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Statin use and risk of hepatocellular carcinoma

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Abstract The objective of this study was to explore the association between statins use and risk of developing hepatocellular carcinoma (HCC). We used the research database of the Taiwan National Health Insurance program to conduct a population-based case–control study. Cases were 3,480 patients with newly diagnosed HCC identified during 2000 and 2009. Controls were 13,920 subjects without HCC and frequency matched for age, sex and duration of observational period of cases (i.e., the duration between year of being enrolled in the insurance program and index year of cases). Six commercially available statins, including simvastatin, lovastatin, fluvastatin, atorvastatin, pravastatin, and rosuvastatin, were analyzed. The adjusted odds ratio [OR] of HCC was 0.72 [95 % (CI) 0.59–0.88] for the group with stains use, when compared to the group with non-use of statins. In sub-analysis, 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 % CI 0.53–0.93) were associated with significant reduction in odds of HCC. Statins use correlates with 28 % decreased risk of HCC. Individual statins, including simvastatin, lovastatin and atorvastatin, are associated with reduced risk of HCC.

Keywords Hepatocellular carcinoma · Statin

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Introduction

HMG-CoA reductase inhibitors, commonly named as statins, are widely used for lowering cholesterol. Their protective effects on cardiovascular disease have been well established. On the other hand, evidence about statins having beneficial or harmful effects on cancer risk remains controversial. Two systematic reviews have shown that statins are not associated with cancer risk in short-term use [1, 2]. However, another two observational studies have shown that statins are associated with 25 % risk reduction of cancer [3, 4].

Hepatocellular carcinoma (HCC) was the second leading cause of cancer deaths after lung cancer in Taiwan in 2010, with a mortality rate of 33.5 per 100,000 persons (7,744 deaths, 18.9 % of the total) [5]. Recently, two case–control studies have shown that statins may correlate with risk reduction of HCC [6, 7]. In the study by El-Serag et al. [6] in US, statins can reduce 26 % risk of HCC among patients with diabetes mellitus. Another study by Chiu et al. [7] in Taiwan revealed that statins can reduce 38 % risk of HCC, compared with non-use of statins. A recent cohort study by Tsan et al. [8], also from Taiwan, reported consistent results, but the analysis was focused on patients with chronic hepatitis B infection.

To date, limited data are available on the association between individual statins and HCC risk in Taiwan. If we can find which statin is associated with HCC risk, more evidence can be established about the role of statins on HCC risk. Therefore, we conducted this population-based case–control study using the database from the National Health Insurance program of Taiwan to investigate the association between commercially available statins and HCC risk. Furthermore, previous studies have shown that statins use is associated with reduction risk in HCC in diabetic patients, but the association is not observed in other lipid-lowering drugs [6]. We thus examined HCC risk in stratification of statins and other lipid-lowering drugs in order to explore whether the association differs by medications in the general population. On the other hand, HCC generally develops on a background of chronic liver disease or inflammation and cirrhosis in 70–90 % of all cases [9]. In Taiwan, more than 90 % of patients with HCC are related to Hepatitis B or Hepatitis C infection [10]. Therefore, we also tested the effect of statins on HCC risk stratified by chronic liver diseases or not.

Materials and methods

Data sources

We conducted this case–control study using the research database of the National Health Insurance program of Taiwan. To reduce the likelihood of misclassification of the disease, we confirmed the occurrence of HCC by linking the longitudinal health insurance database with the registry for catastrophic illness patients. Patients who apply for a cancer catastrophic illness certificate are required to provide pathological reports or other supporting documents, such as laboratory and image studies. The Bureau of National Health Insurance approves the application after reviewing all the required medical documents. The details of insurance program can be found in previous studies [11–14].

Inclusion criteria

In this case–control study, cases were the subjects with newly diagnosed HCC (International Classification of Diseases 9th Revision-Clinical Modification, ICD-9 codes 155, 155.0, and 155.2) during the period of 2000–2009. The index date for each case was the date of diagnosis with HCC. Controls were subjects without HCC randomly selected from the same dataset and frequency matched with sex, age (per 5 years) and duration of observational period of cases (i.e., the duration between year of being enrolled in the insurance program and index year of cases) based on a 1:4 ratio. Subjects with HCC or any other cancer (ICD-9 codes 140–208) before the index date were excluded. In order to explore the association between individual statins and HCC risk, medication history of six commercially available statins before the index date, including simvastatin, lovastatin, fluvastatin, atorvastatin, pravastatin, and rosuvastatin, were searched.

