CLINICAL—LIVER

Statins Are Associated With a Reduced Risk of Hepatocellular Cancer: A Systematic Review and Meta-analysis

SIDDHARTH SINGH,[1] PREET PAUL SINGH,[2] ABHA GOYAL SINGH,[3] MOHAMMAD HASSAN MURAD,[4] and WILLIAM SANCHEZ[1]

[1]Division of Gastroenterology and Hepatology, [2]Department of Medical Oncology, [3]Department of Internal Medicine, and [4]Division of Preventive, Occupational and Aerospace Medicine, Mayo Clinic, Rochester, Minnesota

This article has an accompanying continuing medical education activity on page e13. Learning Objective: Upon completion of the CME activity, successful learners will be able to summarize the association between HMG-CoA reductase inhibitor therapy and reduced rates of hepatocellular carcinoma.

See Covering the Cover synopsis on page 255.

BACKGROUND & AIMS: Hepatocellular carcinoma (HCC) is a leading cause of cancer-related mortality worldwide. Several studies have shown that statins could have chemopreventive effects on HCC. We performed a systematic review and meta-analysis of studies that evaluated the effects of statins on the risk of HCC. **METHODS:** We conducted a systematic search of MEDLINE, Embase, and Web of Science through May 2012 and manually reviewed the literature. Studies were included if they evaluated and clearly defined exposure to statins, reported the incidence of HCC, and reported relative risks or odds ratios (ORs) or provided data for their estimation. Ten studies reporting 4298 cases of HCC in 1,459,417 patients were analyzed. Summary OR estimates with 95% confidence intervals (CIs) were calculated using the random effects model. Statistical heterogeneity was assessed with the Cochran's Q statistic and I^2 statistic. **RESULTS:** Statin users were less likely to develop HCC than statin nonusers (adjusted OR, 0.63; 95% CI, 0.52–0.76), although the results were heterogeneous ($P = .01$, $I^2 = 59\%$). This heterogeneity could be accounted for by study location (Asian population [n = 4]: adjusted OR, 0.52; 95% CI, 0.42–0.64; Western population [n = 6]: adjusted OR, 0.67; 95% CI, 0.53–0.85) and design (observational studies [n = 7]: adjusted OR, 0.60; 95% CI, 0.49–0.73; clinical trials [n = 3]: adjusted OR, 0.95; 95% CI, 0.62–1.45). **CONCLUSIONS: Based on meta-analysis, statin use is associated with a reduced risk of HCC, most strongly in Asian but also in Western populations. Randomized clinical trials in populations at high risk for HCC (especially in Asian populations with hepatitis B) are warranted.**

Keywords: Liver Cancer Prevention; Epidemiology; Cholesterol-Lowering Drugs; HMG-CoA Reductase Inhibitors.

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Hepatocellular cancer (HCC) is the fifth most common cancer worldwide in men and the second most frequent cause of cancer death, with an annual incidence of 0.5 million worldwide.[1] Half of these cases and deaths occur in China, where viral hepatitis B and C are the major risk factors for HCC. On the other hand, in Western countries, 30% to 40% of HCC cases occur in patients without usual risk factors and are probably attributable to nonalcoholic fatty liver disease (NAFLD) or metabolic syndrome.[2,3] The rising prevalence of NAFLD[4] is a major contributing factor to the increasing incidence of HCC in the United States.[5,6] Currently, there are no chemopreventive agents that may reduce risk of HCC, and management of HCC involves surveillance of high-risk populations for early diagnosis and timely treatment.

Statins or 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, used for primary and secondary prevention of cardiovascular diseases, may decrease the risk of cancers.[7,8] In vitro and animal studies have shown that in addition to cholesterol reduction, statins have antiproliferative, proapoptotic, antiangiogenic, immunomodulatory, and anti-infective effects,

Abbreviations used in this paper: CI, confidence interval; CTT, Cholesterol Treatment Trialists', DM, diabetes mellitus; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; NAFLD, nonalcoholic fatty liver disease; OR, odds ratio; RCT, randomized controlled trial.

