Statins in Hepatitis B or C Patients Is Associated With Reduced Hepatocellular Carcinoma Risk: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: *Hepatocellular carcinoma is the world's leading cause of cancer-related death. Chronic hepatitis B virus and hepatitis C virus infection cause liver cancer. The aim of this study was to investigate the relationship between statins and the risk of hepatocellular carcinoma in patients with hepatitis B or C.*

Methods: *We systematically searched Web of Science, Embase, PubMed, Cochrane Library, China National Knowledge Infrastructure, and Wanfang Database from their inception to January 2019. We included studies that reported the hepatocellular carcinoma incidence among hepatitis B virus- or hepatitis C virus-infected patients or hepatitis B virus- or hepatitis C virus-related cirrhotic patients, evaluated and clearly defined exposure to statins, provided effective comparison groups, and reported risk estimates. Inclusion was not otherwise restricted. Summary relative risk estimates with 95% CIs were calculated using a random-effects model.*

Results: *Meta-analysis of 10 studies showed that statin users had a significantly lower risk of hepatocellular carcinoma (relative risk = 0.47, 95% CI = 0.38-0.56) with significant heterogeneity. In 7 hepatitis studies, using statin was associated with a 53% reduction in the incidence of hepatocellular carcinoma (relative risk = 0.47, 95% CI = 0.43-0.50) with substantial heterogeneity. In 3 cirrhosis studies, the incidence of hepatocellular carcinoma in statin users was significantly reduced by 55% (relative risk = 0.45, 95% CI = 0.30-0.61) with no heterogeneity.*

Conclusion: *Statins reduce the hepatocellular carcinoma risk among patients infected with hepatitis B virus or hepatitis C virus. This chemoprotective association is more pronounced in hepatitis B virus or hepatitis C virus-associated cirrhotic patients.*

Keywords: *Hepatitis, hepatocellular carcinoma, meta-analysis, statins*

INTRODUCTION

Liver cancer is a rapidly increasing, highly fatal cancer.[1] In recent decades, the mortality rate of hepatocellular carcinoma (HCC) in most countries is on the rise. Chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infection are major risk factors for HCC.[2,3] With the advent of direct-acting antiviral drugs, the cure rate of hepatitis C has greatly increased. Meanwhile, the advent of highly effective and low-drug-resistant antiviral drugs leads to persistent inhibition of HBV. These result in a significant reduction in the incidence of HCC.[4,5] Although antiviral therapy is an effective etiologically specific chemoprophylactic intervention for HCC, viral clearance does not mean that the risk of HCC can be eliminated, especially when patients develop liver fibrosis or cirrhosis.[6]

Statins are widely prescribed to reduce cholesterol levels and have been used for the prevention and treatment of various cardiovascular diseases (primary and secondary prevention of cardiovascular disease).[7] Hepatitis C virus infection is closely related to liver steatosis and dyslipidemia.[8] A research by Pais et al[9] showed that the prevalence of steatosis in chronic hepatitis B (CHB) paients was 18%-62% in Europe and Middle East and that was 14%-17% in Asia Pacific. These patients take statins while taking antivirals because they have metabolic syndrome or as a preventive drug for cardiovascular diseases.

In recent years, besides its role in cardiovascular diseases, the potential benefits of statins have caught more and more attention around the world. Use of statins has been shown to be inversely related to risk of various

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cancers.[10-12] In addition, researchers observed the relationship between statins and HCC risk in patients with HBV or HCV infection. However, meta-analysis of the effects of statins on the HCC risk has not been published. We therefore examined the association between HCC risk and use of statins in patients infected with HBV or HCV.

MATERIALS AND METHODS

The protocol has been registered in advance (CRD42017077142, http://www.crd.york.ac.uk/PROSPERO) and has been published in *Medicine* (Baltimore).[13]

Inclusion Criteria

Observational studies or randomized controlled trials (RCTs) were included according to the following criteria:

1) Reported the incidence of newly diagnosed HCC among HBV- or HCV-infected patients or HBV- or HCV-related cirrhosis
2) Evaluated and defined exposure to statins
3) Provided no comparison or effective comparison groups
4) Reported relative risks (RRs), hazard ratios (HRs), or odds ratios (ORs) with corresponding 95% CIs

Inclusion was not subject to publication type, language, or research scale.

Literature Search

We conducted a comprehensive electronic literature search on PubMed (Medline), Web of Science, Embase, Cochrane Library, China National Knowledge Infrastructure, and Wanfang Database from their inception to January 2019. The example search strategy used for Medline was listed in Supplementary Table 1. For additional data, attempts were made to contact the corresponding authors. Other eligible trials were manually searched from the references in the included study. All analyses were based on previously published studies; thus, no ethical approval and patient consent are required.

Study Selection and Data Extraction

Two authors (Y Li and ZG Li) independently examined the titles and abstracts to identify potentially eligible trials and then reviewed the full texts to determine the trials meeting the eligibility criteria. For all eligible studies, the following information was extracted: first author, publication year, study population, study location, study design, study period, participants' age, data source, sample size, follow-up duration, definition of non-users, and statin dose, where available, in addition to maximally adjusted risk estimates with corresponding 95% CIs. Adjusted confounding factors were extracted. Crude risk estimates with 95% CIs were extracted when adjusted risk estimates were not available. Disagreements were resolved through discussion and arbitrated by the third author.

