CLINICAL—LIVER

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

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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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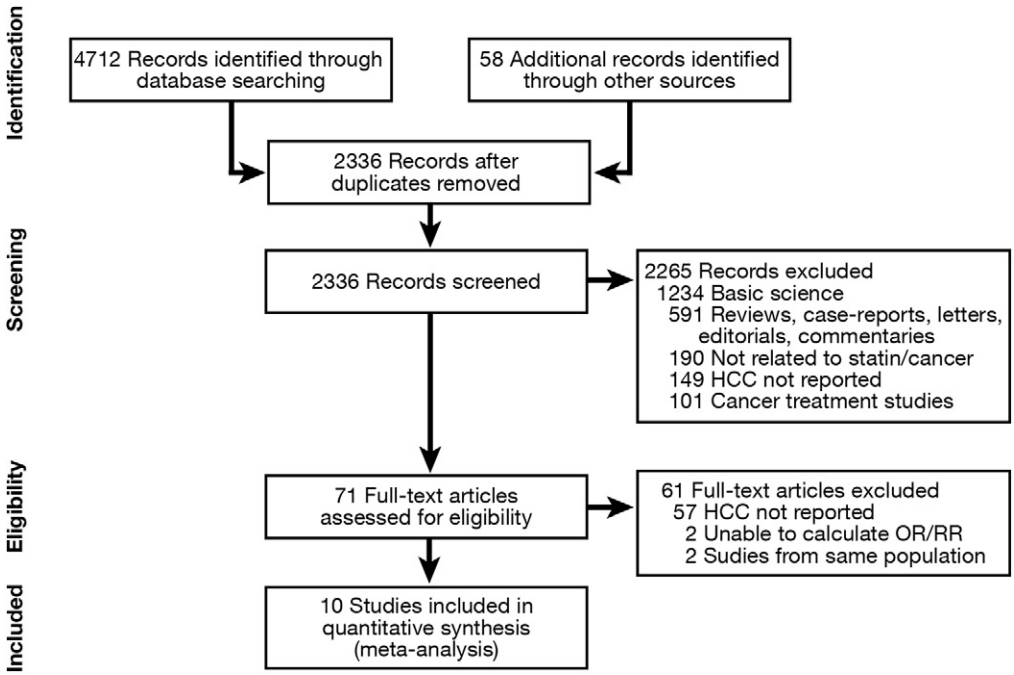

Figure 1. Flow diagram summarizing study identification and selection.

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