Can Statin Treatment Reduce the Risk of Hepatocellular Carcinoma? A Systematic Review and Meta-Analysis

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Abstract
Background: Whether statins can reduce the incidence of cancers has been an interesting topic in recent years. This meta-analysis aimed to determine the relationship between statin treatment with the risk of hepatocellular carcinoma.

Methods: Studies published up to July 2019 were screened from databases. The data from approved studies were pooled. Random-effects or fixed-effects model was used to calculate the relative risk with 95% CIs in the overall group and subgroups. Sensitivity and meta-regression analyses were performed, and publication bias was evaluated.

Results: A total of 18 studies involving 1,611,596 patients were included in this meta-analysis. The overall result showed a significantly reduced risk of hepatocellular carcinoma (relative risk \(= 0.54, 95\% CI: 0.42-0.66\)) in statin users. In comparison to the risk in nonstatin users, the risk of hepatocellular carcinoma was reduced in all subgroups. The dose of statins and their pharmacokinetics can partly explain the heterogeneity in the overall meta-analysis (\(I^2 = 94.6\%, P = .000\)). A dose-dependent effect of statin use for the reduced risk of hepatocellular carcinoma was found.

Conclusions: Findings from this meta-analysis support that statin use can significantly reduce the incidence of hepatocellular carcinoma.

Keywords
hepatocellular carcinoma, statins, risk, meta-analysis, dose-dependent effect

Abbreviations
BCLC, Barcelona Clinic Liver Cancer; DDDs, defined daily doses; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HR, hazard ratio; LDL, low density lipoprotein; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; NOS, Newcastle-Ottawa scale; OR, odds ratio; RR, relative risk; SHR, weighted sub-hazard ratio; VLDL, very low density lipoprotein.

Introduction
Hepatocellular carcinoma (HCC) is a heterogeneous malignant tumor with a dismal prognosis and ranks as the fourth most common primary malignancy and the third leading cause of cancer-related death.1 Hepatocellular carcinoma has a 5-year survival of 18%, and several studies have shown that the prognoses are devastating in patients with HCC.2 The global incidence of primary liver cancer is increasing annually. Globally, as many as 800,000 cases of HCC were diagnosed in 2012. The World Health Organization estimates that the number of HCC-related deaths may reach 1 million in 2030, with more than 50% of new cases and deaths occurring in China.2

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Hepatocellular carcinoma has been a serious threat to global public health. At present, most treatment for HCC is based on the Barcelona Clinic Liver Cancer (BCLC) algorithm, and surgical resection is still the first choice in the very early or early stage (BCLC stage 0 or A, respectively). Additionally, the occurrence of nonalcoholic fatty liver disease (NAFLD), especially nonalcoholic steatohepatitis (NASH), has substantially risen rapidly in the last decades. Nonalcoholic steatohepatitis has become the second leading indication for liver transplantation and is an important cause of HCC or end-stage liver disease in the future. However, the surveillance of patients with HCC is still difficult, so early prevention interventions for high-risk groups have become a key link in reducing the number of patients with HCC. Unfortunately, as far as we know, there is no evidence that there are specific drugs that can eradicate the risk of HCC.

In recent years, studies in the field of oncology have found that long-term use of statins can reduce the incidence of many cancers, such as breast cancer, pancreatic cancer, colon cancer, and ovarian cancer. Statins, a common drug used to lower cholesterol, can delay and reverse the progress of plaques and reduce the long-term mortality of patients with cardiovascular disease. Interestingly, many basic studies have shown that statins play important roles in inhibiting the growth of tumor cells by regulating the methylvalerate pathway and via other pharmacological actions. In the early years, the elevation of transaminase was mistakenly considered a contraindication of statins, which limited the clinical use of statins in patients with liver diseases. Later, studies have proven that statins are safe and effective in patients with hepatitis, cirrhosis, and other liver diseases, especially in patients with NAFLD. An encouraging result from 2 population-based studies recently reported that statin use was associated with risk reduction in liver cancer. The use of statins in patients with HCC has been increasingly reported, while it has also been seen that statin treatment has no relationship with risk reduction in HCC.