Quality Assessment

The quality of the studies included was assessed independently by two authors (Y Li and ZG Li). Disagreements were resolved through discussions and negotiations with the third reviewer (XK Li). We used Jadad score to assess the quality of the included RCTs,[14] with a maximum score of 5. A score of >3 was considered to represent high quality. The Newcastle–Ottawa Scale was adopted to assess the quality of observational studies.[15] Three items were used to evaluate studies: patient selection (4 stars), assessment of outcome/exposure (3 stars), and comparability of the study groups (2 stars). According to this scale (up to 9 stars), a score of 0-6 stars and ≥7 stars were considered low quality and high quality.

Primary Outcome

The primary outcome was the incidence of HCC among HBV- or HCV-infected patients exposed to statins before diagnosed with HCC.

Statistical Analysis

Risk estimates for each study were aggregated using a random-effects model. Relative risk was used as a common indicator for detecting the relationship between statin use and HCC risk. We regarded HRs and ORs as equivalents of RR. Cochrane's *Q* statistic (heterogeneity < 0.10 suggesting statistically significant) and the I^2 statistic ($I^2 > 75.0\%$ representing significant heterogeneity, $I^2 < 50\%$ representing low heterogeneity, and $50.0\% \leq I^2 \leq 75.0\%$ representing moderate heterogeneity) were evaluated qualitatively and quantitatively for the heterogeneity of the study.

Sources of heterogeneity were mainly investigated using subgroup analysis by stratifying the original estimates according to hepatitis virus type, and whether a patient had cirrhosis. For studies that adjusted for any variables and specifically for important confounders of age, body mass index (BMI), cirrhosis, diabetes, race, sex, anti-HBV or HCV treatment, and fibrosis stage, the adjusted estimates were analyzed. Sensitivity analysis was performed to assess the robustness of the results.

Publication bias was detected quantitatively using Begg's test and Egger's test with a significance level of $P \leq .1$.[16,17] All statistical analyses were performed using Stata version 15.0 (StataCorp, College Station, Tex, USA). $P < .05$ was considered a statistically significant difference.

RESULTS

Description of Studies

Initially, 4036 records were obtained from 6 databases. Figure 1 shows the selection process. After reviewing the titles and abstracts, a total of 20 citations were thought to be potentially relevant. After carefully reading the full text, 15 citations were further excluded. Through manual search, a total of 5 studies were found to be eligible for inclusion. Nine studies[18-26] fulfilled the inclusion criteria and were included in the meta-analysis, with 1[22] of the studies published only in abstract form, and another[26] potentially being viewed as 2 studies, as it studied HCC patients with HBV- and HCV-related cirrhosis separately. Cumulatively 35 279 cases of HCC were reported among 548 073 patients, with 1 of the studies not providing the number of patients who developed HCC.[22]

Study Characteristics

Detailed characteristics are shown in Table 1. Six studies were conducted in Asia,[18-20,22,23,26] while the remaining studies were conducted in America.[21,24,25] Among the included studies, 7 were cohort studies[18-21,23-25] and 2 were nested case–control studies.[22,26] This study involved 548 073 individuals, consisting of 274 307 men (50.0%) and 238 198 women (43.5%), with 1 of the studies not providing gender data.[22] Eight studies recruited subjects from population registries and 1 remaining study was hospital-based.[21] Four studies[18,20,22,23] were conducted in populations with HBV infection and 3[19,21,24] in those with HCV infection. Three studies[25,26] were conducted in populations with HBV- or HCV-related cirrhosis. One study[26] was conducted in populations with HBV- and HCV-related cirrhosis separately. Another study[25] was conducted in populations with HCV-related cirrhosis. Six studies[18-20,23,25,26] defined subjects with lower cumulative doses of statins during the study as statin non-users, whereas the remaining studies did not clearly define non-users. All studies provided adjusted risk estimates.

Quality of Included Studies

Because 1[26] of the 9 studies can be viewed as 2 studies, in order to facilitate description, 9 studies were described as 10 studies for meta-analysis. In the observational study, the median score of the Castle-Ottawa mass score was 8 (range, 4-9); 8 of them were considered to be high quality. Table 1 depicts the methodological quality of the included studies. Most studies were adjusted for the following confounding factors: age (10/10), sex (8/10), BMI (3/10), antiviral treatment (7/10), cirrhosis (5/10), diabetes mellitus (DM) (8/10), and non-statin lipid-lowering drugs (8/10) (Table 1).

Overall Meta-Analysis

Based on the 10 studies, statin users had a significantly lower risk of developing HCC than statin non-users (RR = 0.47, 95% CI = 0.38-0.56), with substantial heterogeneity (heterogeneity < 0.01, I^2 = 77.2%) (Figure 2). This risk reduction with statins was adjusted for potential confounders, which was reported in Table 1.

Subgroup Analysis and Analysis of Studies With Specific Adjustment Factors

To verify the robustness of the overall analysis and explore potential sources of heterogeneity, subgroup analysis and analysis of studies with specific adjustment factors were carried out, as described in Table 2.

