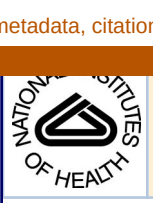

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Statin use and risk of hepatocellular carcinoma in a U.S. population

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Abstract

Purpose—Statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) are medications widely prescribed to reduce cholesterol levels. Observational studies in high-risk populations, mostly in Asia, have suggested that statins are associated with a reduced risk of hepatocellular carcinoma (HCC). The current study sought to evaluate the association of statin use and HCC in a U.S.-based, low-risk, general population.

Methods—A nested case-control study was conducted among members of the Health Alliance Plan HMO of the Henry Ford Health System enrolled between 1999 and 2010. Electronic pharmacy records of statin use were compared among tumor registry-confirmed cases of HCC (n=94) and controls (n=468) matched on age, sex, diagnosis date, and length of HMO enrollment.

Results—In multivariate analyses, ever-use of statins was significantly inversely associated with development of HCC (Odds Ratio (OR):0.32, 95%CI: 0.15–0.67). No clear dose-response relationship was evident as statin use for ≤2 years (OR=0.32, 95%CI=0.13–0.83) and >2 years (OR=0.31, 95CI%=0.12–9.81) resulted in very similar ORs.

Conclusions—The use of statins among populations in low-risk HCC areas may be associated with decreased risk of HCC.

Keywords

statins; liver cancer; epidemiology

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Introduction

Primary liver cancer, of which hepatocellular carcinoma (HCC) is the dominant histologic type, is the sixth most commonly occurring cancer in the world and due to a very poor prognosis, the second most frequent cause of cancer mortality (1). In the majority of high risk HCC areas, the most common risk factors are hepatitis B virus (HBV) infection and aflatoxin contamination of foodstuffs (2). In contrast, in low risk areas, the most common risk factors are excessive alcohol consumption, hepatitis C virus (HCV) infection and diabetes (2). Incidence rates of HCC have begun to decline in some high risk regions, but have been increasing in many low rate regions (2). The declining rates in high risk areas may be related to public health efforts and HBV vaccination, while the rising rates in low risk areas are likely due to the increased prevalence of diabetes, obesity and chronic infection with HCV (3, 4). Unfortunately, HBV vaccination is of no benefit to persons who are already chronically infected with the virus and there is no HCV vaccine. As a result, it is important to examine other means of trying to decrease risk of HCC.

Statins (3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-Co-A) inhibitors) are commonly used cholesterol lowering medications which have demonstrated effectiveness in the primary and secondary prevention of cardiovascular disease (5). Statins also have antiangiogenic and anti-proliferative properties which have suggested a possible role for their use as anti-carcinogenic agents (6–8). A potential for HCC prevention is further indicated as statins, post-administration, are localized to the liver (9). Promising evidence that statins may decrease risk of HCC has been reported in observational studies from Taiwan, a high-risk HCC area (10–14). Two U.S. studies also reported an inverse association between statins and HCC (15, 16), although the population of one of the studies was confined to men with diabetes (15). In contrast, null associations between statins and HCC have been reported by two cohort studies in low-risk areas (17, 18) and by secondary analyses of randomized clinical trials of cardiovascular disease prevention (19–21). Recent meta-analyses (22, 23) have concluded that statins are associated with reduced risk of HCC, although one meta-analysis felt that the effect might be confined to Asian populations (23). Given the ambiguous results to date from low-risk populations, the current study sought to evaluate the risk of HCC among members of a health maintenance organization (HMO) in a low-incidence region (United States).

Materials and Methods

A nested case-control study was conducted among the population of the Health Alliance Plan HMO of the Henry Ford Health System (HFHS), a single integrated health system. The study encompassed the years between 1999 and 2010. Complete, population-based case ascertainment was conducted using an internal cancer registry, which is part of the National Cancer Institute's Detroit Surveillance, Epidemiology and End Results (SEER) registry. In the registry, all potential cancer cases are investigated and, if determined to be a new primary case, are examined in detail. Cancer registry data include basic demographic information (e.g., birthdates, age, sex, race/ethnicity), histopathologic characteristics, stage, and vital status. Use of computerized pharmacy records allowed examination of several measures of statin use, including overall exposure (ever vs. never) and cumulative exposure

(sum of days' supply for all statin prescriptions). All members of the HMO purchase prescription medications at minimal cost. All study variables were obtained from the automated data systems within the HFHS. There was no direct contact with HMO members. The protocol was approved by the HFHS Institutional Review Board and the Human Research Protections Program of the NIH.