The data regarding the association of statins with preventive effects in HCC are conflicting. Thus, we searched studies with a particular focus on the relationship between statin exposure with HCC occurrence and conducted this meta-analysis to answer this question: can statin treatment reduce the risk of hepatocellular carcinoma?

**Materials and Methods**

**Study Identification and Selection**

Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were followed for this meta-analysis, as shown in Figure 1. This meta-analysis was registered on PROSPERO (www.crd.york.ac.uk, ID: CRD42017077142). Databases (PubMed, EMBASE, Web of Science, Scopus, and Cochrane Library) were screened up to July 31, 2019, by 2 investigators (Y.C. and Q.L.) independently. English language studies investigating the relationship between statin exposure with the incidence of HCC was collected. The search terms details are shown in Table S1.

The studies included in this meta-analysis met the following criteria: (1) studies with a clear association between statins exposure with the relative risk (RR)/odds ratio (OR) of HCC; (2) observational studies (cohort studies and case–control studies) or randomized controlled trials; and (3) articles published in English with sufficient usable outcome data. The exclusion criteria were as follows: (1) ongoing trials, (2) studies with a follow-up of less than 12 months, (3) secondary research or studies with overlap reports, and (4) secondary analysis studies (meta-analyses or individual patient data analyses).

**Pooling of the Data**

Two investigators (Y.C. and Q.L.) pooled data from the eligible studies independently. Any discrepancies were resolved by the corresponding author (H.L.). Relevant information was extracted from the full manuscripts of eligible studies, including research design, publication time, location, total sample size, number of patients with HCC, statin exposure group, OR or RR, 95% CI, and the type and dose of statin used.

**Quality Assessment**

Before this review, all investigators trained to comprehend the aim of this meta-analysis. In this investigation, the Newcastle-Ottawa scale (NOS) quality evaluation criteria were used to score the included literature. Patient selections, comparisons between the statin with nonstatin groups, and the outcomes of studies were evaluated by a star system.

**Statistical Analysis**

Different statistical indicators (OR, hazard ratio [HR], or RR) were pooled in this meta-analysis. As the absolute risk of HCC is relatively low (3.3-8.4 per 100,000) in practice, ORs were regarded as approximations of RR. The DerSimonian and Laird method for a random-effects model was used for calculating the RR estimates and 95% CIs. In addition, Cochran Q statistic and the Higgins I² statistic were used to analyze the heterogeneity. Meta-regression was used to explore the potential causes of heterogeneity. Begg test was used to assess publication bias. Stata (version 15.1, StataCorp) was used for statistical analyses and construction of graphs. All statistical tests were 2 sided, and P values < .05 were considered statistically significant.

**Results**

**Study Selection and Study Characteristics**

A total of 18 studies were obtained from the search. The specific literature screening process is shown in Figure 1. A total of 1,611,596 patients were included in this meta-analysis, and the main features of the 18
studies are shown in Table 1. The risks of incomplete data in the results of the included studies were low. At the same time, there was also a low risk of selective reporting in the included studies, as the main results described in the program were reported in the research plan. In the 18 studies, any other potential bias was unclear. The NOS score ranged from 6 to 8 points for the 18 studies, demonstrating that all the included case-control or cohort studies were high-quality investigations.

Among them, 7 studies had high-risk factors for HCC, including 4 studies24,28,29,33 of people with hepatitis B virus (HBV) infection and 3 studies31-33 of people with hepatitis C virus (HCV) infection. In addition, there was also a study20 based on a diabetic population, and the study by Mohanty et al,31 Chang et al,33 and Kaplan et al36 were based on patients with cirrhosis. The study by Chiu et al,23 Tsan et al,24 McGlynn et al,27 Chen et al,30 and Tran et al15 focused on the effects of different types of statins, while the study by Chiu et al,23 Tsan et al,24 Chen et al,30 Hisang et al,29 Kim et al,34 and Tran et al35 contained information on statin dosage. In addition, the study by Tran et al35 included 2 population-based studies.

