Statins intake and risk of liver cancer

A dose–response meta analysis of prospective cohort studies

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**Abstract**

Previous studies have indicated that statins intake was associated with liver cancer risk, but presented controversial results. Studies in PubMed and EMBASE were searched update to February 2017 to identify and quantify the potential dose–response association between statins intake and liver cancer.

Six eligible studies involving a total of 11,8961 participants with 9530 incident cases were included in this meta-analysis. Statistically significant association was observed between increasing statins intake and liver cancer risk reduction (OR = 0.46, 95%CI: 0.24–0.68, P < .001). Furthermore, the relative survival rate of liver cancer for an increase of 50 cumulative defined daily dose per year was 0.86 (95%CI: 0.81–0.90, P < .001). Evidence of a nonlinear dose–response relationship between statins intake and liver cancer risk was found (P for nonlinearity < .01). Subgroups analysis indicated that statins intake was associated with a significantly lower risk of liver cancer risk reduction in Asia (OR = 0.44, 95%CI: 0.11–0.77, P < .001) and Caucasian (OR = 0.49, 95%CI: 0.36–0.61, P < .001). Subgroup meta-analyses in study design, study quality, number of participants, and number of cases showed consistency with the primary findings.

Additional statins intake is associated with liver cancer risk reduction.

**Abbreviations:** CI = confidence intervals, RCS = restricted cubic splines, RRs = relevant risks.

**Keywords:** liver cancer, meta-analysis, prospective cohort studies, statins

1. Introduction

Liver cancer is the fifth most common cancer worldwide in men and the sixth most common cancer worldwide in women, and costs on patients, caregivers, and society that remains the most common malignancy.<sup>[1]</sup> The etiology of liver cancer involves both genetic and environmental factors. According to the American Cancer Association statistics, liver cancer mortality gradually increased, the relative survival rate of liver cancer being 18%.<sup>[2]</sup> Based on cancer registry data available in China, the age-standardized 5-year relative survival for liver cancer is 10.1% in 2015.<sup>[3]</sup> These data reveal the poor prognosis of liver cancer, and thus to prevent the occurrence of liver cancer is essential. Previous studies investigating have showed that statins have a chemopreventive potential in the liver cancer.<sup>[4]</sup>

Statins are inhibitors of 3-hydroxy-3-methyl glutaryl coenzyme reductase A, which is a key enzyme in the rate-limiting step in cholesterol synthesis.<sup>[5]</sup> Statins are widely prescribed in the primary and secondary prevention of heart attack, stroke, and cardiovascular disease.<sup>[6]</sup> Recently, statin use has been reported to have a promising anticancer effect,<sup>[7]</sup> and statin monotherapy could potentially reduce any organ and colorectal cancer-related mortality.<sup>[8,9]</sup> Additionally, studies examining the relationship between statin use and risk of liver cancer have found that statin use is significantly associated with decreased risks in hepatocellular carcinoma,<sup>[10]</sup> pancreatic cancer,<sup>[11]</sup> prostate cancer,<sup>[12]</sup> gastric cancer,<sup>[13]</sup> colorectal cancer,<sup>[14]</sup> and breast cancer.<sup>[15]</sup>

Several meta-analyses of randomized controlled trials have examined the relationship between statin use and risk of liver cancer and have found that statin use is significantly reduce liver cancer risk.<sup>[16–18]</sup> However, there is lack of study to quantitatively assess statin use in relation to liver cancer. Thus, we conducted a dose–response meta-analysis to clarify and quantitatively assess statin use and risk of liver cancer.

2. Methods

Our meta-analysis was conducted according to the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) checklist.<sup>[19]</sup> There are no ethical issues involved in our study for our data were based on published studies.

2.1. Search strategy

We included eligible studies to investigate the relationship between statins intake and liver cancer. To develop a flexible, nonlinear, r meta-regression model, we required that an eligible
study should have been categorized into 3 or more levels. If multiple publications were available for a study, we included the longest follow-up study.

PubMed and EMBASE were searched for studies that were published update to February 2017, with keywords including “liver cancer” OR “hepatocellular” OR “hepatic” OR “intra-hepatic” AND “statin.” We refer to the relevant original essays and commentary articles to determine further relevant research. Eligible study was also included through the reference lists of relevant review articles. The search strategy is shown in detail in the supplementary list S1, http://links.lww.com/MD/B785.