Based on the stage of disease (cirrhosis vs hepatitis), we performed a subgroup analysis. In 7 studies of hepatitis, use of statins can significantly reduce the incidence of HCC by 53%, with significant heterogeneity in the group. In 3 studies of cirrhosis, use of statins can significantly reduce the incidence of HCC by 55%, with no heterogeneity within the group. Stratified analyses by hepatitis virus type demonstrated that the beneficial effect of statins was stable in HBV (RR = 0.42) and HCV patients (RR = 0.49), with significant heterogeneity in both groups.

After adjusting for gender, race, age, BMI, antiviral treatment, cirrhosis, DM, and non-statin lipid-lowering drugs, the association between statin use and lower HCC incidence in CHB/chronic hepatitis C (CHC) patients was stable, with the pooled RRs in the 0.37-0.50 range. Significant heterogeneity was present in most of the analyses of studies with specific adjustment factors, such as age (I^2 = 77.2%), race (I^2 = 81.5%), and cirrhosis (I^2 = 83.3%).

Sensitivity Analysis

We conducted pre-planned stratified analysis based on study design and location (Table 3).

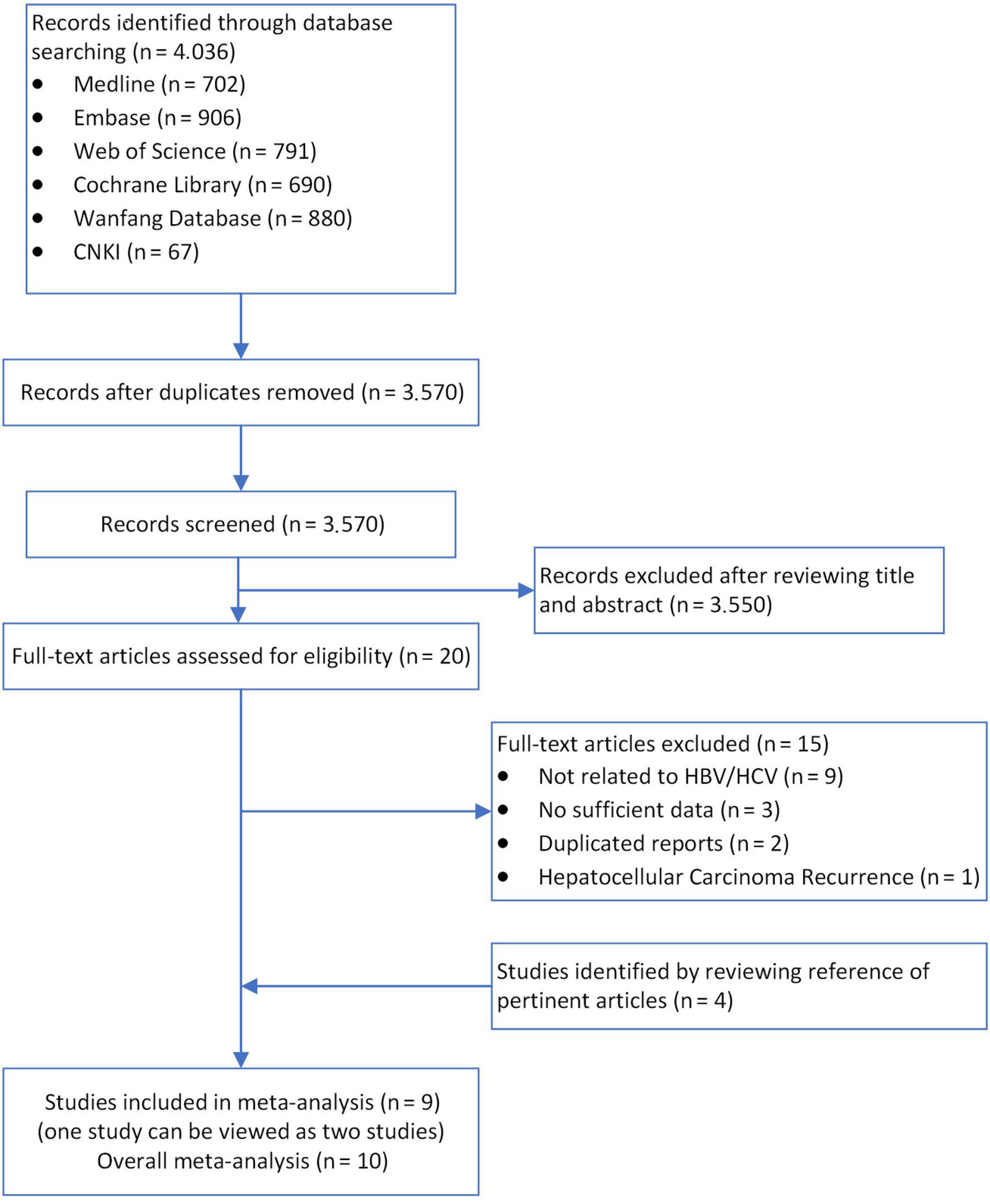

Figure 1. Flow diagram of study selection. HBV, hepatitis B virus; HCV, hepatitis C virus; CNKI, China National Knowledge Infrastructure.