Risk of HCC in Statin Users
A random-effects model was performed in this meta-analysis due to the high heterogeneity of all studies. Pooled risk ratios and 95% CIs for the risk of HCC in statin users in all included
| No. | Study | Location | Setting | Total no. | No. of HCC | Measurement of effect estimates | Crude OR/RR (95% CI) | Adjusted OR/RR (95% CI) | Confounds of adjustment | Follow-up (years) | Literature quality |
|-----|-------|----------|---------|-----------|-----------|-------------------------------|---------------------|------------------------|----------------------|-----------------|------------------|
| 1   | Friis et al\(^{15}\) | Denmark | General Population (30-80 years 1989-2002) | 33 4754 | 171 | RR | 1.16 (0.46-2.90) | 1-5 | 3.3 (0-14) years | 7 |
| 2   | Friedman et al\(^{21}\) | United States | General Population (KPMCP, 1994-2003) | 36 1859 | 42 | HR | NA | 0.40 (0.21-0.75) | NA | 4.91 (1-9.42) years | 8 |
| 3   | El-Serag et al\(^{20}\) | United States | Diabetes patients (VA, 1997-2002) | 6515 | 1303 | OR | 0.42 (0.39-0.46) | 1.2, 6-9 | 2.4 years | 8 |
| 4   | Marelli et al\(^{22}\) | United States | General Population (men ≥45 women ≥55 years, GE Centricity, 1990-2009) | 91 714 | 105 | RR | 0.31 (0.14-0.68) | 1-3, 10-17 | 4.0 (M) years | 8 |
| 5   | Chiu et al\(^{23}\) | Taiwan | General Population (≥50 years, NHIRD, 2005-2008) | 2332 | 1166 | OR | 0.53 (0.41-0.69) | 1, 2, 7, 8, 18-21 | NA | 7 |
| 6   | Tsan et al\(^{24}\) | Taiwan | Patients with HBV infection (NHI, 1997-2008) | 33 413 | 1021 | HR | 0.66 (0.51-0.86) | 1, 2, 6-8, 19 | 10 years | 7 |
| 7   | Leung et al\(^{25}\) | Taiwan | General Population (NHIRD, ≥18 years, 2000-2008) | 34 205 | 424 | HR | 0.45 (0.30-0.67) | 1, 2, 8, 4, 5, 22, 20, | 4.1 (M) years | 8 |
| 8   | Björkhem-Bergman et al\(^{26}\) | Sweden | General Population (SPDR, ≥40 years, 2006-2010) | 23 964 | 3994 | OR | 0.96 (0.88-1.05) | 4.6-9, 16, 18, 19, 23 | NA | 8 |
| 9   | Chen et al\(^{28}\) | Taiwan | Patients with HBV infection (NHIRD, >18 years, 2000-2008) | 71 824 | 1735 | HR | 0.28 (0.23-0.35) | 1, 2, 4, 13, 24-26 | 9 years | 8 |
| 10  | McGlynn et al\(^{27}\) | United Kingdom | General Population (CPRD, 10-90 years, 1988-2011) | 5835 | 1195 | OR | 0.91 (0.77-1.07) | 4.8, 9, 11, 12, 16, 18, 19, 27 | NA | 8 |
| 11  | Mohanty et al\(^{31}\) | United States | Patients with HCV compensated cirrhosis (VA, 1996-2009) | 2747 | 173 | HR | 0.42 (0.27-0.64) | NA | ≥1 year | 7 |
| 12  | Hisang et al\(^{29}\) | Hong Kong | Patients with HBV infection (HA, >18 years, 2000-2012) | 73 499 | 6883 | SHR | 0.68 (0.48-0.97) | NA | NA | 4.6 (M) years | 8 |
| 13  | Chen et al\(^{30}\) | Taiwan | General Population (LHDD2000, 1996-2010) | 1700 | 340 | OR | 0.37 (0.27-0.49) | NA | NA | 7 |
| 14  | Simon et al\(^{32}\) | United States | Patients with HCV infection (VA, 2001-2014) | 9135 | 239 | HR | 0.43 (0.31-0.60) | 3.8, 16, 20, 27-31 | NA | 7 |
| 15  | Chang et al\(^{33}\) | Taiwan | Patients with HBV- and HCV-related cirrhosis (NHIRD, ≥20 years, 2000-2013) | 1350 | 111 | HR | 0.52 (0.35-0.76) | 1, 2, 4, 5, 13, 16, 24, 27, 28, 32-35 | 12 years | 8 |
| 16  | Kim et al\(^{34}\) | Korea | General Population (NHIS-PHEC, >40 years, 2002-2013) | 9852 | 1642 | OR | 0.47 (0.38-0.58) | 4.6-8, 11, 12, 18, 25, 27, 36 | NA | 7 |
| No. | Study | Location | Setting | Total no. | No. of HCC | Measurement of effect estimates | Crude OR/RR (95% CI) | Adjusted OR/RR (95% CI) | Confounds of adjustment | Follow-up (years) | Literature quality |
|-----|-------|----------|---------|-----------|------------|---------------------------------|----------------------|------------------------|------------------------|-------------------|-------------------|
| 17 (a) | Tran et al<sup>35</sup> | United Kingdom | General Population (UK Biobank, 40-69 years, 2006-2010) | 47,185 | 182 | HR | 1.30 (0.80-2.10) | 0.48 (0.24-0.94) | 1,2,11-13,16,37 | 4.6 (3.9-5.3) | 7 |
| 17 (b) | Tran et al<sup>35</sup> | United Kingdom | General Population (PCCIU, 1999.1.1-2011.4.30) | 2103 | 434 | OR | 0.92 (0.72-1.18) | 0.67 (0.49-0.92) | 1,2,4,8,9,13,16,18,19,23,27 | 4.8 (3.1-7.3) | 6 |
| 18 | Kaplan et al<sup>36</sup> | United States | Patients with cirrhosis (VA, 18-85 years, 2008-2016) | 72,944 | NA | HR | 0.94 (0.882-1.003) | NA | NA | NA | 7 |