Persons selected as cases were identified using ICD-O-3 topography code C22 and morphology codes 8170–8175 (24). Persons selected as cases or controls had to be enrolled in the HMO for at least two years prior to diagnosis date or index date (for controls). Once cases were identified through the tumor registry, controls were selected from the same population that gave rise to the cases. Using incidence density matching, controls were matched to cases at a ratio of 5:1 on age (two year strata), length of HMO enrollment (two year strata), diagnosis date, and sex. Controls could have no prior history of HCC up to the diagnosis date of the matched case.

Statistical analysis was initiated by conducting univariate analyses of association using chi-square tests or exact tests for variables with small numbers in any cell. Odds ratios (OR) and their 95% confidence intervals (95%CI) were calculated as estimates of the relative risk for HCC associated with statin use, using conditional logistic regression. Exposure to statins was defined in several different ways. First, assessment of ever having a statin prescription filled was analyzed. A second analysis assessed the cumulative exposure to statins. Cumulative exposure was defined as the sum of days' supply for all prescriptions filled prior to diagnosis or index date. A categorical analysis was conducted which dichotomized cumulative exposure based on the median exposure among the cases who were exposed. Finally, an analysis of medication possession ratio was conducted where medication possession ratio was defined as cumulative years' supply of statins divided by the length of HMO enrollment prior to diagnosis/index date. The categorical analysis dichotomized the medication possession ratio on the median among the cases who were exposed. Both univariate and multivariate analyses were conducted for each exposure definition. Multivariate analyses adjusted for pre-existing medical conditions and known risk factors for HCC that were significantly related to case/control status in the univariate analysis. Conditions examined included type 2 diabetes, hepatitis B virus (HBV) infection, hepatitis C virus (HCV) infection, hypertension, alcohol-related conditions (alcoholic fatty liver, acute alcoholic hepatitis, alcoholic cirrhosis of liver, cirrhosis of the liver without mention of alcohol in combination with alcohol-induced mental disorders or alcohol dependence syndrome or nondependent abuse of drugs) and chronic obstructive pulmonary disease (COPD). COPD was included as a proxy variable for heavy cigarette smoking. The medical conditions were identified in the electronic medical records by use of ICD-9 codes (Supplemental Table). In addition to the main analyses, a sensitivity analysis examined the statins-liver cancer relationship after eliminating any exposed user who had taken statins less than 6 months.

Results

Overall, 94 cases of HCC were identified and matched to 468 controls. Table 1 displays the distribution of characteristics in the study participants by case-control status. Cases were

more likely than controls to have alcohol-related conditions, diabetes, chronic obstructive pulmonary disease and hypertension and to be positive for HCV. Cases were also more likely than controls to be of known racial designation. There were no differences between cases and controls in HBV positivity. There were also no differences, as expected, in the distributions of the matching factors: sex, age at index date, diagnosis date and length of HMO enrollment. While at least 2 years of HMO enrollment prior to diagnosis or index date was required, the average length of enrollment was 8.1 years (SD ± 3.8) with a range of 2 years to 15 years.

Table 2 displays the results of the univariate and multivariate conditional logistic regression analyses. In both the univariate (OR=0.34, 95%CI=0.21–0.57) and multivariate (OR: 0.32, 95%CI: 0.15–0.67) analyses, ever use of statins was significantly inversely related to HCC. An analysis of the cumulative supply of statins found that, compared with non-use, there was a significantly decreased risk of HCC with use of <2 years (OR=0.32, 95%CI=0.13–0.83) and use of >2 years (OR=0.31, 95%CI=0.12–0.81). Similarly, compared to non-use, there was a significantly decreased statins possession ratio (supply of statins/length of HMO enrollment) with both lower use (OR: 0.26, 95%CI: 0.10–0.70) and greater use (OR=0.38, 95%CI=0.15–0.93).

The sensitivity analysis which dropped exposed person who had taken statins less than 6 months resulted in a finding very similar to the main result (OR=0.26, 95%CI=0.11–0.66).

Discussion and Conclusions

In the current study, statin use was significantly inversely associated with HCC. These findings suggest that statin use may protect against the development of HCC in populations living in low-risk HCC areas.