Table 1. Characteristics and Quality of Included Studies Assessing the Risk of HCC With Statin Use

Study	Design	Location	Setting	Time Period	Types of Hepatitis Virus	Total No. of Subjects	No. of HCC Cases	Adjusted Factors	Quality Score
Tsan et al[18] 2012	Cohort	Taiwan	Population based	1997-2008	HBV	33 413	1021	1-3, 5-7, 9, 10	NOS: 9
Tsan et al. 2013[19]	Cohort	Taiwan	Population based	1999-2010	HCV	260 864	27 883	1, 2, 4-7, 9, 10	NOS: 9
Chen et al[20] 2015	Cohort	Taiwan	Population based	2000-2008	HBV	61 898	1735	1-3, 9, 10	NOS: 9
Hsiang et al[21] 2015	Cohort	Hong Kong	Hospital based	2000-2012	HBV	53 513	1298	1-3, 5, 7, 9, 10	NOS: 9
Nyberg et al[22] 2015	Case–control	United States	Population based	2002-2012	HCV	35 712	NR	1, 5, 7, 8, 11	NOS: 4
Tsan et al[23] 2015	Cohort	Taiwan	Population based	2003-2010	HBV	91 265	2841	1, 2, 5-7, 9, 10	NOS: 6
Simon et al[24] 2016	Cohort	United States	Population based	2001-2014	HCV	9135	233	1, 2, 4, 6-12	NOS: 8
Mohanty et al[25] 2016	Cohort	United States	Population based	1996-2009	HCV*	1370	173	1, 7, 11, 12	NOS: 7
Chang et al[26] 2017 (HBV)	Case–control	Taiwan	Population based	2000-2013	HBV*	605	64	1-3, 7, 10	NOS: 7
Chang et al[26] 2017 (HCV)	Case–control	Taiwan	Population based	2000-2013	HCV*	298	31	1-3, 7, 10	NOS: 7

Adjusted factors: 1, age; 2, sex; 3, anti-HBV; 4, anti-HCV; 5, cirrhosis; 6, alcoholic liver disease; 7, diabetes mellitus; 8, race; 9, other medications (aspirin/non-steroidal anti-inflammatory medications, angiotensin-converting enzymes inhibitors); 10, other lipid-lowering agents; 11, body mass index; 12, smoking.
*HBV- or HCV-related cirrhosis. HBV, hepatitis B virus; HCV, hepatitis C virus; NOS, Newcastle-Ottawa scale; HCC, hepatocellular carcinoma.

In 7 cohort studies, statin use was associated with a significant 51% reduction in the incidence of HCC, although there was moderate heterogeneity within the group. In 3 case–control studies, statin use can significantly reduce the incidence of HCC by 61%, with moderate heterogeneity within the group. This explained the significant heterogeneity in the overall analysis.

In a stratified analysis based on research sites, in the Asian population, statin use was associated with a statistically significant 49% reduction in the incidence of HCC, with moderate heterogeneity among studies. Similarly, in the Western population, the incidence of HCC in patients using statins was significantly reduced by 62%, although there was moderate heterogeneity within the group. This subgroup analysis also partly explained the significant heterogeneity in the overall analysis.

We performed additional sensitivity analysis based on study quality (high quality vs low quality) to further explore the heterogeneity of the included studies. Low-quality studies demonstrated a significantly greater protective effect of statins on HCC than high-quality studies, explaining the heterogeneity seen in the analysis of observational studies.

To assess whether any study had a significant effect on the RR of meta-analysis, each study was excluded and its effect on the heterogeneity of the primary summary estimate and the Cochran's *Q* test *P* value was evaluated (Figure 3). No study had significantly affected the *P* value of heterogeneity in summary estimates or other aggregate estimates.

Publication Bias

The Begg's and Egger's tests were not performed because of incomplete data of the included studies.

DISCUSSION

This systematic review summarized the relationship between the use of statins and the risk of HCC in HBV- or HCV-infected patients in 10 studies involving 548 073 individuals. Considering the potential confounding factors in the original studies, adjusted estimates were used rather than unadjusted estimates to make the summary