Abbreviations: ACE, angiotensin-converting enzyme; BMI, body mass index; HCC, hepatocellular carcinoma; HR, hazard ratio; NA, not applicable; OR, odds ratio; RR, relative risk; SHR, weighted sub-hazard ratio; VLDL, very low density lipoprotein; LDL, low density lipoprotein; HBV, hepatitis B virus; HCV, hepatitis C virus.

<sup>a</sup>Adjusted: 1 = age, 2 = sex, 3 = calendar year, 4 = cardiovascular medications (aspirin, nonsteroidal anti-inflammatory medications, or ACE inhibitors), 5 = hormone-replacement therapy, 6 = socioeconomic status, 7 = cirrhosis, 8 = diabetes mellitus, 9 = HCV infection, 10 = race, 11 = BMI, 12 = smoking status, 13 = concomitant diagnoses (unspecified), 14 = cholesterol (total cholesterol, VLDL, LDL, or triglycerides), 15 = prostate-specific antigen, 16 = medications taken (unspecified), 17 = number of office visits, 18 = alcoholic liver disease, 19 = HBV infection, 20 = other lipid-lowering agents, 21 = hospital stay, 22 = Charlson score, 23 = nonalcoholic fatty liver disease, 24 = HBV treatment, 25 = area, 26 = index year, 27 = metformin or thiazolidinedione, 28 = HCV treatment, 29 = caffeine intake, 30 = baseline FIB-4 score, 31 = attainment of SVR, 32 = cirrhosis with different etiologies, 33 = the presence of nonhemorrhagic varices at the time of enrollment, 34 = follow-up duration, 35 = cirrhosis etiology, 36 = Charlson comorbidity index, 37 = ethanol intake.
studies were determined in overall and subgroup meta-analyses. In Figure 2, the results of all studies showed a significantly reduced risk of HCC (RR = 0.54, 95% CI: 0.42-0.66) for statin users. However, a statistically noteworthy heterogeneity was observed among the studies ($I^2 = 94.6\%$, $P = .000$).