2.2. Study selection
Two independent researchers (CY and ZS) investigated the information regarding the correlation between statin use and liver cancer: outcome was liver cancer; the relative risks (RR) at least 3 quantitative categories. Moreover, we precluded nonhuman studies, reviews, meta-analyses, editorials, and published letters. To ensure the correct identification of qualified research, the 2 researchers read the reports independently, and the disagreements were resolved through consensus by all of the researchers.

2.3. Data extraction
Each eligible article’s information was extracted by 2 independent researchers (MW and YC). We extracted the following information: first author; publication year; mean value of age; country; study name; sex; cases and participants; the categories of statin use; and RR or odds ratio (OR). We collected the risk estimates with multivariable-adjusted. Quality assessment was performed according to the Newcastle-Ottawa scale for nonrandomized studies.120

2.4. Statistical analysis
We pooled RR estimates as the common measure of association statin use and liver cancer risk; the hazard ratio was considered equivalent to the RR. Any results stratified by different subgroups of statin use and liver cancer risk in any single article were treated as 2 separate reports.

Due to different cut-off points for categories in the included studies, we performed a RR with 95% confidence intervals (CI) by an increase of 50 cumulative defined daily dose per year using the method recommended by Greenland, Longnecker and Orsini and colleagues.23 The dose of statin intake used the median statin intake. If the median statin intake category was not available, the midpoint of the upper and lower boundaries was considered as the dose of each category. In addition, using restricted cubic splines (RCS) to evaluate the nonlinear association between statin intake and liver cancer risk, with 3 knots at the 10th, 50th, and 90th percentiles of the distribution. A flexible meta-regression based on RCS function was used to fit the potential nonlinear trend, and generalized least-square method was used to estimate the parameters.21 This procedure treats statin use (continuous data) as an independent variable and logRR of diseases as a dependent variable, with both tails of the curve restricted to linear. A P value is calculated for linear or nonlinear by testing the null hypothesis that the coefficient of the second spline is equal to zero.23

STATA software 12.0 (STATA Corp, College Station, TX) was used to evaluate the relationships between statin use and liver cancer risk. Q test and I² statistic were used to assess heterogeneity among studies. The random-effect model was chosen if P<.10 or I²>50%, otherwise, the fixed-effect model was applied. Begg and Egger tests were done to assess the publication bias of each study. P<.05 was considered significant for all tests.

3. Results literature search results
Figure 1 shows the results of literature research and selection. We identified 2601 articles from PubMed and 3723 articles from EMBASE. After exclusion of duplicates and studies that did not fulfill the inclusion criteria, 6 studies were chosen24–29 and the data were extracted, and a total of 6 reports datasets were included in the final meta-analysis. These studies were published update to February 2017.

3.1. Study characteristics
The characteristics of the included studies are shown in the Tables 1 and 2. Among the selected studies, 6 eligible studies involving 4 cohort studies and 2 case-control studies, 2 studies are from Caucasians and 4 from Asia, a total of 11,896 participants with 9530 incident cases were included in this meta-analysis.

3.2. Overall meta-analysis
The results of statin use and the risk of liver cancer are shown in Table 3. The pooled results suggest that statin use is significantly associated with liver cancer risk, which was suggested both by the highest and lowest categories (RR = 0.46; 95% CI: 0.24–0.68; P<.001) (Table 3). We found evidence of between-study heterogeneity (I² = 91.8%, P<.001) but we observed no evidence of publication bias (Egger asymmetry test, P = .063) (Table S1, http://links.lww.com/MD/B785).

3.3. Dose–response meta-analyses between statins intake and liver cancer
Using RCS function, the test for a nonlinear dose–response relationship was significant (likelihood ratio test, P<.001), suggesting curvature in the relationship, with an increase of...
Table 1
Characteristics of participants in included studies of statins intake in relation to risk of Liver cancer.