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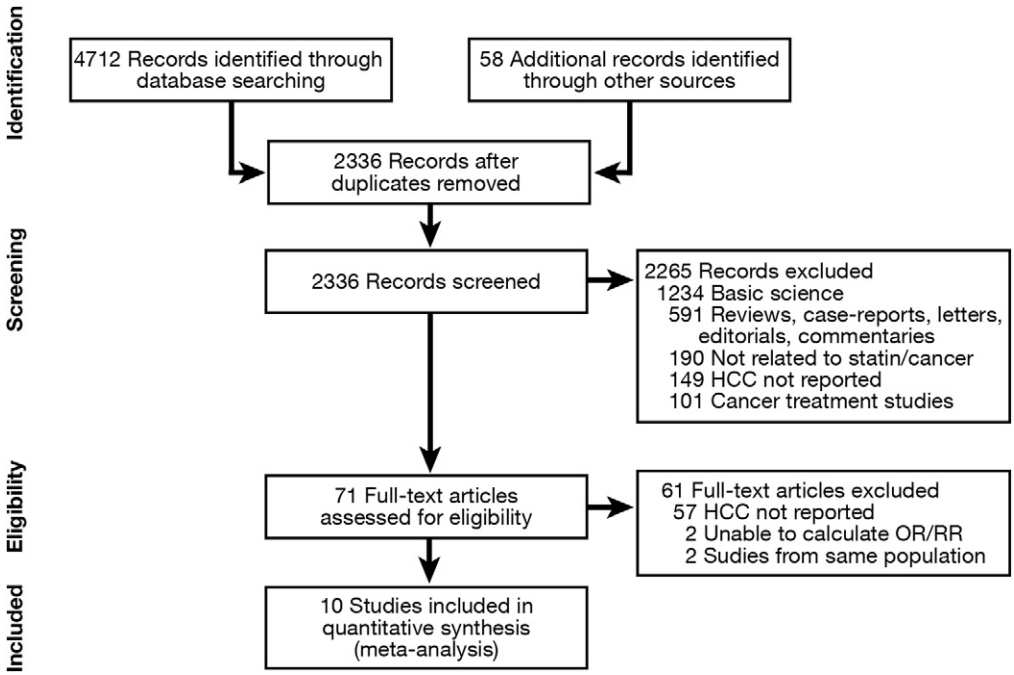


Figure 1. Flow diagram summarizing study identification and selection.

which prevent cancer growth.[9,10] Some recent observational studies have shown that use of statins may be associated with a lower risk of HCC,[11–13] whereas others have shown no beneficial effect.[14]

To better understand this issue, we performed a systematic review with meta-analysis of existing randomized controlled trials (RCTs) and observational studies that investigated the association between use of statins and the risk of developing HCC.

Subjects and Methods

Search Strategy

A systematic literature search of MEDLINE (1966 through May 25, 2012), Embase (1988 through May 25, 2012), and Web of Science (1993 through May 25, 2012) databases was conducted by 2 study investigators (S.S. and P.P.S.) independently for all relevant articles on the effect of statin use on the risk of HCC. Keywords used in the search included "HMG-CoA reductase inhibitor(s)," "statin(s)," "atorvastatin," "fluvastatin," "lovastatin," "pravastatin," "rosuvastatin," or "simvastatin" combined with "cancer" or "neoplasm(s)." The title and abstract of studies identified in the search were reviewed by 2 authors independently (S.S. and P.P.S) to exclude studies that did not answer the research question of interest. The full text of the remaining articles, including the references, was examined to determine whether it contained relevant information. We also manually searched the abstracts from major gastroenterology and oncology conferences (2003–2012). When incomplete information was available, attempts were made to contact the corresponding authors of the studies for additional information.

Selection Criteria

Studies considered in this meta-analysis were either RCTs or observational studies that met the following inclusion criteria: (1) evaluated and clearly defined exposure to statins, (2) reported HCC incidence, and (3) reported relative risks or odds ratios (ORs) or provided data for their calculation. Inclusion was not otherwise restricted by study size, language, or publication type. When there were multiple publications from the same population, only data from the most recent comprehensive report were included. The flow diagram summarizing study identification and selection is shown in Figure 1.

To understand the risk of bias in individual studies, a formal quality assessment of studies was performed along with subgroup analysis. The methodological quality of observational studies was assessed by 2 authors independently (A.G.S. and P.P.S.) using the Newcastle–Ottawa scale.[15] In this scale, observational studies were scored across 3 categories: selection (4 questions) and comparability (2 questions) of study groups and ascertainment of the outcome of interest (3 questions); all questions had a score of 1 except for comparability of study groups, in which separate points were awarded for controlling age and/or sex (maximum of 2 points). Studies with a cumulative score ≥ 7 were considered high quality.[16] The Jadad scale, a 5-point score based on randomization strategy (maximum of 2 points), blinding (maximum of 2 points), and withdrawals and dropouts (maximum of 1 point), was used to assess the methodological quality of RCTs.[17] Any discrepancies were addressed by a joint reevaluation of the original article.

Data Abstraction

Data were independently abstracted onto a standardized form by 2 reviewers (S.S. and A.G.S.). The following data were collected from each study: study design, time period of study/year of publication, country of the population studied, primary outcome reported, type of medication, dose and duration of statin use (if reported), information source for exposure measurement, total number of persons in each group (exposed vs not exposed), ORs, and 95% confidence intervals (CIs) with and without adjustment for confounding factors. Data on the following confounding risk factors for HCC were extracted from each study: age, sex, presence of cirrhosis, hepatitis B infection, hepatitis C infection, alcoholic liver disease, diabetes mellitus

(DM), and NAFLD. Conflicts in data abstraction were resolved by consensus, referring back to the original article.

