Do Statins Reduce Patients’ Risk of Hepatocellular Carcinoma?


Statins, a class of drugs used to lower cholesterol, are known to help prevent against cardiovascular disease and stroke. Interestingly, statins have also been explored as anticancer agents, with several lines of preclinical evidence pointing to potential anticancer activity. For example, statins have antiproliferative, proapoptotic, prodifferentiation, anti-invasive, and radiosensitizing properties. One of the potential mechanisms explaining the antitumor effect of statins involves suppression of the mevalonate pathway, resulting in depletion of isoprenoids; these downstream products have a role in cell cycle progression, cell signaling, and membrane integrity.

Multiple studies have shown that statins demonstrate growth-inhibition activity in both cancer cell lines and preclinical tumor models, including models of pancreatic cancer, renal cancer, and squamous cell carcinoma. While observational studies have suggested a relationship between statin use and decreased risk of cancer, epidemiologic studies and meta-analyses have failed to support this association. For example, in a meta-analysis of over 86,000 individuals, Dale and colleagues found no reduction in either the risk of cancer incidence or cancer-related deaths. Browning and colleagues found similar results in a separate meta-analysis.

However, a population-based case-control study from Taiwan recently suggested a link between statin use and a reduction in the risk of hepatocellular carcinoma (HCC). Because individuals infected with hepatitis B virus (HBV) have a heightened risk of HCC, Tsan and colleagues explored the potential link between statin use and HCC risk in this population.

Study Description

In this study, statin use was defined by the presence of a filled prescription for statins in the patient’s ambulatory care or inpatient file between January 1, 1997 and up to 365 days prior to the index date for HCC. The statins of major interest in this analysis were simvastatin, lovastatin, atorvastatin, fluvastatin, pravastatin, and rosuvastatin. In order to compare statin use among patients taking different drugs, the investigators used the defined daily dose (DDD), a unit recommended by the World Health Organization, which is the assumed average maintenance dose per day of a drug consumed for its main indication. In this study, the number of DDDs was calculated as the total amount of the drug divided by the amount of drug in a DDD. This number was then used to estimate the sum of dispensed statins, which resulted in the cumulative DDD (cDDD); this latter value is an indicator of the exposed duration. Statin nonusers were defined as those with fewer than 28 cDDDs.

In this population-based cohort study, a total of 33,413 patients (58.2% male) were identified from the Taiwan National Health Insurance Research Database between January 1, 1997 and December 31, 2008. The median patient age was 35.6 years (interquartile range [IQR], 27.2–45.1), with most patients being younger than 50 years of age (18–29 years: 32.8%, 30–39 years: 29.6%, 40–49 years: 21.6%, 50–59 years: 9.5%, and 60 years and older: 6.4%). When statin users and statin nonusers were compared (≥28 cDDDs vs <28 cDDDs, respectively), the median patient age was lower among those who used statins (34.7 years vs 46.3 years, respectively). However, the proportional distribution of patients indicated that more individuals age 18–29 years were classified as statin nonusers (35.1% vs 7.4%), and more individuals in the 50–59-year and 60-years-and-older age groups were classified as statin users (37.7% vs 13.9% for both age groups combined).

A total of 8.3% of the study cohort were statin users. Of the 2,785 patients who used statins, the median cDDD was 138.7 (IQR, 63.5–315.0). A total of 33.5% of statin users had a cDDD of 28–90, 45.9% had a cDDD of 91–365, and 20.6% had a cDDD greater than 365. Nearly half of individuals who used statins had a history of atorvastatin use (46.2%); the remaining statins used were simvastatin (28.4%), lovastatin (27.5%), pravastatin (28.2%), rosuvastatin (15.6%), and fluvastatin (18.6%). Other significant drug use in the overall patient cohort included nonstatin lipid-lowering drugs (median, 84.0 cDDD; IQR, 42.0–188.0), fibrate (median, 106.8 cDDD; IQR, 56.0–268.8), and angiotensin-converting enzyme (ACE) inhibitors (median, 220.5 cDDD; IQR, 75.0–699.0).
All patients had a first-time diagnosis of HBV infection, and none of the enrolled patients were co-infected with hepatitis C virus. The majority of patients (97.6%) had not received anti-HBV treatment. The proportion of patients who were HBV treatment-naïve was similar for the group of patients who used statins and the group with no statin use. Significant comorbidities were present in the overall study cohort, including hypertension (28.9%), hyperlipidemia (38.1%), liver cirrhosis (10.7%), diabetes (26.4%), biliary stones (12.4%), alcohol-related disease (7.0%), and chronic renal injury (3.7%). Each of these comorbidities was present in a higher proportion of patients among those who used statins compared to patients with no statin use, including hypertension (70.8% vs 25.1%), hyperlipidemia (95.5% vs 32.9%), and diabetes (61.9% vs 23.1%).