| Author (year) | Study name | Country | Sex of population | Age at baseline, years | No. of participants | Mean length of follow-up, years | Endpoints (no. of cases) | Quality score |
|---------------|------------|---------|-------------------|-----------------------|---------------------|-------------------------------|--------------------------|---------------|
| Chen et al (2015) | The Taiwan Longitudinal Health Insurance | China | Mix | >20 | 61,898 | 9 | Liver cancer (1735) | 7 |
| Chiu et al (2011) | NIH | China | Mix | 66.0 | 2332 | 4 | Liver cancer (1166) | 6 |
| McGlynn et al (2015) | CPRD | UK | Mix | 67.0 | 5835 | 23 | Liver cancer (1195) | 7 |
| Peng et al (2015) | RCIPD | China | Mix | 68 | 6348 | 7 | Liver cancer (3174) | 6 |
| Simon et al (2016) | ERCHIVES | USA | Mix | 53 | 9135 | 7.4 | Liver cancer (239) | 8 |
| Tsan et al (2012) | The Taiwan Longitudinal Health Insurance | China | Mix | 35.6 | 33,413 | 9.8 | Liver cancer (2021) | 6 |

CPRD = The United Kingdom’s Clinical Practice Research Datalink, ERCHIVES = The Electronically Retrieved Cohort of HCV Infected Veterans, NIH = National Health Insurance, RCIPD = The Registry of Catastrophic Illnesses Patient Database.

Table 2
Outcomes and covariates of included studies of statins intake in relation to risk of Liver cancer.

| Author (year) | Endpoints | Data source | Category and relative risk (95% CI) | Covariates in fully adjusted model |
|---------------|------------|-------------|-----------------------------------|-----------------------------------|
| Chen et al (2015) | Liver cancer (1735) | Hospital-based | <28 ≥DDD/day, 1.0 (reference); >28–<30, 0.97 (0.85–1.10); ≥30, 0.90 (0.80–1.01) | Age, sex, ACE inhibitors, anti-HBV drugs, aspirin, comorbidities, index year, and nonstatin |
| Chiu et al (2011) | Liver cancer (1166) | Population-based | <20 <DDD/day, 1.0 (reference); ≥20, 0.88 (0.80–0.98); ≥30, 0.85 (0.77–0.93) | Adjusted for matching variables, number of hospitalizations, diabetes, HBV infection, HCV infection, cirrhosis, alcoholic liver disease, and use of other lipid-lowering drugs |
| McGlynn et al (2015) | Liver cancer (1195) | Population-based | <28 <DDD/day, 1.0 (reference); >28–<30, 0.88 (0.80–0.98); ≥30, 0.85 (0.77–0.93) | Adjusted for body mass index, smoking, alcohol-related disorders, HBV or HCV, diabetes, paracetamol use, rare metabolic disorders, aspirin, and antidiabetics, and conditional on matching variables |
| Peng et al (2015) | Liver cancer (3174) | Population-based | <28 ≥DDD/day, 1.0 (reference); >28–<30, 0.97 (0.85–1.10) | Age, sex, aspirin, alcohol-related illness, biliary tract disease, coronary artery disease, Charlson comorbidity index score, chronic pancreatitis, cirrhosis, chronic obstructive pulmonary disease, diabetes, parietic disease, hemochromatosis, HBV, HCV, inflammatory bowel disease, stroke, and metformin |
| Simon et al (2016) | Liver cancer (239) | Population-based | <28 ≥DDD/day, 1.0 (reference); >28–<30, 0.97 (0.85–1.10) | Adjusted for age, sex, race, smoking history, alcohol abuse history, caffeine intake, body mass index, diabetes, baseline FIB-4 score, metformin use, ACE inhibitor use, other lipid-lowering agent use, nonsteroidal anti-inflammatory medication use, past completed HCV treatment, attainment of SVR, and daily caffeine intake |
| Tsan et al (2012) | Liver cancer (2021) | Population-based | <28 ≥DDD/day, 1.0 (reference); >28–<30, 0.97 (0.85–1.10) | Adjusted for age, sex, income, urbanization, diabetes, and liver cirrhosis |

ACE = acetylcholinesterase, CI = confidence interval, CDD = cumulative defined daily dose, FIB-4 = fibrosis-4, HBV = hepatitis B virus, HCV = hepatitis C virus, SVR = sustained virological response.