Outcomes Assessed

Our primary analysis focused on assessing the risk of HCC among users of statins. A priori hypotheses to explain potential heterogeneity in the direction and magnitude of effect included study design (observational studies vs RCTs) and location of study (Asian population vs Western population).

Statistical Analysis

We used the random effects model described by DerSimonian and Laird to calculate pooled ORs and 95% CIs.[18] Because outcomes were relatively rare, ORs were considered approximations of relative risk. Adjusted ORs reported in studies were used for analysis to account for confounding variables. We assessed heterogeneity using 2 methods: Cochran's Q statistic, which was considered statistically significant for heterogeneity if $P < .10$, and the I^2 statistic, with values >50% suggestive of significant heterogeneity.[19] We assessed for publication bias quantitatively using the Begg and Mazumdar adjusted rank correlation test (publication bias considered present if $P \leq .10$)[20] and qualitatively by visual inspection of funnel plots of the logarithmic OR versus their standard errors.[21] All *P* values were 2-tailed. For all tests (except for heterogeneity and publication bias), a probability level <.05 was considered statistically significant. Analysis and reporting were performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[22] All calculations and graphs were performed using Comprehensive Meta-Analysis (CMA) version 2 (Biostat, Englewood, NJ).

Results

Search Results

Of the 2336 unique studies identified using our search criteria, 10 studies fulfilled our inclusion criteria and were included in the meta-analysis (7 observational studies and 3 studies reporting pooled data from 26 RCTs), with one of the studies published only in abstract form.[11–14,23–28] These studies cumulatively reported 4298 cases of HCC in 1,459,417 patients. Two studies included as RCTs represented individual patient data analysis of patients enrolled in prospective controlled trials of cholesterol in heart disease.[26,27] Two studies were excluded because they represented an already included population,[29,30] and 2 studies were excluded because of a lack of sufficient information.[31,32]

Characteristics of Included Studies

The characteristics of these studies are shown in Table 1. Risk factors for HCC varied widely in the populations studied, with Asian studies reporting hepatitis B virus (HBV) infection and Western studies reporting cirrhosis related to hepatitis C virus (HCV) and probable metabolic syndrome or DM as the leading etiology (Table 2). Chiu et al performed a case-control study on Taiwanese patients older than 50 years with a new diagnosis of HCC from 2005 to 2008 (only 24% with HBV),[11] and Tsan et al studied a cohort of patients older than 18 years with HBV with a new diagnosis of HCC from 1999 to 2008.[12] El-Serag et al performed a case-control population-based study on US veterans with DM from 2001 to 2002.[13] Khurana et al conducted a retrospective case-control study using data from the South Central VA Health Care Network, including all patients with HCC from 1997 to 2002, irrespective of diabetes status.[25] Marelli et al performed a propensity matched cohort analysis of the incidence of cancer in older adults who had or had not used statins, using the General Electric Centricity electronic medical records database of >11 million patients.[23] Friedman et al used the pharmacy information management system and cancer registry of the Kaiser Permanente Medical Care Program of northern California to estimate the risk of cancer in patients exposed to statins.[24] Friis et al used the pharmacoepidemiological prescription database of North Jutland County in Denmark and data from the Danish Central Population Register and Danish Cancer Registry to identify 171 cases of HCC in 334,754 patients.[14] Matsushita et al performed an analysis of individual patient data from 3 large-scale clinical trials in patients with hyperlipidemia in Japan.[26] Emberson et al performed an individual patient data analysis of 22 RCTs of statins versus controls conducted by the Cholesterol Treatment Trialists' (CTT) collaboration to assess cancer incidence with statin exposure.[27] In all of these studies, a temporal relation of development of HCC to statin use was established by excluding cases of HCC developing before exposure to statins. Sato et al observed 17 patients with cancer after long-term follow-up of 263 patients with coronary artery disease from Osaka, Japan, enrolled in the Prevention of Coronary Sclerosis study.[28] Eight of these patients had cancer before study entry, although the authors included them in the analysis because results after exclusion were similar.

Quality of Included Studies

The median Newcastle–Ottawa quality score for observational studies was 7 (range, 2–9); 5 of 7 studies were considered high quality. Table 1 depicts the methodological quality of all studies. Most studies adjusted for the following confounders: age (8/10), sex (7/10), viral hepatitis (5/10), cirrhosis (3/10), DM (6/10), alcoholic liver disease (3/10), and medications (6/10) (Tables 1 and 2). Four of 7 observational studies included only new cases of HCC diagnosed after a minimum of 1 year of initial statin prescription (or at least 2 prescriptions),[11–14] whereas for 2 studies all incident cases of HCC after initial statin prescription were included.[23,24] This information was not available for one observational study and was not explicitly stated in the clinical trials.[25–28]