**Sensitivity Analysis**

We performed a sensitivity analysis to verify the impact of each study on the pooled estimates by omitting one study at a time to explore the possible sources of statistical heterogeneity. We demonstrated that no one study contributed greatly to the heterogeneity of the overall meta-analysis. Figure 3 shows the results of the sensitivity analysis, which indicated that the omission of any study did not influence the overall meta-analysis results. Next, we conducted meta-regression analysis according to study design, baseline risk, confounders, study area, age, number of participants, number of HCC cases, the dose of statins, and statins pharmacokinetics. The results show that the $P$ value associated with the statins pharmacokinetics was less than .1, and thus the type of statins used in the studies can explain the heterogeneity rather than other factors by meta-regression analysis (see Table S2 for details).

**Subgroup Analysis**

To further explore the potential factors leading to heterogeneity, subgroup analyses were performed as summarized in Table 2. In comparison to the risk in nonstatin users, the risk of HCC was lower in all other subgroups. The effects of statins in HCC were confirmed regardless of the study design, and the pooled RR for cohort or case–control studies was reduced, but the difference was not significant. The association between statin therapy with low RR in HCC in different subgroups was similar regardless of the number of patients with HCC or the number of participants, as shown in Table 2. The pooled RR for HCC of studies from Asia was 0.45 (95% CI: 0.42-0.66; $P = .000$), while the heterogeneity decreased to 74.5%. The RR of studies involving patients older than 40 years was 0.56 (95% CI: 0.31-0.81; $I^2 = 95.0\%$; $P = .000$). Similarly, the RR of studies involving patients of any age or older than 18 years was 0.53 (95% CI: 0.39-0.67; $F = 91.8\%$; $P = .000$).

The cumulative dose of statins and their pharmacokinetics was also analyzed. The associations between defined daily doses (DDDs) of statins with low RR for HCC were found. The pooled RR for HCC in the group with cumulative statin use $>365$ DDDs was 0.29 (95% CI: 0.22-0.36; $F = 73.4\%$; $P = .001$). In addition, the pooled RR for HCC in the group with cumulative statin use $\leq365$ DDDs was 0.46 (95% CI: 0.40-0.52; $F = 50.8\%$; $P = .032$). There were significant differences between subgroups with different DDDs ($P = .001$). This may indicate that the differences can partly explain the heterogeneity and also indicate that HCC risk declines with the increasing cumulative DDDs of statins. The subgroup meta-analysis according to the type of statins showed low heterogeneity, and the result showed that the effect on reducing the risk of HCC for hydrophilic (RR = 0.47, 95% CI: 0.30-0.64; $F = 42.4\%$; $P = .075$) was similar to that of lipophilic statins (HR = 0.50, 95% CI: 0.42-0.66; $F = 74.5\%$; $P = .000$).
Table 2. Subgroup Analysis of Statin Use and HCC Risk.