Potential co-morbidities associated with hepatocellular carcinoma risk

In order to explore the potential co-morbidities associated with HCC risk [9, 10, 14], co-morbidities before the index date were included as follows: diabetes mellitus (ICD-9 codes 250), cirrhosis (ICD-9 codes 571.2, 571.5 and 571.6), alcoholic liver damage (ICD-9 codes 571.0, 571.1 and 571.3), nonalcoholic fatty liver disease (ICD-9 codes 571.8), hepatitis B infection (ICD-9 codes V02.61, 070.20, 070.22, 070.30 and 070.32), and hepatitis C infection (ICD-9 codes V02.62, 070.41, 070.44, 070.51 and 070.54).

Statistical analysis

We compared the difference in sex, age, and co-morbidities between the HCC cases and the controls by the Chi square test, *t* test, and Wilcoxon Rank Sums test. The significant variables were further included in the multiple logistic regression analysis to measure odds ratio (OR) and 95 % (CI) for HCC. We performed test for trend using Wald tests across levels and duration of drug exposures. In the tests,

the exposure categories were treated as ordinal categorical variables. The statistical significance level was set at probability value of <0.05 (SAS software version 9.1, SAS Institute Inc., Cary, North Carolina, USA).

Results

Basic characteristics of the study population

We identified 3,480 HCC cases and 13,920 non-HCC control subjects during 2000–2009. HCC cases were 0.5 year older than were control subjects ($p = 0.048$). The difference may be due to the matching on 5-year age band rather than the exact age (Table 1). In univariate analysis, HCC cases were more likely to have diabetes mellitus, cirrhosis, alcoholic liver damage, nonalcoholic fatty liver disease, hepatitis B infection, and hepatitis C infection. Cases also tended to have received treatments for hepatitis B and hepatitis C, and prescription of thiazolidinediones. In multivariable analysis, diabetes (OR = 1.46, 95 % CI = 1.26–1.68), cirrhosis (OR = 44.2, 95 % CI = 37.1–52.7), hepatitis B infection (OR = 14.1, 95 % CI = 12.1–16.3) and hepatitis C infection (OR = 9.88, 95 % CI = 8.22–11.9) were associated with increased odds of HCC.

Hepatocellular carcinoma associated with statins use

Use of statins was significantly associated with reduced risk of HCC (adjusted OR = 0.72, 95 % CI = 0.59–0.88) (Table 1). The mean (SD) duration of exposure was 16.7 (37.9) months in patients with HCC and 18.6 (30.9) months in the control group. The corresponding figures for median (interquartile) exposure were 5 (2–16) months in patients with HCC and 8 (3–21) months in the control group. We also observed reduced risk of HCC in subjects prescribed for non-statin lipid lowering drugs compared with those who did not use non-statin lipid lowering drugs (OR = 0.79, 95 % CI = 0.64–0.97). Similar results were observed in the multivariable-adjusted analysis using subjects prescribed for neither statins nor non-statins lipid lowering drugs as the reference group (Table 2). The adjusted OR was 0.71 (95 % CI = 0.56–0.89) for subjects treated with statins only, 0.77 (95 % CI = 0.60–1.00) for subjects on non-statins lipid lowering drugs only, and 0.59 (95 % CI = 0.43–0.80) for those who had been prescribed for both statins and non-statins lipid lowering drugs.

Interactions between chronic liver diseases and use of statins

To assess whether the association between statins use and risk of HCC differs in patient subgroups, we measured the interactions between age, sex, comorbidities and use of statins on HCC risk (Table 3). Among patients without chronic liver diseases, the adjusted OR for HCC in subjects prescribed for statins was 0.78 (95 % CI = 0.62–0.99), as compared with those not on statins. The adjusted OR for statins use was reduced to 0.41 (95 % CI = 0.31–0.54) among patients with chronic liver diseases (the likelihood ratio test for interaction, $p < 0.0001$). The estimated OR was greater in men (OR 0.77) than in women (OR 0.61), and the reduced odds associated with statins was observed in subjects aged 45 years and older but not in those less than 45 years old. However, the test for interaction effect showed that the association between statins use and HCC risk was not different by sex and age (p values of likelihood ratio test, 0.48 and 0.06, respectively).