Risk of HCC

On meta-analysis of all studies assessing the risk of HCC, use of statins was associated with a statistically significant 41% reduction in the incidence of HCC (Figure 2*A*). The results showed considerable heterogeneity (Cochran's Q test $P = .08$, $I^2 = 58\%$). There was no evidence

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

Study	Design	Location	Setting	Time period	Total no. of subjects	No. of HCC cases	Variables adjusted for[a]	Study quality[b]		
Observational studies								Selection	Comparability	Outcome/exposure
Chiu et al, 2011[11]	Case-control	Taiwan	Population based	2005–2008	2332	1166	1–7, 10	***	**	**
El-Serag et al, 2009[13]	Case-control	United States	Population based	2001–2002	6515	1303	1–6, 9	***	**	***
Tsan et al, 2012[12]	Cohort	Taiwan	Population based	1997–2008	33,413	1021	1, 2, 5, 7, 11	***	**	***
Friis et al, 2005[14]	Cohort	Denmark	Population based	1989–2002	334,754	171	1, 2, 9, 15	****	*	***
Marelli et al, 2011[23]	Cohort	United States	Population based	1991–2009	91,714	105	1, 2, 8, 12, 13, 14	****	**	***
Friedman et al, 2008[24]	Cohort	United States	Population based	1994–2003	361,859	42	15	****	—	**
Khurana et al, 2005 (abstract)[25]	Case-control	United States	Population based	1997–2002	480,306	409	1, 3	*	*	—
RCTs								Randomized	Double-blind	Withdrawals/dropouts
Matsushita et al, 2010[26]	RCT	Japan	Individual patient data analysis of trials	2010	13,724	12	NR	N/A	N/A	N/A
CTT, 2012[27]	RCT	Europe, Australia, North America	Individual patient data analysis of RCT	2012	134,537	68	NR	N/A	N/A	N/A
Sato et al, 2006[28]	RCT	Japan	Secondary analysis of RCT	1991–1995	263	1	1, 2, 13	1	1	—

N/A, not applicable.

[a]1, age; 2, sex; 3, HBV; 4, HCV; 5, cirrhosis; 6, alcoholic liver disease; 7, diabetes mellitus; 8, race; 9, other medications (aspirin/nonsteroidal anti-inflammatory medications, angiotensin-converting enzymes inhibitors); 10, other lipid-lowering agents; 11, socioeconomic status; 12, body mass index; 13, smoking; 14, comorbidities; 15, calendar year.

[b]Study quality assessment of observational studies was performed using the Newcastle–Ottawa scale; each asterisk represents if an individual criterion within the subsection was fulfilled. For RCTs, study quality was assessed using the Jadad scale.

Table 2. Comparison of Reported Baseline Risk Factors for HCC and Analysis of Potential Confounders in Included Studies

Study	Age (y)		Sex (% male)		Diabetes (% total)		Cirrhosis (% total)		HBV/HCV (% total)		Alcoholic liver disease or alcohol use (% total)		Angiotensin-converting enzyme inhibitor/nonsteroidal anti-inflammatory drug/aspirin (% total)		Nonstatin lipid-lowering drug (% total)	
	Case	Control	Case	Control	Case	Control	Case	Control	Case	Control	Case	Control	Case	Control	Case	Control
Chiu et al[11]	66.1	65.9	68.9	68.9	40.8[a]	34.1	39.4[a]	4.9	23.9[a]/25.1[a]	5.3/3.5	5.8[a]	2.5[a]	10.5/55.9[a]/6.9	11.3/61.7/6.9	2.2[a]	3.9
El-Serag et al[13]	72	72	99	99	100	100	28.2[a]	1.6	1.9[a]/14.7[a]	0.2/1.8	16.5[a]	1.2	64[a]/21.2/44.6[a]	67.4/20.6/47.9	4.1	3.9
Tsan et al[12]	34.7	46.3	57.1	58.3	61.9[a]	23.1	11.6	10.6	100/0	100/0	8.9	6.9	52.6[a]/NR/54.6[a]	13.8/NR/14.1	7.8	1.2
Friis et al[14]	60.7	46.6[a]	57	50	NR	NR			NR	NR	NR	NR	NR/NR/80[a]	NR/NR/48		NR
Marelli et al[23]	64.2	64.2	52.2	52.6	16.1	15.8		NR	0.06	0.07		NR	—/28.4/19.4	—/28.2/19.6		NR
Friedman et al[24b]		NR		NR		NR		NR		NR		NR				NR
Khurana et al (abstract)[25]		61.1		91.7		NR		NR		NR/2.9		NR				NR
Matsushita et al[26]	57.9	57.1	52.6	50.5	19.7	21.5		NR		NR		NR		NR		NR
CTT[27]		63		71		NR		NR		NR		NR		NR		NR
Sato et al[28]		NR		81.7		NR		NR		NR		NR		NR		NR

NOTE. For case-control study design, case refers to patients with HCC and control refers to patients without HCC; for cohort study design, case refers to statin users and control refers to statin nonusers.
NR, not reported.
[a]$P < .05$, cases vs controls.
[b]Separate analyses of male and female subjects.

of publication bias, both quantitatively ($P = .53$) and qualitatively, on visual inspection of the funnel plot. This risk reduction with statins persisted even after adjusting for potential confounders where reported in studies (Table 2), although the heterogeneity persisted (Cochran's Q test $P = .01$, $I^2 = 59\%$).