Much of the prior evidence on statins and HCC has been drawn from studies that utilized the Taiwan National Health Insurance Research Database (10–14). In a case-control analysis of 1,166 liver cancer cases and 1,166 controls in the database, Chiu *et al* (10) reported a significant inverse association between statin use and HCC (OR=0.53, 95%CI=0.45–0.83), which was replicated by Leung et al. (OR=0.44, 95%CI=0.28–0.72) (12). Using the same database, Tsan *et al* reported significant inverse associations of statins and HCC among persons infected with HBV (OR=0.47, 95%CI=0.36–0.61) (14) and persons infected with HCV (OR=0.53, 95%CI=0.49–0.58) (13). Lai et al. (11), also using the database, reported that the inverse association between statin use and HCC was statistically significant for use of simvastatin (OR=0.69, 95%CI=0.50–0.94), lovastatin (OR=0.52, 95%CI=0.36–0.76) and atorvastatin (OR=0.70, 95%=0.53–0.93), but not for use of fluvastatin, pravastatin or rosuvastatin, although the odds ratios for the latter three statins were less than one.

The effect of statins on liver cancer or HCC risk has also been examined in several studies conducted in low-risk liver cancer countries. In a prospective study from Denmark, Friis *et al* found no support (OR=1.16, 95%CI=0.46–2.90) for an association between statin use and liver cancer (17). Conversely, support was found in two U.S. studies of HCC conducted among the U.S. Department of Veterans Affairs' patient population. Both El-Serag et al.

(15), studying men with diabetes (OR=0.74, 95%CI=0.64–0.87), and Khurana et al. (25), studying men with HCV infection (OR=0.52, 95%CI=0.41–0.67) reported significantly reduced risks. In an analysis of the General Electric Centricity electronic medical records database of the U.S., Marelli and colleagues (18) reported that there was no significant association between statin use and liver cancer although they did find that liver cancer occurred among 0.37% of non-statin users, but only among 0.10% of statin users. Why the results of Friis et al. (17) and Marelli et al. (18) differ from those of El-Serag et al. (15) and Khurana et al. (25) is not certain, although the specificity of the study outcomes differ in that the Veterans Affairs' studies examined HCC, while the other two studies included all primary liver cancers. Two meta-analyses that have specifically examined statins and liver cancer/HCC both concluded that statin use was associated with a reduced risk (22, 23).

In addition to observational studies, secondary analyses of cardiovascular disease randomized controlled trials have attempted to examine the risk of cancer in relation to statins. The great majority of secondary analyses, however, have not included information on liver cancer. Of the trials that have reported on liver cancer, none have found a statistically significant association. Sato et al. (21) reported an observed/expected ratio of 0.63 (95%CI=0.01–3.49) in a pravastatin trial that included 179 participants in the statins arm, one of whom developed liver cancer. Matsushita et al. (20), in a meta-analysis of three Japanese studies of pravastatin, reported a hazard ratio of 0.58 (0.18–1.84) based on 7 liver cancers in the control group and 5 liver cancers in the pravastatin group. Similarly, in a large meta-analysis of cancer outcomes in 27 trials (19), no relationship between statin use and liver cancer was identified (p=0.39), with 42 liver cancers reported in the statins arm and 51 in the control arm. None of the RCTs have reported on HCC as an outcome. Overall, the information from the secondary analysis of cardiovascular disease trials is limited by the fact that liver cancer is a rare outcome, and HCC even rarer, and it is an outcome that takes years to develop.

One concern raised about the statins-liver cancer findings is that they could result from persons with liver disease not being as likely to receive statin therapy as persons without liver disease. Statins have been associated with elevated aminotransferase levels in fewer than 5% of persons (26), but questions about liver damage may have led to reluctance to prescribe them to persons with liver disease. As the majority of individuals who develop liver cancer have pre-existing liver disease, the failure to prescribe statins for these individuals could result in what appears to be a protective association. Several studies have attempted to address this concern by doing stratified analyses of their data. In a stratified analysis that only included persons without liver disease, El-Serag et al. (15) found that statins remained significantly inversely related to liver cancer. Similarly, Chiu et al. (10) stratified participants into those with and without cirrhosis and found a dose-dependent reduction in risk among both groups. No stratification on liver disease status was possible in the current study given the sample size. Further analysis in future studies, however, may help to clarify this issue. In addition, recent reports suggest that concerns about prescribing statins to persons with liver disease may have been overstated (27, 28).

The mechanism by which statins might prevent HCC is not certain, but may be related to the inhibition of HMG-CoA reductase in the mevalonate pathway which could decrease the

likelihood of tumor initiation and progression (29). Statins may also exert effects downstream of the mevalonate pathway by disrupting the growth of transformed cells and stimulating apoptosis (6). In persons infected with HCV, statins have also been demonstrated to inhibit viral replication via depletion of mevalonate which leads to low levels of geranylgeranyl phosphate which is needed for HCV replication (30). In persons infected with HBV, a possible mechanism of action is simply the lowering of cholesterol levels as cholesterol depletion impairs the ability of HBV to infect target cells (31).