Sub-analysis of association between six types of statins and hepatocellular carcinoma

Table 4 shows the ORs of HCC in relation to treatment duration for various statins. In multivariable-adjusted analysis, the point estimates (ORs) showed potential protective effect (ORs <1.0) among all statins, as compared with their non-use counterparts. The ORs were not statistically significant among fluvastatin, pravastatin and rosuvastatin. The risk reduction was greater in subjects with at least 12-months prescription than in those prescribed for less than or equal to 12 months for simvastatin (p value of test for trend, 0.01) and lovastatin (p value of test for trend, 0.0004).

We also performed an analysis on the dose-related response, using non-use of statins as the reference group (Table 5). The average dose per day was calculated by using the total prescribed dose divided by total number of days supplied. We classified study subjects into two groups (high dose and low dose groups) according to the second tertile of dose distribution because the first and the second tertile of dose of some statins were the same. Fluvastatin and atorvastatin were associated with significant reduction in odds of HCC in high dose group, but the reduced risk was not statistically significant for low dose group (p value of test for trend, 0.06 and 0.004, respectively). Both high and low doses of lovastatin were associated with reduced risk of HCC. A lower odd of HCC was observed for low dose of simvastatin, but the OR for high dose of simvastatin was not statistically significant. Both high and low doses of pravastatin and rosuvastatin were not associated with HCC risk.

Discussion

The present paper is not completely novel as the previous studies have already published data about statins use and

Table 1 Baseline characteristics between hepatocellular carcinoma group and non-hepatocellular carcinoma group

	Hepatocellular carcinoma				*p* value	Odds ratio (95 % CI)	
	No ($N = 13,920$)		Yes ($N = 3,480$)			Crude	Adjusted[a]
	n	%	*n*	%			
Sex					1.00		
Women	3,820	27.4	955	27.4			
Men	10,100	72.6	2525	72.6			
Age (year), Mean (SD)	62.2	(13.7)	62.7	(13.4)	0.048*		
Co-morbidities before index date							
Diabetes mellitus	2,221	16.0	877	25.2	<0.0001	1.78 (1.62–1.94)	1.46 (1.26–1.68)
Cirrhosis	179	1.29	1825	52.4	<0.0001	84.6 (72.0–99.5)	44.2 (37.1–52.7)
Alcoholic liver damage	75	0.54	66	1.90	<0.0001	3.90 (2.82–5.40)	0.73 (0.43–1.24)
Non-alcoholic fatty liver disease	86	0.62	72	2.07	<0.0001	3.11 (2.25–4.30)	0.92 (0.56–1.51)
Hepatitis B infection	424	3.05	1,295	37.2	<0.0001	18.9 (16.8–21.2)	14.1 (12.1–16.3)
Hepatitis C infection	274	1.97	1,005	28.9	<0.0001	20.2 (17.6–23.3)	9.88 (8.22–11.9)
Use of statins	1,635	11.8	255	7.33	<0.0001	0.59 (0.52–0.68)	0.72 (0.59–0.88)
Duration of exposure to statins (month)							
Mean (SD)	18.6	(30.9)	16.7	(37.9)	0.44*		
Median (interquartile)	8	(3–21)	5	(2–16)	0.002**		
Other medications							
Use of non-statin lipid-lowering drugs	1,344	9.66	263	7.56	0.0001	0.77 (0.67–0.88)	0.79 (0.64–0.97)
Medications for Hepatitis B	6	0.04	56	1.61	<0.0001	37.9 (16.3–88.0)	2.28 (0.84–6.17)
Medications for Hepatitis C	11	0.08	28	0.80	<0.0001	10.3 (5.10–20.6)	0.32 (0.11–0.90)
Use of metformin	1,052	7.56	240	6.90	0.18	0.91 (0.78–1.05)	–
Use of thiazolidinediones	345	2.48	135	3.88	<0.0001	1.59 (1.30–1.95)	1.17 (0.84–1.62)

* *t* test, and ** Wilcoxon Rank Sums test comparing patients with and without hepatocellular carcinoma. Rest of comparisons using Chi-Square test

[a] Adjusted for all variables listed in the table

Table 2 Odds ratio and 95 % CI of hepatocellular carcinoma in relation to statins and non-statins lipid lowering drugs