Subgroup Analysis

We performed preplanned stratified analyses of studies based on study design and location (Table 3). In 7 observational studies, use of statins was associated with a significant 40% risk reduction in incidence of HCC, although there was moderate heterogeneity within the group. In the 3 studies reporting pooled data from multiple RCTs, there was no evidence of a chemoprotective effect of statins, with no significant heterogeneity within the group. This analysis explained the significant heterogeneity seen in the overall analysis.

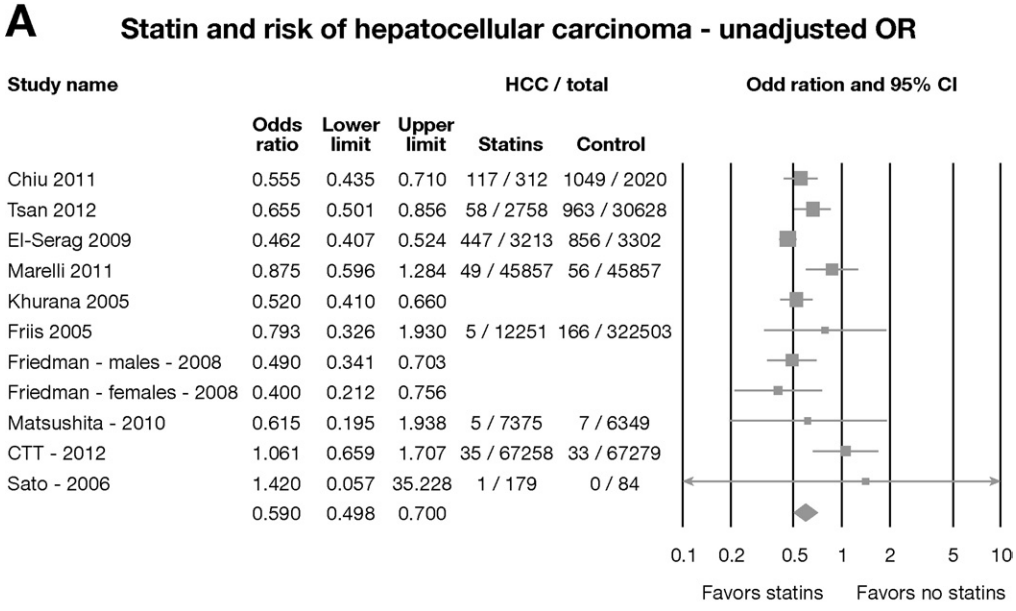
On stratified analysis based on location of study, in studies in the Asian population, use of statins was associated with a significant 48% risk reduction in incidence of HCC, with consistent results across studies. Likewise, there was a significant 33% risk reduction in incidence of HCC with statin use in the Western population, although there was considerable heterogeneity within the group. This subgroup analysis also partly explained the significant heterogeneity seen in the overall analysis.

Sufficient data were not available to perform stratified analyses based on age, sex, statin type (hydrophobic or hydrophilic), or dose/duration of statins.

Sensitivity Analysis

To further explore the sources of heterogeneity seen within observational studies, we performed additional sensitivity analysis based on study design (case-control vs cohort) and quality of included studies (high quality vs low quality) (Table 3). Both case-control and cohort study designs confirmed the protective association between statin exposure and HCC incidence with no significant difference between these groups. When analysis of observational studies was performed based on study quality, low-quality studies showed a significantly greater protective effect of statins on HCC than high-quality studies, explaining the heterogeneity seen on analysis of observational studies (Table 3). When restricting analysis to high-quality observational studies,[11–14,23] use of statins continued to have a protective association with the risk of HCC, although there was still some heterogeneity between studies. This heterogeneity was completely explained by study location (Table 3).

To assess whether any one study had a dominant effect on the meta-analytic OR, each study was excluded and its effect on the main summary estimate and Cochran's Q test P value for heterogeneity was evaluated. No study markedly affected the summary estimate or P value for heterogeneity among the other summary estimates.



