Purpose: Statins may have protective effects against cancer, but no studies have focused on their effects in patients with chronic hepatitis C virus (HCV) infection. The purpose of this study was to investigate the association between use of statins and risk of hepatocellular carcinoma (HCC) in HCV-infected patients.

Patients and Methods: Ours was a population-based cohort study of 260,864 HCV-infected patients enrolled in the Taiwan National Health Insurance Research Database since January 1, 1999, and observed through December 31, 2010. Cox proportional hazards regression with time-dependent covariates for drug exposures was employed to evaluate the association between statin use and HCC risk. Results: There were 27,883 cases of HCC in the HCV cohort during a follow-up period of 2,792,016.6 person-years. Among the 35,023 patients using statins (defined as ≥28 cumulative defined daily doses [cDDDs]), 1,378 had HCC. Among the 225,841 patients not using statins (<28 cDDDs), 26,505 were diagnosed with HCC. A dose-response relationship between statin use and HCC risk was observed. The adjusted hazard ratios were 0.66 (95% CI, 0.59 to 0.74), 0.47 (95% CI, 0.40 to 0.56), and 0.33 (95% CI, 0.25 to 0.42) for patients with 28 to 89, 90 to 180, and >180 cDDDs per year, respectively, relative to nonusers. The reduction in risk also demonstrated a progressive duration-response relationship in patients with ≥28 cDDDs per year when compared with nonusers. Conclusion: Among patients with HCV infection, statin use was associated with reduced risk of HCC. Further research is needed to elucidate the mechanism responsible for this effect.

Comment

Hepatocellular cancer (HCC) is the sixth most common cancer worldwide and the second leading cause of cancer death, with a rising incidence in the Western population. Chemopreventive strategies to prevent or delay the development of HCC are appealing.

Nearly one in four Americans age 45 years or older are prescribed statins for cardiovascular diseases, making them the second most common prescription medication in the United States. Preclinical as well as epidemiologic studies have shown that besides cholesterol reduction, statins may be protective against inflammation-driven cancers. Statins have antiproliferative, proapoptotic, antiangiogenic, immunomodulatory, and antiinfective effects. By competitive inhibition of 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase, statins inhibit products of the mevalonate pathway, preventing posttranslational modification of Ras/Rho proteins. Myc activation is a critical step in hepatocarcinogenesis, and its inactivation using atorvastatins has been shown to induce sustained regression of HCC. Besides their direct effect on hepatocarcinogenesis, statins have also been shown to have antiinfective effects against HCV. There is a growing body of evidence suggesting a protective association between statin use and risk of incident HCC.

In their population-based cohort study, Tsan et al. used the comprehensive Taiwanese National Health Insurance Database to study the association between statin use and risk of HCV-associated HCC. They followed 260,864 HCV-infected patients (13.4% statin users) over a mean 10.7 years, and observed 27,883 cases of HCC (~1% risk of HCC/year). The incidence rate of HCC was 340.5 and 1,110.2 cases per 100,000 person-years among statin users and statin nonusers, respectively. After adjusting for potential confounders, including age, sex, cirrhosis, diabetes, medications such as anti-HCV therapy, aspirin, and angiotensin converting enzyme inhibitors, they observed that statin users had a 47% lower risk of HCC as compared to statin nonusers (adjusted hazard ratio [HR], 0.53; 95% confidence interval [CI], 0.49-0.58). A dose-response relationship was also observed: compared to statin nonusers, patients dispensed 28-89, 90-180, and >180 cumulative defined daily dose (which encompasses both dosage and duration of exposure) of statins were 34%, 53%, and 67% less likely to develop HCC, respectively (P-trend < 0.001). The results were stable in several subgroup analyses, by patient age, sex, and presence or absence of cirrhosis and diabetes. These results are similar to the 53% risk reduction observed in statin users that the authors’ had previously reported in their cohort of 33,413 HBV-infected adults.