	Hepatocellular carcinoma					Odds ratio (95 % CI)	
	No ($N = 13\ 920$)		Yes ($N = 3\ 480$)			Crude	Adjusted[a]
	n	%	*n*	%	*p* value		
Single treatment on statins and/or non-statins lipid lowering drugs					<0.0001		
Neither use of statins and nor other lipid lowering drugs	1,1526	82.8	3,047	87.6		1.00	1.00
Statins only	1,050	7.54	170	4.89		0.61 (0.52–0.72)	0.71 (0.56–0.89)
Non-statins lipid lowering drugs only	759	5.45	178	5.11		0.89 (0.75–1.05)	0.77 (0.60–1.00)*
Use of both drugs	585	4.20	85	2.44		0.55 (0.44–0.69)	0.59 (0.43–0.80)

[a] Adjusted for age, sex, diabetes mellitus, cirrhosis, alcoholic liver damage, non-alcoholic fatty liver disease, hepatitis B infection, hepatitis C infection, treatments for Hepatitis B and Hepatitis C and thiazolidinediones

* $p = 0.045$

Table 3 Interactions between age, sex, comoribidities and use of statins associated with hepatocellular carcinoma

	Non-use of statins	Use of statins OR (95 % CI)	*P* value of interaction test
Chronic liver diseases[e, a]			<0.0001
No	as reference	0.78 (0.62–0.99)	
Yes	as reference	0.41 (0.31–0.54)	
Diabetes mellitus[b]			0.33
No	as reference	0.69 (0.52–0.91)	
Yes	as reference	0.77 (0.58–1.02)	
Sex[c]			0.48
Women	as reference	0.61 (0.43–0.86)	
Men	as reference	0.77 (0.61–0.98)	
Age(year)[d]			0.06
< 45	as reference	2.71 (0.96–7.67)	
45–64	as reference	0.61 (0.43–0.87)	
≥ 65	as reference	0.74 (0.58–0.95)	

[a] Adjusted for age, sex, diabetes mellitus, thiazolidinediones, treatments for Hepatitis B, treatments for Hepatitis C, and non-statins lipid-lower drugs

[b] Adjusted for age, sex, cirrhosis, alcoholic liver damage, non-alcoholic fatty liver disease, hepatitis B infection, hepatitis C infection, thiazolidinediones, treatments for Hepatitis B, treatments for Hepatitis C, statins, and non-statins lipid-lower drugs

[c] Adjusted for age, diabetes mellitus, cirrhosis, alcoholic liver damage, non-alcoholic fatty liver disease, hepatitis B infection, hepatitis C infection, thiazolidinediones, treatments for Hepatitis B, treatments for Hepatitis C, statins, and non-statins lipid-lower drugs

[d] Adjusted for sex, diabetes mellitus, cirrhosis, alcoholic liver damage, non-alcoholic fatty liver disease, hepatitis B infection, hepatitis C infection, thiazolidinediones, treatments for Hepatitis B, treatments for Hepatitis C, statins, and non-statins lipid-lower drugs

[e] Chronic liver diseases included cirrhosis, alcoholic liver damage, non-alcoholic fatty liver disease, hepatitis B infection, and hepatitis C infection

HCC risk [6, 7]. Nonetheless, it focused on the general population, not on specific patient populations. We also extended the study period from 2000 to 2009 and collected more HCC cases to explore individual statin effects, which was not found in Chiu et al. It appears to be informative and influential on the association between individual statins and HCC risk. The mechanism why statins may correlate with HCC risk cannot be well explained in this present study, but a growing body of evidence has shown that inhibition of the mevalonate pathway by statins, which is the rate-limiting step, causes the reduced levels of mevalonate and its downstream products. That may further decrease the neoplasm-related risk [15–17].

In the present study, the overall risk can be reduced to 28 % in patients with statins use, when compared with non-use of statins. Because use of statins could potentially cause abnormal liver function tests [18], patients with chronic liver diseases might be less likely to be prescribed

Table 4 Odds ratio and 95 % CI of hepatocellular carcinoma in relation to cumulative duration of using statins by logistical regression model