Strengths of the current study are that it examined HCC risk in a general population setting and that statin exposure was documented via use of pharmacy prescription records. In addition, all study participants were able to obtain their medications at minimal cost. The study was able to adjust for major known HCC risk factors such as alcohol-related conditions, HCV, HBV and diabetes. Limitations of the study are its relatively small size and lack of information on lifestyle exposures such as alcohol consumption and cigarette smoking. Proxy medical conditions for these exposures, however, were examined. In addition, concomitant use of other possible chemopreventive medications, such as metformin (32) and non-steroidal anti-inflammatory drugs (33), was not included in the analysis.

In conclusion, the majority of the evidence, including that in the current study, suggests that statins may reduce the risk of HCC. Further studies of this question, however, are warranted to examine dose-response relationships and to be certain that the association is not due to failure to prescribe statins to persons with liver disease. In addition, the benefits of use of any pharmaceutical agent, particularly as a chemopreventive agent, should be carefully balanced against the possible risks of adverse effects. However, it is possible that if these results hold up in other studies, statins may offer an opportunity to intervene in the rising incidence of HCC now seen in many populations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- The inclusion of the larger dataset is explicitly detailed to the Reveiwers.
- The analyses were dichotomized on the medians of cumulative exposure among the statins-exposed individuals.
- The use of exact test and their p-values has been added to the Material and Methods section.
- The results of the sensitivity analysis which persons on statins for <6 months are reported.
- The results remain consistent with a significant inverse association between statin use and HCC.

Table 1

Characteristics of study participants, Health Alliance Plan (HFHS), 1999–2010

	Cases (n=94)		Controls (n=468)		OR[1]	p-value[1]
	n	%	n	%		
Sex						
Female	24	25.53%	120	25.64%		
Male	70	74.47%	348	74.36%		
Age at index date (yrs)						
<=59	21	22.34%	106	22.65%		
60–69	23	24.47%	115	24.57%		
70–79	38	40.43%	186	39.74%		
80–89	12	12.77%	61	13.03%		
Race						
White	51	54.26%	235	50.21%		
Black	35	37.23%	95	20.30%	1.64	*<.0001*
Other/Unknown	8	8.51%	138	29.49%	0.24	*<.0001*
Alcohol Related Conditions[2]						
No	70	74.47%	464	99.15%		
Yes	24	25.53%	4	0.85%	6.20	*<.0001*
Hepatitis B virus[2]						
Negative	93	98.94%	467	99.79%		
Positive	1	1.06%	1	0.21%	2.24	*0.61*
Hepatitis C virus						
Negative	48	51.06%	460	98.29%		
Positive	46	48.94%	8	1.71%	72.43	*<.0001*
Diabetes						
No	54	57.45%	347	74.15%		
Yes	40	42.55%	121	25.85%	2.27	*0.0009*
COPD[3]						
No	75	79.79%	435	92.95%		

	Cases (n=94)		Controls (n=468)		OR[1]	p-value[1]
	n	%	n	%		
Yes	19	20.21%	33	7.05%	3.24	*0.0002*
Hypertension						
No	28	29.79%	199	42.52%		
Yes	66	70.21%	269	57.48%	1.81	*0.02*

[1] OR and p-value were computed by univariate conditional logistic regression except where noted beside variable name.

[2] Exact statistics and associated p-values were calculated due to small cell sizes.

[3] COPD=chronic obstructive pulmonary disease

Table 2

Relationship of statin use and HCC, Health Alliance Plan (HFHS), 1999–2010

			Univariate		Multivariate[1]	
	Cases	**Controls**	**OR**	**95%CI**	**OR**	**95%CI**
Ever use of statins						
No	69	235	1.00		1.00	
Yes	25	233	0.34	(0.21 – 0.57)	0.32	(0.15 – 0.67)
Cumulative supply						
non use	69	235	1.00		1.00	
≤2 Years	13	105	0.41	(0.21–0.77)	0.32	(0.13–0.83)
>2 Years	12	128	0.29	(0.15–0.56)	0.31	(0.12–0.81)
Medication possession ratio[2]						
non use	69	235	1.00		1.00	
≤0.244	12	105	0.37	(0.19–0.72)	0.26	(0.10–0.70)
>0.244	13	128	0.32	(0.17–0.61)	0.38	(0.15–0.93)

[1] adjusted for race, HCV, alcohol-related conditions, diabetes, chronic obstructive pulmonary disease, hypertension.

[2] medication possession ratio=cumulative years' supply of statins divided by the length of HMO enrollment prior to diagnosis/index date.