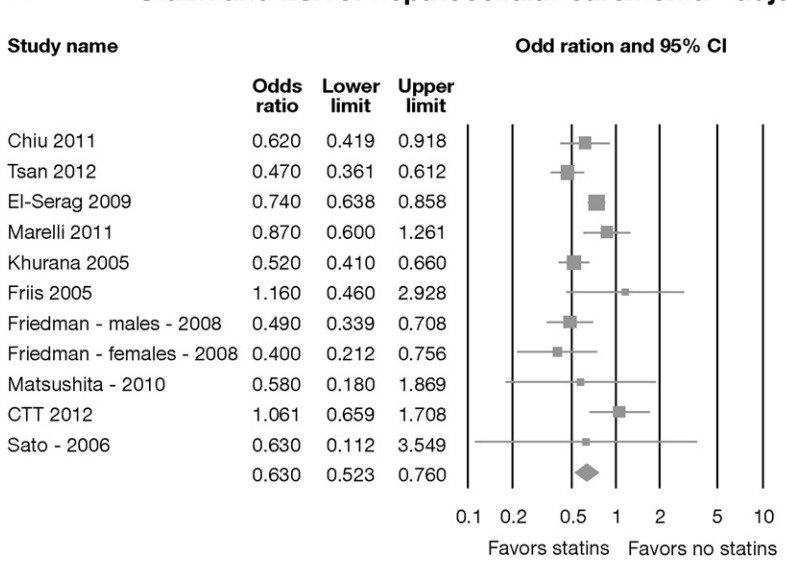


Figure 2. (*A*) Summary of unadjusted ORs assessing the risk of HCC with statin exposure. (*B*) Summary of adjusted ORs assessing the risk of HCC with statin exposure.

Number Needed to Treat

Because of significant heterogeneity between studies, a single summary estimate for number needed to treat with statins to prevent one case of HCC could not be inferred. However, on restricting analysis to the Asian population (where studies were homogeneous), using an age-adjusted incidence rate of HCC in men in East Asia of 40 per 100,000 person-years and a 48% reduction in HCC risk with statin use, 5209 East Asian men would need to be treated with statins to prevent one case of HCC per year.[33] When limiting analysis to a very high risk population of East Asian men with chronic HBV-associated cirrhosis with an estimated incidence rate of HCC of 3.7 per 100 person-years, the number needed to treat with statins to prevent one case of HCC per year would be 57.[34]

Discussion

As a result of our comprehensive meta-analysis of all existing studies in more than 1.4 million patients with 4298 cases of HCC, we found that use of statins is associated with a significant 37% reduction in the risk of HCC after adjusting for confounding variables. This effect was more pronounced and consistent in the Asian population and in observational studies as opposed to clinical trials. This effect of statins was independent of its lipid-lowering effects, because nonstatin lipid-lowering agents were not associated with reduction in the risk of HCC.[12,14] The likelihood of important selection or publication bias in our meta-analysis is small. During the identification and selection process, we did not exclude any article because of methodological characteristics.

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

Subgroup analysis	No. of studies	No. of HCC cases	Total no. of subjects	Adjusted OR	95% CI	Tests of heterogeneity		Heterogeneity between groups (*P*)
						P	I^2 (%)	
Study design								
Observational	7	4217	1,791,199	0.60	0.49–0.73	.01	65	.06[a]
RCT[b]	3	81	148,524	0.95	0.62–1.45	.86	0	
Study location								
Asian	4	2200	49,732	0.52	0.42–0.64	.70	0	.10[a]
Western	6	2098	1,889,991	0.67	0.53–0.85	.01	67	
Sensitivity analysis (to examine source of heterogeneity seen in observational studies)								
Study quality								
High quality	5	3766	949,034	0.68	0.61–0.77	.02	52	.06[a]
Low quality	2	451	842,165	0.50	0.41–0.60	.75	0	
Study design								
Case-control	3	2878	489,153	0.63	0.49–0.81	.04	68	.71
Cohort	4	1339	1,302,046	0.58	0.42–0.81	.03	64	
Sensitivity analysis (to examine source of heterogeneity seen in high-quality observational studies)								
Study location								
Asian	2	2469	35,745	0.51	0.41–0.64	.25	24	.01[a]
Western	3	1297	913,289	0.76	0.67–0.87	.49	0	

[a]$P \leq .10$, explains source of heterogeneity between groups.
[b]OR represents relative risk.

Antineoplastic Effects of Statins

In vitro and animal studies have shown that statins exert antineoplastic effects through both HMG-CoA reductase–dependent and HMG-CoA reductase–independent pathways. By competitive inhibition of HMG-CoA reductase, blocking the conversion of HMG-CoA into mevalonate, statins can inhibit several downstream products of the mevalonate pathway, including the generation of isoprenoids. This prevents posttranslational prenylation of small signaling G proteins of the Ras/Rho superfamily, which are important mediators of cell growth, differentiation, and survival.[9] They also exert proapoptotic effects through regulation of the RAF/mitogen-activated protein kinase 1/extracellular signal–regulated kinase (MEK-ERK) pathway through an HMG-CoA reductase–dependent mechanism by activating caspases and decreasing Bcl-2.[35,36] Statins inhibit the activation of the proteasome pathway, limiting the breakdown of cyclin-dependent kinase inhibitors p21 and p27, thus allowing these molecules to exert their growth-inhibitory effects.[37] In addition, they exert anti-inflammatory and immunomodulatory effects, modifying the cell adhesion cascade through both HMG-CoA reductase–dependent and HMG-CoA reductase–independent effects.[9]