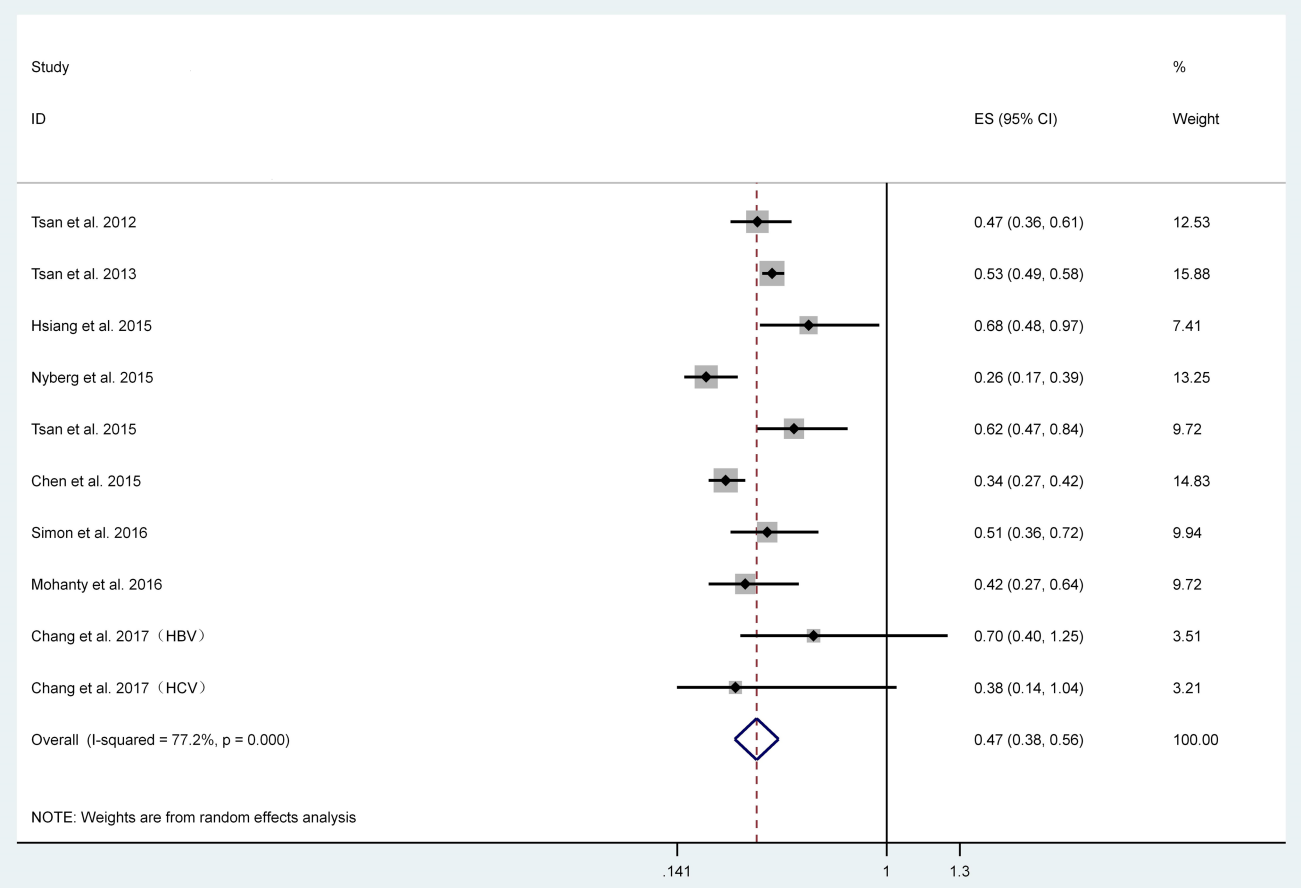

Figure 2. Forest plot of the association between the use of statins and the risk of hepatocellular carcinoma in patients with hepatitis B or C. ES, effect size; HBV, hepatitis B virus; HCV, hepatitis C virus.

results more believable. This meta-analysis revealed that statins significantly reduced the risk of HCC in CHB or CHC patients (RR = 0.47; 95% CI = 0.38-0.56; I^2 = 77.2%). This significant effect was validated in our subgroup analyses. Hierarchies of study design, study location, study quality, presence/absence of cirrhosis, and hepatitis virus type did not change with the significant decrease in HCC rate among statin users. We made one key observation: statin-treated patients with CHB or CHC have a reduced risk of HCC than untreated patients, especially among HBV- and HCV-related cirrhotic patients. These findings are consistent with previous meta-analyses.[27,28]

There is no doubt that HBV and HCV are related to HCC. Patients who develop chronic liver injury, and ultimately cirrhosis, are very likely to develop HCC,[29] and HBV- and HCV-related cirrhosis is one of the independent risk factors for HCC.[30] Our meta-analysis of 3 studies that included HBV- and HCV-related cirrhotic patients found that the use of statins significantly reduced the risk of liver cancer by 55% with no heterogeneity. However, substantial heterogeneity was observed in CHB and CHC patients using statins. Besides the limited sample size and study quality, the different hepatitis virus types and study locations in each study might have also contributed to the observed heterogeneity.

The common side effects of statins are hepatotoxicity, myopathy, and myoglobinuria, as well as acute renal failure. Given the concern of possible hepatotoxicity, statins are unlikely to be used in patients with chronic liver disease.[31] However, a prospective study demonstrated that it was safe for statins to treat hypercholesterolemia in patients with chronic liver disease.[32] A cohort study found that among CHB patients, the incidence of unspecified hepatitis was lower in the statins cohort than in the non-statins cohort.[33] Patients with chronic viral hepatitis who used statins did not experience an increased risk of liver decompensation and death compared to patients who do not use statins.[34] Some studies have also found

Table 2. Summary Results of Subgroup Analyses

Group or Adjustment	Number of Studies	Summary Result		
		RE (95% CI)	*P*	I^2 (%)
Cirrhosis or not				
Hepatitis (18-24)	7	0.47 (0.43-0.50)	0	84.2
Cirrhosis (25,26)	3	0.45 (0.30-0.61)	.468	0
Hepatitis virus type				
HBV (18,20,21,23)	4	0.42 (0.36-0.48)	.003	78.2
HCV (19,22,24)	3	0.49 (0.45-0.53)	0	89.9
Adjustment				
Age (18-26)	10	0.47 (0.38-0.56)	0	77.2
Sex (18-21,23,24,26)	8	0.50 (0.41-0.60)	.001	70.7
Race (22,24)	2	0.37 (0.13-0.62)	.02	81.5
BMI (22,24,25)	3	0.47 (0.38-0.56)	.791	0
DM (18,19,21-26)	9	0.49 (0.39-0.58)	.001	68.9
Anti-virus (18-21,24,26)	7	0.49 (0.39-0.59)	.001	72.7
Cirrhosis (18,19,21-23)	5	0.49 (0.36-0.62)	0	83.3
Non-statin lipid-lowering drugs (18-21,23,24,26)	8	0.50 (0.41-0.60)	.001	70.7

RE, risk estimate; HBV, hepatitis B virus; HCV, hepatitis C virus; BMI, body mass index; DM, diabetes mellitus.

that it is safe to use statins in patients with cirrhosis.[31,35] Moreover, regarding the use of statins in patients with liver disease state, the National Lipid Association Statin Liver Safety Task Force recommended that the presence of chronic liver disease or compensated cirrhosis is not a contraindication to statins.[36] Statins are safe and have been shown to be beneficial for morbidity and mortality in patients infected with HBV or HCV and eventually cirrhosis. However, most data are from observational studies, and data from randomized studies are currently unavailable.