Over a follow-up period of 328,946 person-years, the overall HCC incidence rate was 310.4 per 100,000 person-years. The incidence of HCC was significantly higher among men (adjusted hazard ratio, 2.66; 95% confidence interval [CI], 2.24–3.15; P<.001). Among the 2,785 patients who had used statins, the HCC incidence (per 100,000 person-years) was 260.5 for patients with 28–90 cDDDs, 198.1 for patients with 91–365 cDDDs, and 158.7 for patients with more than 365 cDDDs. In comparison, the HCC incidence among patients who had not used statins was significantly higher: 319.5 per 100,000 person-years (P<.001).

Accordingly, a dose-response relationship emerged between the risk of HCC and statin use, with the risk of HCC being lowest among patients with the highest cumulative statin use: The adjusted hazard ratio was 0.66 for patients with statin use of 28–90 cDDDs (95% CI, 0.44–0.99), 0.41 for patients with statin use of 91–365 cDDDs (95% CI, 0.27–0.61), and 0.34 for patients with statin use above 365 cDDDs (95% CI, 0.18–0.67). This trend achieved statistical significance (P<.001).

Both lipophilic statins (including simvastatin, lovastatin, atorvastatin, and fluvastatin) and hydrophilic statins (including pravastatin and rosuvastatin) were associated with a significant decrease in the risk of HCC (lipophilic statins: adjusted hazard ratio, 0.44; 95% CI, 0.33–0.59; P<.001; hydrophilic statins: adjusted hazard ratio, 0.51; 95% CI, 0.31–0.85). The adjusted hazard ratios for HCC risk for each statin were: 0.53 for simvastatin (95% CI, 0.32–0.85), 0.60 for lovastatin (95% CI, 0.39–0.92), 0.37 for atorvastatin (95% CI, 0.24–0.58), 0.32 for fluvastatin (95% CI, 0.14–0.71), 0.80 for pravastatin (95% CI, 0.46–1.38), and 0.14 for rosuvastatin (95% CI, 0.03–0.55). The difference in HCC risk did not differ significantly when each statin was considered individually.

The association between increased statin use and lowered HCC risk was also observed in a sensitivity analysis that aimed to examine potential effect modifiers. The effect of statins remained significant among male patients and patients 50 years of age and older. The adjusted hazard ratios among males were 0.68 (95% CI, 0.44–1.07), 0.49 (95% CI, 0.32–0.74), and 0.33 (95% CI, 0.16–0.69) for statin use of 28–90 cDDDs, 91–365 cDDDs, and more than 365 cDDDs, respectively. The adjusted hazard ratios among females were 0.55 (95% CI, 0.20–1.50), 0.14 (95% CI, 0.03–0.56), and 0.48 (95% CI, 0.12–1.96) for each statin use group, respectively. For patients 18–49 years of age, the adjusted hazard ratios were 0.52 (95% CI, 0.26–1.05), 0.69 (95% CI, 0.39–1.19), and 0.16 (95% CI, 0.02–1.17) for statin use of 28–90 cDDDs, 91–365 cDDDs, and more than 365 cDDDs, respectively. For patients 50 years of age and older, the adjusted hazard ratios were 0.76 (95% CI, 0.46–1.25), 0.31 (95% CI, 0.17–0.55), and 0.42 (95% CI, 0.21–0.85) for each statin use group, respectively. In the sensitivity analysis, a trend was also apparent in subgroups of patients according to anti-HBV treatment, ACE inhibitor use, and aspirin use; however, the hazard ratios among these subgroups did not decrease with increasing statin use.