Myc activation is a critical step in hepatocarcinogenesis, and its inactivation has been shown to induce sustained regression of HCC.[38,39] In a transgenic model of Myc-induced HCC as well as in human HCC-derived cell lines, atorvastatin has been shown to block Myc phosphorylation and activation, suppressing tumor initiation and growth through a HMG-CoA reductase–dependent pathway.[40] Shimizu et al showed that pitavastatin can inhibit the early phase of obesity-related liver tumorigenesis in male C57BL/KsJ-*db/db* obese mice.[41]

Differences in Asian and Western Populations

The chemopreventive association of statins with HCC was evident in both Asian and Western populations, although the effect was stronger and more homogeneous in the Asian population. Chronic HBV is the dominant risk factor in most areas of Asia and sub-Saharan Africa, whereas it accounts for only 23% of HCC cases in developed countries. In the United States and several other Western countries, alcohol-related cirrhosis, HCV, and NAFLD, associated with obesity and metabolic syndrome, are believed to account for the majority of cases of liver cancer.[5]

HBV genome integration has been associated with host DNA microdeletions that can target cancer-relevant genes such as mitogen-activated protein kinase 1 (MAPK), among others, potentially providing these cells with a growth advantage.[42] Also, HBV protein X transcriptional activation activity can alter the expression of several growth control genes, such as Ras, Raf, MAPK, ERK, and others.[43,44] Statins, by inhibiting the mevalonate pathway, can prevent potential detrimental effects of these growth signaling proteins.[9] Likewise, HCV stimulates the nuclear factor κB pathway, leading to immune activation, and inflammation, which is inhibited by statins.[9,45] HCV also promotes cell growth by down-regulation of growth arrest and DNA damage (Gadd45) gene family.[46] This effect can be countered by statins, which have antigrowth effects.[9]

Unlike the Asian population, where statins exert most of their effect by antagonizing the oncogenic effect of HBV, the mechanisms by which statins alter the risk of HCC in the Western population are unclear. The protective effect of statins in this population may be related to modification of metabolic syndrome, insulin-mediated cell proliferation, and obesity-associated inflammation. Additionally, because pa-

tients with HCV are at higher risk for developing type 2 DM,[47] statins may exert their antineoplastic beneficial effects through anti-infective properties.[10]

Dose, Duration, and Type of Statins

A meta-analysis of dose and duration effects of statins was not possible. However, a systematic review of the literature suggests that a higher cumulative dose of statins probably has a greater chemopreventive effect than low-dose statins. Tsan et al reported that a high dose-duration statin product was associated with greater protective effects on HCC in their cohort of patients with HBV.[12] The adjusted hazard ratios were 0.66 (95% CI, 0.44–0.99), 0.41 (95% CI, 0.27–0.61), and 0.34 (95% CI, 0.18–0.67) for patients with statin use of 28 to 90, 91 to 365, and more than 365 cumulative daily defined doses, respectively, compared with patients with no statin use (P for trend $<.001$). Likewise, statin use for more than 6 months was associated with a significant decrease in risk of HCC in the study by El-Serag et al, although no significant differences were found between the patients in the lowest dose-duration quartile as compared with the highest dose-duration quartile.[13] In the individual patient data analysis of 5 RCTs conducted by the CTT collaboration, "more" statin use was associated with a statistically significant chemopreventive effect as compared with "less" statin use (HCC incidence, "more" vs "less": 7/19,829 vs 18/19,783; $P = .05$).[27] On the other hand, Chiu et al did not find a significant dose-response relationship, with no significant difference in the group with a cumulative defined daily dose of statin <215.4, as compared with patients with a dose ≥ 215.4, although the numbers were small in the latter group.[11] Friedman et al also did not find a significant difference in the protective effect of statins on HCC with use for more than 5 years, although both of these studies were limited by a small number of cases with prolonged statin exposure.[24] A dose-response relation between statin use and development of cancer is plausible. Statins have been shown to have a dose-dependent effect on angiogenesis, with probably a proangiogenic effect at low doses and an antiangiogenic effect at high doses in in vivo studies.[48] On the other hand, studies with low-dose pravastatin (10–20 mg/kg every other day) were associated with decreased risk of development of neoplastic hepatic nodules in Sprague–Dawley rats,[49] whereas high-dose lovastatin (500 mg/kg per day) was associated with a higher incidence of HCC.[50] However, the findings of Tsan et al, in which even patients with only 28 to 90 cumulative defined daily doses of statins were noted to have a 34% reduction in risk of HCC, need to be interpreted with caution and likely represent confounding due to healthy user effect.[12]