Basic studies have demonstrated that statins exert a range of anti-neoplastic effects. Statins have been found to have beneficial effects on a number of pathways involved in the development and progression of cancer, such as blocking Myc phosphorylation and activation,[37] limiting p21 and p27 degradation,[38] and decreasing

Table 3. Sensitivity Analysis to Examine Sources of Heterogeneity Observed in Summary Estimates

Subgroup Analysis	No. of Studies	No. of HCC Cases	Total No. of Subjects	Adjusted RR	95% CI	Tests of Heterogeneity		Heterogeneity Between Groups (*P*)
						P	I^2 (%)	
Study design								
Cohort[18-21,23-25]	7	35 184	547 170	0.49	0.40-0.58	.001	74.2	.000[a]
Non-cohort[22,26]	3	95	36 615	0.39	0.13-0.64	.135	50.2	
Study location								
China[18-21,23,26]	7	34 873	501 856	0.51	0.40-0.61	.001	74.9	.002[a]
United States[22,24,25]	3	406	46 217	0.38	0.22-0.54	.046	67.5	
Study quality								
High quality[18-21,24-26]	8	32 438	421 096	0.48	0.39-0.57	.002	68.8	.012
Low quality[22,23]	2	2841	126 977	0.43	0.08-0.78	.001	90.7	

HCC, hepatocellular carcinoma; RR, relative risk.

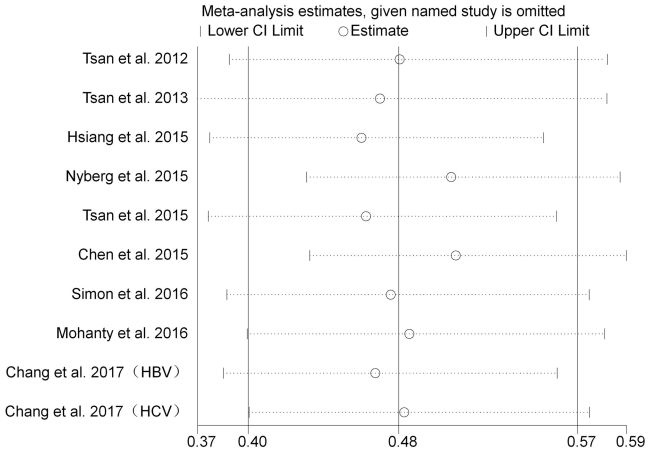

Figure 3. Sensitivity analysis of the association between the use of statins and the risk of hepatocellular carcinoma in patients with hepatitis B or C. HBV, hepatitis B virus; HCV, hepatitis C virus.

HBx-induced phospho-Akt in hepatocytes via P2X receptors.[39] Hepatic fibrosis caused by hepatitis has been shown to increase the risk of liver cancer. Therefore, the anti-fibrotic effects of statins may have a positive impact on the pathogenesis of liver cancer, lessening its incidence.[40] Some studies have demonstrated that statins inhibit fibrogenic hepatic stellate cell activation by nitric oxide synthase,[41] as well as the paracrine effects of hepatocytes[42] and endothelial cells.[43]

Several potential limitations of this study should be noted. First, the outcome was an association, which is necessarily subject to confounding bias. Although we considered several adjusting factors, there remain many potential factors that are unknown, such as cholesterol level, triglyceride level, or the use of other over-the-counter drugs. Second, significant heterogeneity was present in our analysis. Although heterogeneity could be explained by some subgroup and sensitivity analyses, the source of most of the heterogeneity was unclear. A potential explanation could be that the inherent relationship between HCC, cirrhosis, and the type of statin used would influence the result and produce heterogeneity. Despite the use of a random-effects model in this analysis, estimates with high heterogeneity are vulnerable. Third, only 10 studies were included, as data from some studies that would otherwise have been essential for assessing publication bias were not available.

CONCLUSION

In summary, the results of this meta-analysis suggest that statin use is associated with a reduced risk of HCC in patients infected with HBV or HCV. This chemical protection is more pronounced in people with HBV- or HCV-related cirrhosis. However, given the potential for bias and confusion, these results should be interpreted with caution. Future randomized or prospective cohort studies of hepatitis B or C patients are warranted.

Ethics Committee Approval: All analyses were based on previously published studies; thus, no ethical approval is required for this study.

Informed Consent: All analyses were based on previously published studies; thus, no patient consent is required for this study.

Peer Review: Externally peer-reviewed.

Author Contributions: Consept – Z.G.L., Y.A.Y.; Design – Z.G.L., Y.A.Y.; Data Collection and/or Processing – Y.L., Z.G.L., N.Q.Z., L.D.Z.; Analysis and/or Interpretation – Y.L., Z.G.L.; Critical Review – Y.A.Y., H.B.D., B.Z., X.K.L.