**Clinical Relevance**

The study by Tsan and colleagues was the first to show a dose-dependent relationship between statin use and decreased risk of HCC among HBV-infected individuals. A sensitivity analysis demonstrated that this effect remained significant even in the presence of potential confounders. Because no such relationship was apparent between HCC risk and the use of nonstatin cholesterol-lowering drugs, the authors concluded that the decreased HCC risk was specifically due to the use of statins.

The exact mechanism for this relationship remains unclear. The investigators put forth several potential explanations, including (1) inhibition of downstream tumor-promoting products in the mevalonate pathway; (2) inhibition of proteasome pathway activation; (3) disruption of HBV RNA replication via mevalonic acid suppression; and (4) anti-HBV activity through inhibition of cholesterol synthesis and HBV replication.

The authors noted that many clinicians are hesitant to prescribe statins in patients with liver disease due to the risk of hepatotoxicity associated with these drugs. In trying to address this potential confounding bias, several steps were taken during the data analysis. Importantly, no significant difference was observed in the proportion of patients who used statins between patients with and without liver cirrhosis (P=.76).

**References**

G & H LITERATURE REVIEW


Commentary

Improved Understanding of Risk Factors Could Help to Reduce the Incidence of Hepatocellular Carcinoma

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Using data from the Taiwan National Health Insurance Research Database, Tsan and colleagues identified over 33,000 patients who had been infected with hepatitis B virus (HBV). These patients had been followed for 11 years (1997–2008), and the subset of patients who developed hepatocellular carcinoma (HCC) during this period was identified. Tsan and colleagues then extracted data on statin usage and assessed the relationship between statin usage and liver cancer in this HBV-infected population. A total of 1,021 patients in the study cohort developed cancer, and the incidence of liver cancer during the follow-up period was lower among those who had used statins. This study noted that this association between statin use and HCC risk was dose-dependent, with longer durations of statin use being associated with lower incidences of cancer. While these findings are intriguing, future mechanistic research is needed to explain this association.

If statins can reduce the risk of cancer in high-risk patients such as those infected with HBV, then these drugs may also reduce the risk of HCC in a broader patient population. While suggesting that statins may have benefit in some patients, this conclusion does not mean that clinicians should treat all patients with statins, as a small percentage of patients will develop liver toxicity or muscle toxicity due to these drugs. Indeed, clinicians who are caring for patients with chronic liver disease may be reluctant to use statins in some instances due to concerns about an increased risk of statin-induced liver damage in these patients. In fact, some of the patients included in the study by Tsan and coauthors may have not received statins because their physicians were influenced by such concerns. This caveat should be kept in mind when considering the limitations of this particular study.

Another caution regarding this study is that it is a retrospective study based on a database review; such study designs always include the possibility of retrospective bias. A second limitation of this study is that the database used to gather information on statin usage was only established in January 1997, so information about statin use prior to that time was not included in the analysis. Thus, this study was not able to distinguish between first-time prescriptions for statins and continuation of therapy started prior to 1997. Also, the study by Tsan and coworkers does not include information about when statins were used during the 10-year follow-up period.

Finally, this study showed a dose-response depending on the duration of statin use, with varying reductions in HCC risk among patients who used statins for less than 28 days, 28–90 days, 91–365 days, or greater than 1 year. For example, this study showed a 34% reduction in cancer among patients who had used statins for 28–90 days and a 66% reduction among patients who used statins for over 365 days. However, I find it implausible that cancer rates would be reduced with only 3 months of statin use.