| Subgroup                  | No. of reports | Adjusted OR (95% CI) | Tests of heterogeneity P value | Tests of heterogeneity I² | Heterogeneity between groups P value |
|---------------------------|----------------|----------------------|--------------------------------|--------------------------|-------------------------------------|
| Study design              |                |                      |                                |                          |                                     |
| Cohort                    | 11             | 0.50 (0.38-0.67)     | .000                           | 95.3%                    | .518                                |
| Case–control              | 8              | 0.57 (0.43-0.75)     | .000                           | 88.8%                    |                                     |
| Baseline risk             |                |                      |                                |                          |                                     |
| High risk                 | 8              | 0.52 (0.37-0.72)     | .000                           | 86.4%                    | .883                                |
| General population        | 11             | 0.54 (0.42-0.89)     | .000                           | 96.8%                    |                                     |
| Confounders adjustment    |                |                      |                                |                          |                                     |
| Adequate                  | 15             | 0.52 (0.41-0.63)     | .000                           | 91.3%                    | .691                                |
| Inadequate                | 4              | 0.60 (0.25-0.96)     | .000                           | 96.9%                    |                                     |
| Area                      |                |                      |                                |                          |                                     |
| Western                   | 11             | 0.59 (0.44-0.75)     | .000                           | 94.1%                    | .129                                |
| Asian                     | 8              | 0.45 (0.42-0.66)     | .000                           | 74.5%                    |                                     |
| No. of participants       |                |                      |                                |                          |                                     |
| ≥10 000                   | 11             | 0.56 (0.35-0.77)     | .000                           | 96.6%                    | .590                                |
| <10 000                   | 8              | 0.50 (0.44-0.56)     | .000                           | 45.9%                    |                                     |
| No. of HCC                |                |                      |                                |                          |                                     |
| ≥1000                     | 8              | 0.55 (0.40-0.70)     | .000                           | 95.5%                    | .213                                |
| <1000                     | 10             | 0.45 (0.38-0.51)     | .392                           | 5.3%                     |                                     |
| Age                       |                |                      |                                |                          |                                     |
| >40 years                 | 6              | 0.56 (0.31-0.81)     | .000                           | 95.0%                    | .845                                |
| >18 years or any age      | 13             | 0.53 (0.39-0.67)     | .000                           | 91.8%                    |                                     |
| Pharmacokinetics          |                |                      |                                |                          |                                     |
| Lipophilic statin         | 6              | 0.50 (0.44-0.57)     | .386                           | 5.8%                     | .761                                |
| Hydrophilic statin        | 6              | 0.47 (0.30-0.64)     | .075                           | 42.4%                    |                                     |
| DDDs of statin            |                |                      |                                |                          |                                     |
| >365                      | 6              | 0.29 (0.22-0.36)     | .001                           | 73.4%                    | .001                                |
| ≤365                      | 5              | 0.46 (0.40-0.52)     | .032                           | 50.32%                   |                                     |

Abbreviations: DDDs, defined daily doses; HCC, hepatocellular carcinoma; OR, odds ratio.
95% CI: 0.44-0.57; $I^2 = 5.8\%$; $P = .386$). Although the lowest RR was observed in rosuvastatin users (RR = 0.30, 95% CI: 0.15-0.45; $I^2 = 3.7\%$; $P = .386$), there was not significantly different from that of other types of statins by the test of interaction. Figure 4 shows the detailed results of other types of statins.

**Publication Bias**

Begg test was used to assess publication bias in cohort and case–control studies separately. The $P$ value of Begg test was 0.805 ($z = 0.25$) in cohort studies (Figure S1A). Meanwhile, the $P$ value was 0.139 ($z = 1.48$) in case–control studies (Figure S1B). It can be found that there is no obvious publication bias in this study.

**Discussion**

To our knowledge, this present meta-analysis is the most comprehensive analysis of the relationship between statin use with the risk of HCC to date, as it involved more participants, more subgroup analyses and newly published data. Overall, the risk of HCC decreased by 54% in statin users compared with non-statin users. This study may offer a new avenue for reducing the incidence of HCC. This meta-analysis indicated that increasing cumulative DDDs of statins are associated with a reduction in

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**Figure 4.** Subgroup meta-analysis of the use of different types of statins.
HCC risk. In addition, rosuvastatin may have a superior effect on clinical practice.

Our current study has several strengths. First, compared with past meta-analyses, this meta-analysis used a more in-depth and comprehensive search strategy and a new subgroup analysis and included 18 studies and a total of 1,611,596 patients.37 Second, the methodology included in this study is of good quality and confounders were fully analyzed; as such, the conclusions are more convincing. Of course, several potential limitations should also be noted. (1) As the incidence of HCC in males is twice as high as that in females,38 we were unable to distinguish the effects of statins in different sexes due to insufficient data. (2) Publication bias may still merit further consideration, as surveys with negative results or with small sample sizes may be difficult to publish. Additionally, there may be fewer studies in areas with a low incidence of HCC. (3) According to previous results, statins might offer more benefits in patients with NAFLD than in patients with HCC.39 Moreover, NAFLD has become the most common etiology of chronic liver disease. Currently, NASH-related cirrhosis was the fastest growing and the second leading indication for liver transplantation in the United States.40-42 However, there is still a lack of studies on the relationship between statin use with HCC risk reduction in patients with NAFLD.