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Conflict of Interest: The authors have declared that no conflicts of interest exist.

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REFERENCES

1. Bertuccio P, Turati F, Carioli G, et al. Global trends and predictions in hepatocellular carcinoma mortality. J Hepatol. 2017;67(2):302-309. [CrossRef]
2. Liu Z, Jiang Y, Yuan H, et al. The trends in incidence of primary liver cancer caused by specific etiologies: results from the Global Burden of Disease Study 2016 and implications for liver cancer prevention. J Hepatol. 2019;70(4):674-683. [CrossRef]
3. Axley P, Ahmed Z, Ravi S, Singal AK. Hepatitis C virus and hepatocellular carcinoma: a narrative review. J Clin Transl Hepatol. 2018;6(1):79-84. [CrossRef]
4. Wei L, Kao JH. Benefits of long-term therapy with nucleos(t)ide analogues in treatment-naive patients with chronic hepatitis B. Curr Med Res Opin. 2017;33(3):495-504. [CrossRef]
5. Baumert TF, Jühling F, Ono A, Hoshida Y. Hepatitis C-related hepatocellular carcinoma in the era of new generation antivirals. BMC Med. 2017;15(1):52. [CrossRef]
6. Papatheodoridis GV, Lampertico P, Manolakopoulos S, Lok A. Incidence of hepatocellular carcinoma in chronic hepatitis B patients receiving nucleos(t)ide therapy: a systematic review. J Hepatol. 2010;53(2):348-356. [CrossRef]
7. Cholesterol Treatment Trialists' (CTT) Collaboration, Baigent C, Blackwell L, et al. Efficacy and safety of more intensive lowering of

LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet. 2010;376(9753):1670-1681. [CrossRef]
8. Bugianesi E, Salamone F, Negro F. The interaction of metabolic factors with HCV infection: does it matter? J Hepatol. 2012;56(suppl 1):S56-S65. [CrossRef]
9. Pais R, Rusu E, Ratziu V. The impact of obesity and metabolic syndrome on chronic hepatitis B and drug-induced liver disease. Clin Liver Dis. 2014;18(1):165-178. [CrossRef]
10. Langballe R, Cronin-Fenton D, Dehlendorff C, et al. Statin use and risk of contralateral breast cancer: a nationwide cohort study. Br J Cancer. 2018;119(10):1297-1305. [CrossRef]
11. Archibugi L, Arcidiacono PG, Capurso G. Statin use is associated to a reduced risk of pancreatic cancer: a meta-analysis. Dig Liver Dis. 2019;51(1):28-37. [CrossRef]
12. Shi M, Zheng H, Nie B, Gong W, Cui X. Statin use and risk of liver cancer: an update meta-analysis. BMJ Open. 2014;4(9):e005399. [CrossRef]
13. Li Z, Li Y, Li X, et al. Statins on hepatocellular carcinoma risk in hepatitis B or C patients protocol for a systematic review and meta-analysis. Med. 2018;97(34):e11950. [CrossRef]
14. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials. 1996;17(1):1-12. [CrossRef]
15. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol. 2010;25(9):603-605. [CrossRef]
16. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics. 1994;50(4):1088-1101. [CrossRef]
17. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315(7109):629-634. [CrossRef]
18. Tsan YT, Lee CH, Wang JD, Chen PC. Statins and the risk of hepatocellular carcinoma in patients with hepatitis B virus infection. J Clin Oncol. 2012;30(6):623-630. [CrossRef]
19. Tsan YT, Lee CH, Ho WC, Lin MH, Wang JD, Chen PC. Statins and the risk of hepatocellular carcinoma in patients with hepatitis C virus infection. J Clin Oncol. 2013;31(12):1514-1521. [CrossRef]
20. Chen CI, Kuan CF, Fang YA, et al. Cancer risk in HBV patients with statin and metformin use: a population-based cohort study. Med. 2015;94(6):e462. [CrossRef]
21. Hsiang JC, Wong GL, Tse YK, Wong VWS, Yip TCF, Chan HLY. Statin and the risk of hepatocellular carcinoma and death in a hospital-based hepatitis B-infected population: a propensity score landmark analysis. J Hepatol. 2015;63(5):1190-1197. [CrossRef]
22. Nyberg AH, Sadikova E, Shi JX, et al. Treatment with statins reduces liver cancer risk in patients with chronic hepatitis C. Hepatology. 2015;62:1079A-180A.
23. Tsan Y, Lin M, Ho W, Chen P. Nucleoside analogues, statins and the risk of hepatocellular carcinoma in patients with hepatitis B virus infection. Value Health. 2015;18(3):A193. [CrossRef]
24. Simon TG, Bonilla H, Yan P, Chung RT, Butt AA. Atorvastatin and fluvastatin are associated with dose-dependent reductions in cirrhosis and hepatocellular carcinoma, among patients with hepatitis C virus: results from ERCHIVES. Hepatology. 2016;64(1):47-57. [CrossRef]
25. Mohanty A, Tate JP, Garcia-Tsao G. Statins are associated with a decreased risk of decompensation and death in veterans with hepatitis C-related compensated cirrhosis. Gastroenterology. 2016;150(2):430-40.e1. [CrossRef]
26. Chang FM, Wang YP, Lang HC, et al. Statins decrease the risk of decompensation in hepatitis B virus- and hepatitis C virus-related cirrhosis: a population-based study. Hepatology. 2017;66(3):896-907. [CrossRef]
27. Zheng YX, Zhou PC, Zhou RR, Fan XG. The benefit of statins in chronic hepatitis C patients: a systematic review and meta-analysis. Eur J Gastroenterol Hepatol. 2017;29(7):759-766. [CrossRef]
28. Zhong GC, Liu Y, Ye YY, Hao FB, Wang K, Gong JP. Meta-analysis of studies using statins as a reducer for primary liver cancer risk. Sci Rep. 2016;6:26256. [CrossRef]
29. Marrero JA, Kulik LM, Sirlin CB, et al. Diagnosis, staging and management of hepatocellular carcinoma: 2018 practice guidance by the American Association for the Study of Liver Diseases. Hepatology. 2018;68(2):723-750. [CrossRef]
30. Fattovich G, Stroffolini T, Zagni I, Donato F. Hepatocellular carcinoma in cirrhosis: incidence and risk factors. Gastroenterology. 2004;127(5)(suppl 1):S35-S50. [CrossRef]
31. Vargas JI, Arrese M, Shah VH, Arab JP. Use of statins in patients with chronic liver disease and cirrhosis: current views and prospects. Curr Gastroenterol Rep. 2017;19(9):43. [CrossRef]
32. Alqahtani SA, Sanchez W. Statins are safe for the treatment of hypercholesterolemia in patients with chronic liver disease. Gastroenterology. 2008;135(2):702-704. [CrossRef]
33. Huang YW, Hsieh AC, Yang SS. Safety of statins in chronic hepatitis B patients. Am J Gastroenterol. 2017;112(2):385-386. [CrossRef]
34. Wong JCT, Chan HLY, Tse YK, Yip TCF, Wong VWS, Wong GLH. Statins reduce the risk of liver decompensation and death in chronic viral hepatitis: a propensity score weighted landmark analysis. Aliment Pharmacol Ther. 2017;46(10):1001-1010. [CrossRef]
35. Souk K, Al-Badri M, Azar ST. The safety and benefit of statins in liver cirrhosis: a review. Exp Clin Endocrinol Diabetes. 2015;123(10):577-580. [CrossRef]
36. Bays H, Cohen DE, Chalasani N, Harrison SA, The National Lipid Association's Statin Safety Task Force. An assessment by the Statin Liver Safety Task Force: 2014 update. J Clin Lipidol. 2014;8(suppl 3):S47-S57. [CrossRef]
37. Cao ZW, Fan-Minogue H, Bellovin DI, et al. MYC phosphorylation, activation, and tumorigenic potential in hepatocellular carcinoma are regulated by HMG-CoA reductase. Cancer Res. 2011;71(6):2286-2297. [CrossRef]
38. Singh S, Singh PP, Roberts LR, Sanchez W. Chemopreventive strategies in hepatocellular carcinoma. Nat Rev Gastroenterol Hepatol. 2014;11(1):45-54. [CrossRef]
39. Ghalali A, Martin-Renedo J, Högberg J, Stenius U. Atorvastatin decreases HBx-induced phospho-Akt in hepatocytes via P2X receptors. Mol Cancer Res. 2017;15(6):714-722. [CrossRef]
40. Imprialos KP, Stavropoulos K, Doumas M, Skalkou A, Zografou I, Athyros VG. The potential role of statins in treating liver disease. Expert Rev Gastroenterol Hepatol. 2018;12(4):331-339. [CrossRef]
41. Wang W, Zhao C, Zhou J, Zhen Z, Wang Y, Shen C. Simvastatin ameliorates liver fibrosis via mediating nitric oxide synthase in rats with non-alcoholic steatohepatitis-related liver fibrosis. PLoS One. 2013;8(10):e76538. [CrossRef]
42. Chong LW, Hsu YC, Lee TF, et al. Fluvastatin attenuates hepatic steatosis-induced fibrogenesis in rats through inhibiting paracrine effect of hepatocyte on hepatic stellate cells. BMC Gastroenterol. 2015;15:22. [CrossRef]
43. Marrone G, Russo L, Rosado E, et al. The transcription factor KLF2 mediates hepatic endothelial protection and paracrine endothelial-stellate cell deactivation induced by statins. J Hepatol. 2013;58(1):98-103. [CrossRef]

Supplementary Table 1. Search Strategy Used in PubMed Database

No.	Search Terms
1	chronic hepatitis B[MeSH Terms]
2	chronic hepatitis C[MeSH Terms]
3	hepatitis B virus
4	hepatitis C virus
5	HBV
6	HCV
7	#1 OR #2 OR #3 OR #4 OR #5 OR #6
8	statin[MeSH Terms]
9	statin*
10	atorvastatin
11	fluvastatin
12	cerivastatin
13	lovastatin
14	pravastatin
15	rosuvastatin
16	simvastatin
17	pitavastatin
18	#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17
19	hepatocellular carcinoma[MeSH Terms]
20	Liver Neoplasms[MeSH Terms]
21	liver cancer
22	HCC
23	#19 OR #20 OR #21 OR #22
24	#7 AND #18
25	#18 AND #23
26	#24 OR #25