It is hypothesized that lipophilic statins (eg, lovastatin, simvastatin) may have a greater chemoprotective effect than lipophobic statins (eg, pravastatin) due to greater lipid solubility and membrane permeability.[51] Tsan et al reported no significant differences in the risk reduction of HCC with hydrophilic or lipophilic statins.[12] Two meta-analyses that studied cancer risk with statin type found no difference in the risk of cancer with hydrophilic versus hydrophobic statins.[52,53]

Differences in Observational Studies and Clinical Trials

The chemopreventive effect of statins was seen primarily in observational studies, which accounted for a large majority of the included HCC cases (4217 cases; 98.1%). RCTs included in the study did not show any significant chemopreventive effect of statins, although these accounted for a small minority of the included HCC cases (81 cases; 1.9%). Importantly, the clinical trials included in the meta-analysis represented post hoc analysis of 26 RCTs performed on the effect of statins on cardiovascular mortality. By design, the patients enrolled in these RCTs were at low risk for development of HCC. Most of the RCTs were performed in the Western population (22/26). Also, given the small number of cases of HCC, the studies were not adequately powered to detect a significant difference in the placebo and statin groups with regard to development of HCC. Moreover, because the occurrence of HCC was not the primary objective of these trials, patients were not routinely screened for development of HCC; this might have affected the detection rate of HCC. The follow-up duration in these RCTs was short. These factors may explain why current clinical trials of statins for prevention of cardiovascular mortality do not show a chemopreventive effect of statins against HCC.

On the other hand, the chemopreventive effect of statins seen in observational studies may also represent an overestimate of its true effect. Observational studies lack the experimental random allocation of the intervention necessary to test exposure-outcome hypotheses optimally. Despite adjusting for numerous covariates, it is not possible to eliminate the potential of residual confounding, in particular, confounding by indication. Even though statins have been found to be safe in patients with chronic liver disease,[54] primary care physicians may be less likely to prescribe statins to patients with chronic liver diseases, a group that is inherently at higher risk for HCC.

Limitations

Besides the previously described limitations in our analysis, there were several other limitations that merit further discussion. All studies did not adjust for the same confounders. They generally failed to account for one or more of the following risk factors for HCC: cirrhosis, viral hepatitis, alcoholic liver disease, NAFLD, diabetes, or treatment for HBV and/or HCV. In most of the population-based observational studies, HCC was diagnosed based on medical diagnostic codes. It is unclear whether all patients at high risk for HCC were undergoing routine surveillance and what was the compliance of the population to surveillance guidelines. Therefore, there may be undiagnosed clinically silent HCC in high-risk patients and these may have been differently distributed between patients on statins and patients not on statins. In most

included studies, only incident cases of HCC diagnosed at least 1 year after initial statin prescription (or after at least 2 prescriptions) were included in the analysis to minimize the risk of confounding by prevalent but undetected HCC. Another potential limitation that particularly applies to case-control studies evaluating HCC is recall bias. However, in most studies, because pharmacy drug prescription information from population-based databases was used, the effects of this are likely minimal.

A major omission of all included studies was failure to adjust for antidiabetic therapy on risk modification in HCC.[55] Metformin was associated with an estimated 62% reduction in the risk of HCC among patients with type 2 DM in a recent meta-analysis (OR, 0.38; 95% CI, 0.24–0.59).[56] Likewise, use of thiazolidinediones has been associated with reduced risk of HCC.[57,58] On the other hand, use of sulfonylureas has been associated with increased risk of HCC in some studies of patients with type 2 DM.[57–59] Given that a significant proportion of patients with HCC had DM in these studies, it is likely that a significant proportion of patients would have been on metformin, thiazolidinediones, or sulfonylureas. In response to our query, Tsan et al reanalyzed their data after adjustment for antidiabetic medications and noted that statins continued to have a chemopreventive effect on HCC.[55] This effect was not analyzed in other studies.

Implications for Practice

With such a high number needed to treat with statins to prevent one case of HCC, it does not seem prudent to prescribe statins for chemoprevention. Adverse effects and cost for such a long-term therapy would be prohibitive. However, in patients with multiple risk factors (eg, East Asian men with chronic HBV infection), statins may have a clinically relevant chemoprotective effect against HCC.

Conclusion

In summary, our meta-analysis suggests that use of statins is associated with a reduced risk of HCC. This chemoprotective association is more pronounced in the Asian population, where viral hepatitis is the most important risk factor for HCC, but is also seen in the Western population, where HCC is predominantly associated with metabolic syndrome. However, these results should be interpreted with caution given the possibility of residual confounding. Future randomized clinical trials or prospective cohort studies in populations at high risk for HCC (especially in the Asian HBV-infected population) are warranted.

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Reprint requests

Address requests for reprints to: William Sanchez, MD, Mayo Clinic, 200 First Street Southwest, Rochester, Minnesota 55905. e-mail: sanchez.william@mayo.edu; fax: (507) 266-1856.

Conflicts of interest

The authors disclose no conflicts.