While clinicians should keep these considerations in mind when reviewing this study’s results, the analysis by Tsan and colleagues has several strengths. First, it used a very large database, which improves the statistical power of the results. Also, it used computer-based information to determine which patients were infected with HBV, who subsequently developed liver cancer, and who were using statins during the course of the observation period.
Related Research

In addition to the study by Tsan and coworkers, several related studies have reached similar conclusions.1 In a study by El-Serag and colleagues, data from the Veterans Affairs (VA) health system were analyzed to show that statins were associated with a reduced risk of HCC among patients with diabetes.2 This study used the VA electronic medical record database to identify patients who had diabetes and then excluded those with HBV or hepatitis C virus (HCV) infection; this group of diabetic patients was then followed to identify the subset of patients who developed liver cancer. These researchers also examined the VA prescription database to gather information on statin use among the study cohort. Thus, El-Serag and coauthors were able to compare diabetic patients with and without liver cancer.2 Similar to the study by Tsan and coauthors, this study concluded that use of statins was associated with a significant reduction in the risk of cancer.1 The fact that the study by El-Serag and coworkers found the same association as that seen in the study by Tsan and colleagues is very interesting, given that the study by El-Serag and associates looked at diabetic patients without HBV or HCV infection.1,2 Seeing the same association in 2 different populations indicates that this effect is independent of the etiology of the liver cancer.

In addition to the study by El-Serag and coauthors, another study that is very similar to the study by Tsan and colleagues deserves mention.3,4 A 2011 paper by Chiu and colleagues also used the Taiwan National Health Insurance Research Database to analyze the impact of statins on HCC risk among patients with HBV infection.3 The study by Chiu and coworkers was a case-control study that compared a group of patients with liver cancer to a control group comprised of patients matched for age, sex, and index date.3 Using this method, Chiu and coauthors found that, compared to the control group, the adjusted odds ratios for cancer were 0.62 (95% confidence interval, 0.42–0.91) in the lower-dose statin group (<215.4 defined daily dose) and 0.63 (95% confidence interval, 0.37–1.06) in the higher-dose statin group (≥215.4 defined daily dose).3 Thus, the study by Tsan and colleagues was not the original paper on this topic; rather, it built on the earlier study by Chiu and coauthors and strengthened the conclusions from this previous study.1,3

Going forward, researchers will likely try to replicate the study by Tsan and colleagues among HCC-infected patients, as this group is also at high risk for HCC.1 Additionally, further research should include a prospective study in a population of patients at high risk for liver cancer, such as HBV-infected patients, HCC-infected patients, or patients with diabetes. In such a study, the treatment group would be assigned to statin therapy while the control group would be assigned to placebo, and both groups would be followed to see which patients develop liver cancer. Comparison of the 2 treatment groups could then prospectively validate the association between statin use and HCC risk that was retrospectively observed in the study by Tsan and coauthors.1 Unfortunately, such a study would require 10–20 years of follow-up before any conclusions could be drawn, and long-term studies of this nature are expensive and difficult to perform.

Laboratory studies could also help to clarify the association revealed by Tsan and colleagues.1 For example, a rat hepatoma model could potentially help to determine whether administration of statins reduces the incidence of cancer in these animals. Another model that could be used is a murine model of HBV infection, as these animals also show high rates of liver cancer. By assessing the effect of statins in animal models of liver cancer, such studies could help to elucidate some of the mechanisms underlying the observed association.

Conclusion

The take-home message of the study by Tsan and colleagues is that certain medications may decrease a person’s risk of liver cancer.1 Tsan and colleagues showed such an association with statins, and other investigators should use similar, large, population-based studies to look for similar associations with other medications—either prescription or nonprescription medicines.1 The findings of the study by Tsan and colleagues probably will not change clinical practice in the near future, as prospective data showing that statins reduce patients’ risk of HCC will not be available for at least 10 years.1 Further studies will also need to tease out whether high cholesterol levels directly affect a patient’s risk of developing HCC, as this finding could potentially confound the observed association between statin use and HCC risk.

Thus, I do not believe the study by Tsan and colleagues will have an immediate impact on clinical practice, as we do not yet have enough data to support the use of statins to reduce HCC risk in all patients with HBV infection and/or diabetes.1 Overall, these observations are very important in the ongoing search for factors that may help clinicians to reduce the incidence of liver cancer in high-risk patients, but more studies are needed to determine its true effect.

References