There are several inherent limitations to such a population-based observational study. Observational
studies lack the experimental random allocation of the intervention necessary to test exposure-outcome hypotheses optimally. The 34% lower risk of HCC observed with a short dose-duration of statin use suggests the presence of unmeasured factors, such as healthy-user bias, contributing to this association. It is not possible to exclude residual confounding, in particular, confounding by indication and by severity of liver disease. Primary care physicians may be less likely to prescribe statins to patients with cirrhosis, leading to overestimation of the protective effect of statins. However, a dose-dependent association between statins and HCC risk was observed both in patients with and without cirrhosis; this association persisted even after excluding statin use recorded within 2 years before HCC diagnosis. Hence, the likelihood of significant confounding by indication was minimal. Besides acknowledged limitations of not adjusting for smoking, alcohol and coffee consumption, and obesity, the authors failed to adjust for the concomitant use of antidiabetic medications (27.6% patients in their cohort had diabetes), which have inherent cancer-modifying effects. However, in their previous study on the association between statins and HBV-associated HCC risk, reanalysis of their data after adjusting for antidiabetic medications showed a persistent independent protective effect of statins.

In contrast to observational studies where six out of eight published studies have shown a protective association between statin use and risk of HCC (including all studies performed in patients at high risk for HCC such as cirrhosis, HBV, diabetics), randomized controlled trials (RCTs) have failed to show such an association. In a post-hoc analysis of 22 RCTs from the Cholesterol Treatment Trials’ collaboration, there was no difference in the risk of HCC among statin users and nonusers (adjusted odds ratio [OR], 1.06; 95% CI, 0.66-1.71). However, these statin RCTs for cardiovascular endpoints have several intrinsic limitations: (1) patients enrolled in these RCTs performed in the Western population were inherently at low risk for development of HCC, limiting the power of these studies to detect a significant difference between placebo and statin groups with regard to development of HCC; (2) the follow-up in these RCTs was short and at the end of the study, patients assigned to placebo were likely to have switched to statins, hence attenuating any potential effect that may have been observed with longer duration of follow-up; and (3) statin nonusers in these groups had a competing, elevated risk of cardiovascular mortality.

Hence, there is mounting evidence from epidemiological studies that statin use may be associated with a lower risk of HCC. In a meta-analysis of 10 studies, we observed a 37% lower risk of HCC in statin users as compared to nonusers, in both Asian and Western populations. So, should we proceed with an RCT to definitively study the effect of statins against HCC? From observational studies, it is difficult to know the appropriate dose, duration, frequency, as well as timing of initiation of statins for chemoprevention. Moreover, such an RCT would be logistically and ethically challenging given the relatively low incidence of HCC. Assuming a 4% annual rate of progression to HCC among patients with cirrhosis-stage HCV and a 50% decline in the risk of HCC with the use of statins, as compared to placebo, 2,396 patients would need to be followed for 1 year, with strict adherence to therapy. Factoring in patient dropout, disease progression requiring additional therapies such as liver transplantation and competing risk of mortality in patients with cirrhosis, the number of patients needed to perform such a chemoprevention trial would be much higher. Additionally, even if this was logistically possible, it would be ethically impermissible since one would have to withhold antiviral therapy to minimize confounding. Whether statins have a chemopreventive effect over and above that observed with anti-HCV therapy is unclear; in their study, Tsan et al. observed a decrease in HCC risk with statin use even in patients treated with antiviral therapy, although this was not statistically significant due to the small number of HCC cases developing in treated HCV patients. Not surprisingly, a search of the World Health Organization International Clinical Trials Registry Platform did not identify any registered clinical trials on chemoprevention against HCC. In comparison, well-designed population-based prospective cohort studies with complete long-term follow-up in a susceptible population may be more feasible, yet well suited, to answer the question. Any such study would require careful adjustment for known risk factors for HCC such as age, sex, presence and severity of chronic liver disease, diabetes, use of other medications with putative chemopreventive effect and also account for the propensity to prescribe these medications.

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References


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