cases by age, gender, ethnicity and residence. |
| Diagnosis of CCA | Potential cases were first identified from the database of the Mayo Clinic using ICD codes. Diagnosis of CCA was confirmed by review of histopathology and the anatomic location of the tumor by radiology (CT, MRI or ERCP). ICC was defined by the lesion arose within the hepatic parenchyma and did not extend beyond the secondary hilar branches of the biliary tree. | Presence of diagnostic ICD-9-CM codes 155.1 and 156.1 of CCA in the database. | Presence of diagnostic codes of CCA in the database. | Presence of diagnostic codes of CCA in the database. | Presence of ICD-10 diagnostic codes of CCA in the Swedish Cancer Registry. | Presence of diagnostic ICD-10 codes of ICC in the database. | |

**Table I** (continued)

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Definition of statins exposure | Any use of statins within one year before the diagnosis of ICC. | Any use of pravastatin, lovastatin, rosuvastatin, atorvastatin, simvastatin or fluvastatin before the diagnosis of CCA. | Received at least two prescriptions for statins. | Any use of statins | Any use of statins (which was calculated as time-varying variable) | Use of statins at the entrance of the cohort | Use of statins for more than 3 months |
| Exposure measurement | Review of medication list from the electronic medical record database of the study. | Data on prescriptions of statins were retrieved from the databases. | Data on prescriptions of statins were retrieved from the databases. | Review of medication list from the electronic medical record database of the study. | Data on prescriptions of statins were retrieved from the databases. | Health questionnaire and verbal interview at the entrance of the cohort | Review of medication list from the electronic medical record database of the study. |
| Age of participants, years (mean ± SD) | NA | Cases: 67.4 ± 12.3<br>Controls: 68.5 ± 13.2 | NA | NA | NA | NA | Cases: 65.7<br>Controls: 65.6 |
| Percentage of females | NA | Cases: 49.1%<br>Controls: 48.8% | NA | NA | NA | Overall: 54.4% | Cases: 32<br>Controls: 31.7 |
| Percentage of statins users | Cases: 43.6% Controls: 64.5% | Cases: 22.7%<br>Controls: 26.5% | Cases: 24.1% Controls: 24.2% | NA | NA | NA | ECC: 19<br>Controls: 51 |
| Confounder adjusted in multivariate analysis | Age, sex, ethnicity and residence | Age, gender, healthcare costs, medication with aspirin and metformin, Charlson comorbidity index score, diabetes, cirrhosis, chronic pancreatitis, hepatitis B infection, hepatitis C infection, gastric disease, haemochromatosis, inflammatory bowel disease, biliary tract disease, stroke, CAD, COPD and alcohol related illness | Age, gender, number of years in the general practice and in the database prior to diagnosis/selection date, BMI, smoking, alcohol drinking, diabetes and cirrhosis | Age, gender,, practice | Age and gender | Age, gender, deprivation, BMI, alcohol, smoking, comorbidities and other medication use at baseline | Age, gender, ethnicity and residence |
| Quality assessment (Newcastle-Ottawa scale) | Selection: 3 Comparability: 1 Exposure: 3 | Selection: 4<br>Comparability: 2<br>Exposure: 3 | Selection: 4 Comparability: 2<br>Exposure: 3 | Selection: 4<br>Comparability: 1<br>Exposure: 3 | Selection: 3<br>Comparability: 1<br>Outcome: 3 | Selection: 4<br>Comparability: 2<br>Outcome: 3 | Selection: 3<br>Comparability: 1<br>Exposure: 3 |

BMI: body mass index; CAD: coronary artery disease; CCA: cholangiocarcinoma; COPD; chronic obstructive pulmonary diseases; CT: computed tomography; ECC: extrahepatic cholangiocarcinoma; ERCP: endoscopic retrograde cholangiopancreatography; GERD: gastroesophageal reflux disease; ICC: Intrahepatic cholangiocarcinoma; ICD: International Statistical Classification of Diseases and Related Health Problems; MRI: magnetic resonance imaging; NA: not applicable; SD: standard deviation; UK: United Kingdom; USA: United States of America.

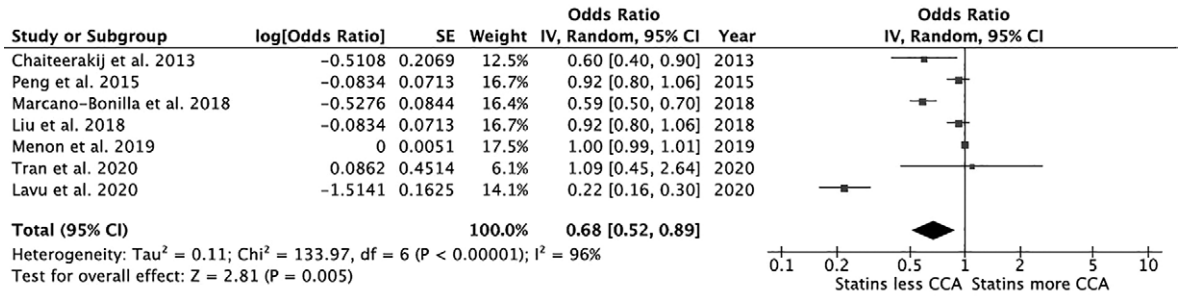


**Fig. 2**. Forest plot of the meta-analysis

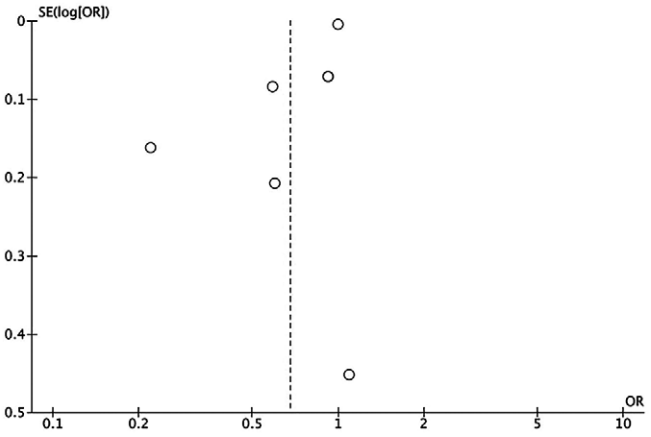


**Fig. 3.** Funnel plot of the meta-analysis.

Lastly, the power of the funnel plot to detect publication bias is low in meta-analysis with fewer than 10 included studies, such as the current one. Therefore, publication bias may have been present in this study.

## CONCLUSIONS

The current systematic review and meta-analysis found a significant association between the use of statins and the decreased risk of CCA.

Limitations include the observational nature of the included studies, high between-study heterogeneity and unclear statin exposure time. Further studies with more comprehensive confounder adjustment and more restrictive definition of statins exposure are still warranted.

**Conflicts of interest**: None to declare.

**Authors' contributions:** K.W, E.S.A., F.J.L., D.M.H., P.U. conceived and designed the study. K.W., E.S.A., H.G., W.C., P.U. collected and analyzed the data. K.W., H.G., W.C., P.U. drafted the manuscript. E.S.A., F.J.L., D.M.H. and P.U. critically revised the manuscript. F.J.L., D.M.H. and P.U. supervised the study.

**Supplementary material**: To access the supplementary materials visit the online version of the *J Gastrointestin Liver Dis* at http://dx.doi.org/10.15403/jgld-2990

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