Table 3
Stratified analyses of relative risk of liver cancer.

| No. of reports | Relative risk (95% CI) | P for heterogeneity | F², % | P for test |
|----------------|------------------------|---------------------|-------|-----------|
| Total | 0.46 (0.24–0.68) | .000 | 91.8 | .001 |
| Subgroup analyses for liver cancer | | | | |
| Study location | | | | |
| Asia | 2 | 0.49 (0.36–0.61) | .752 | 0.0 | <.001 |
| Study design | | | | |
| Case-control | 4 | 0.44 (0.21–0.57) | .000 | 94.9 | .009 |
| Cohort | 4 | 0.37 (0.18–0.55) | .001 | 83.8 | <.001 |
| No. of participants ≥10,000 | 2 | 0.20 (0.12–0.28) | .230 | 30.7 | <.001 |
| <10,000 | 4 | 0.57 (0.39–0.74) | .006 | 76.2 | <.001 |
| No. of cases ≥1500 | 3 | 0.44 (0.21–0.57) | .000 | 94.9 | <.001 |
| <1500 | 3 | 0.48 (0.28–0.68) | .940 | 0.0 | <.001 |
| Study quality | | | | |
| Score ≥7 | 4 | 0.44 (0.11–0.77) | .000 | 94.9 | .009 |
| Score <7 | 2 | 0.49 (0.36–0.61) | .752 | 0.0 | <.001 |

CI = confidence interval.
50 cumulative defined daily dose per year was associated with a 14% decrement in the risk of liver cancer. The summary RR of liver cancer for an increase of 50 cumulative defined daily dose per year was 0.86 (95%CI: 0.81–0.90, P < .001) (Fig. 2).

### 3.4. Subgroup analyses

Subgroup analysis was performed to check the stability of the primary outcome (Table 3). Subgroup analyses based on the study location found a similar risk reduction of liver cancer in Asia (OR = 0.44, 95%CI: 0.11–0.77, P < .001) and Caucasian (OR = 0.49, 95%CI: 0.36–0.61, P < .001) (Table 3). The relationship between statin use and liver cancer risk was similar in subgroup analyses, which were defined by study design, number of cases or participants, and study quality. An increment of 50 cumulative defined daily dose per year significantly decreased the liver cancer risk in any of the categories.

### 3.5. Publication bias

Each study in this meta-analysis was performed to evaluate the publication bias by both Begg funnel plot and Egger test. P > .05 was considered no publication bias. The results show that no obvious evidence of publication bias was found in the associations between statin use and liver cancer risk (supplementary Table S1, http://links.lww.com/MD/B785). A funnel plot for publication bias assessment is illustrated in supplementary Figure S1, http://links.lww.com/MD/B785.

### 4. Discussion

Statinas are the most commonly used prescription drugs for the treatment of dyslipidemia. Recently, there has been an interest in a possible protective effect of statins on cancer risk,[30] and statin use has been reported to have a promising anticancer effect. Studies have shown that bone morphogenetic protein (BMP) pathway also has certain relationship with the incidence of tumor; statins can activate the BMP and BMP gene to induce cell apoptosis.[31] Furthermore, statin inhibits the proteasome pathway activation, limits cell cycle–dependent kinase inhibitor p21, and p27 protein decomposition, so it plays a role of a growth inhibitor of these molecules.[32]

To our knowledge, several meta-analyses of observational studies and randomized controlled trials have examined the association between statin use and risk of liver cancer.[16–18] However, no study has been done to quantitatively assess statin use in relation to liver cancer. This is the first study to quantify the potential dose–response association between statin use and risk of liver cancer in a large cohort of both men and women. The primary finding in our meta-analysis is that statin use is significantly associated with liver cancer risk; an increase of 50 cumulative defined daily dose per year was associated with a 14% decrement in the risk of liver cancer. Subgroup analysis also proved the stability of the primary outcome. Previously it was hypothesized that the highest category of statins may have a greater chemoprotective effect in liver cancer, but in our hypothesis an increase of 50 cumulative defined daily dose per year was associated with a 14% decrement in the risk of liver cancer.

Although, we performed this meta-analysis very carefully, however, some limitations must be considered in the current meta-analysis. First, different sex of population should be included in this meta-analysis to explore the impact of different sex of population on statin use and liver cancer. Second, we only select literature that was written in English, which may have resulted in a language or cultural bias, other language should be chosen in further study. Third, there might be insufficient statistical power to check the association.

In conclusion, our meta-analysis suggests that statin use was independently associated with deleterious liver cancer risk reduction. However, large sample size, different ethnic, and different sex population of population are warranted to validate this association.

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