Our meta-analysis showed that the reduction in HCC risk was significant among all users. Moreover, the beneficial effects of statin treatment persisted after adjustment for many potential confounders. As the heterogeneity of the overall analysis was significant, we explored the potential source of heterogeneity. As was seen, most of the study populations came from health-related databases; as such, the baseline level of the population was different than that in the patients of Mohanty’s study.31 Chang’s study33 and Kaplan’s study36 in the United States, in which the patients had cirrhosis. However, the sensitivity analysis did not find any study that influenced the overall meta-analysis result. Fortunately, the results of the subgroup analysis showed that the dose of statins and their pharmacokinetics were the causes of heterogeneity. In particular, the heterogeneity almost disappeared when the effect was analyzed according to the specific type of statin used. We consider that the reason for the heterogeneity due to the type of statin may be related to the study design or the limitations of drug-to-drug interactions. In particular, rosuvastatin showed a potential beneficial effect on the reduction in HCC risk. However, not all studies contained information about the dose or type of statins, so the post hoc subgroup analyses of the dose of statins and their pharmacokinetics can only partly explain the heterogeneity in the overall meta-analysis.43

We found that as the cumulative DDDs of statins increased, the risk of HCC in the population decreased significantly in a dose-dependent manner. Due to the lack of necessary data, it was not possible to analyze the compliance of patients using statins and the total time that statins were used. It is well known that the oxidative metabolism of lipophilic statins depends on the CYP450 system.44 In addition, lipophilic statins can be easily embedded in the cell membrane, which presents a risk of interactions with other drugs. Patients with liver disease often use a variety of liver-protecting drugs, direct antiviral drugs, antifibrosis drugs, and diuretics. In addition, lipophilic statins metabolized through the CYP450 system are more likely to produce muscle toxicity than unmetabolized statins.45 Therefore, hydrophilic statins may have more application prospects for reducing the risk of HCC.

Hepatocellular carcinoma is the main outcome of various end-stage liver diseases. Unfortunately, although HCC is known to have serious prognostic problems, specific drugs for the prevention of HCC have not yet been developed. Fortunately, many studies have found that statins have good clinical value in the prevention of colorectal cancer,46 prostate cancer,47 and other cancers.48 Although statins are not classic anti-neoplastic drugs, some recent studies have also demonstrated that the incidence of liver cancer can be reduced by taking statins.13,36 Surprisingly, as a potential treatment option for liver diseases, statins have beneficial pleiotropic effects, such as anti-inflammatory49 and antifibrotic effects,50 reduction in portal hypertension,51 inhibition of intrahepatic angiogenesis, and induction of hepatocyte apoptosis.52 Because of the potential concern about the side effects of statins, they are used cautiously. Paradoxically, only <1% of treated patients had an observable elevation of aspartate or alanine aminotransferase.53 Therefore, the use of statins in patients with liver disease was generally well-tolerated, and the overly cautious strategy may not be needed.11 A mild increase in transaminase of fewer than 3 times the upper limit of normal is not a contraindication for treatment, and patients can continue to take statins. In some patients, elevated transaminase levels may decrease on their own within 12 weeks. In addition, the incidence of drug-induced liver injury and other severe side effects caused by statins is extremely rare (less than 2/million/per year).54 Thus, the safety of using statins is not concerning.

In summary, the overall results suggest that statin use is associated with a reduced risk of HCC. Moreover, HCC risk declines with the increasing cumulative DDDs of statins and rosuvastatin may be favorable for the reduction in HCC risk in patients. However, despite our promising findings, this review does not identify the most effective dose or frequency of use. We suggest that more well-designed randomized controlled trials and cohort studies with larger sample sizes and long-term follow-up data are required before statins can be used in practice.

Authors’ Note
Y.C. and Q.L. contributed equally to this work. This article did not require an ethical board approval because the study data were downloaded from the open database.

Declaration of Conflicting Interests
The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.
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