Non-use of statins as a reference	HCC group/control group, no of subjects 3,225/12,285	Crude odds ratio 1.00	(95 % CI) (reference)	Adjusted odds ratio[a] 1.00	(95 % CI) (reference)
Simvastatin					
All	90/616	0.56	(0.45–0.70)	0.69	(0.50–0.94)
≤12 months	69/444	0.59	(0.46–0.77)	0.75	(0.53–1.07)
>12 months	21/172	0.47	(0.30–0.73)	0.54	(0.29–0.99)
P for trend		<0.0001		0.01	
Lovastatin					
All	72/478	0.57	(0.45–0.74)	0.52	(0.36–0.76)
≤12 months	66/399	0.63	(0.48–0.82)	0.65	(0.38–0.83)
>12 months	6/79	0.29	(0.13–0.67)	0.31	(0.11–0.91)
P for trend		<0.0001		0.0004	
Fluvastatin					
All	55/386	0.54	(0.41–0.72)	0.76	(0.52–1.10)
≤12 months	45/276	0.62	(0.45–0.85)	0.92	(0.61–1.38)
>12 months	10/110	0.35	(0.18–0.66)	0.40	(0.17–0.91)
P for trend		<0.0001		0.08	
Atorvastatin					
All	101/757	0.51	(0.41–0.63)	0.70	(0.53–0.93)
≤12 months	72/535	0.51	(0.40–0.66)	0.69	(0.50–0.96)
>12 months	29/222	0.50	(0.34–0.73)	0.73	(0.44–1.19)
P for trend		<0.0001		0.02	
Pravastatin					
All	32/186	0.66	(0.45–0.96)	0.94	(0.57–1.54)
≤12 months	25/147	0.65	(0.42–0.99)	0.85	(0.48–1.49)
>12 months	7/39	0.68	(0.31–1.53)	1.35	(0.51–3.57)
P for trend		0.03		0.92	
Rosuvastatin					
All	27/174	0.59	(0.39–0.89)	0.64	(0.36–1.12)
≤12 months	20/133	0.57	(0.38–0.92)	0.65	(0.34–1.24)
>12 months	7/41	0.65	(0.29–1.45)	0.60	(0.20–1.84)
P for trend		0.01		0.12	

[a] Adjusted for age, sex, diabetes mellitus, cirrhosis, alcoholic liver damage, non-alcoholic fatty liver disease, hepatitis B infection, hepatitis C infection, thiazolidinediones, treatments for Hepatitis B, treatments for Hepatitis C, and non-statins lipid-lower drugs

with statins in clinical practice. To clarify whether there is an interaction between use of statins and chronic liver diseases on HCC risk, in further analysis, we found statins use can reduce 22 % risk of HCC for those without chronic liver diseases and can particularly reduce 59 % risk for those with chronic liver diseases. This means that the protective effects of statins use can be more obvious among patients with chronic liver diseases, which is compatible with Tsan et al. [8] study.

In sub-analysis, individual statins demonstrate the beneficial effects on HCC risk and duration-response relationship. The point estimates (ORs) were not statistically significant among fluvastatin, pravastatin and rosuvastatin, partly because of the small number of cases which could result in insufficient statistical power. Despite whether statins could be beneficial or harmful effects on cancer risk remains inconclusive, this present study showed that individual statins have the beneficial effects on HCC risk. A previous study has shown that the association between lipid-lowering medication and reduced risk of HCC is unique to statins [6]. In this study, we also found a reduced risk associated with non-statin lipid lowering drugs after adjusting for the potential confounding factors, which was compatible with Chiu et al. [7] study, but not compatible with El-Serag et al. [6] study. Therefore, further prospective randomized trials of statins and non-statin lipid lowering drugs are warranted to confirm these results.

Some limitations should be addressed. First, less than 1 % prevalence of non-alcoholic fatty liver disease was found in this population studied. At present, non-alcoholic fatty liver disease is usually diagnosed by ultrasound. If this patient did not performed ultrasound, we cannot diagnose this disease by physical examination. Thus, a systematic underestimation of non-alcoholic fatty liver

Table 5 Odds ratio and 95 % CI of hepatocellular carcinoma in relation to statins dose by logistical regression model

Non-use of statins as a reference	HCC group/control group, no. of subjects 3,225/12,285	Crude odds ratio 1.00	(95 % CI) (reference)	Adjusted odds ratio[a] 1.00	(95 % CI) (reference)
Simvastatin					
<20 mg	52/393	0.50	(0.38–0.68)	0.63	(0.42–0.94)
≥20 mg	38/223	0.65	(0.46–0.92)	0.79	(0.50–1.26)
P for trend		<0.0001		0.054	
Lovastatin					
<20 mg	12/114	0.40	(0.22–0.73)	0.28	(0.11–0.72)
≥20 mg	60/364	0.63	(0.48–0.83)	0.60	(0.40–0.88)
P for trend		<0.0001		0.002	
Fluvastatin					
<48 mg	37/245	0.58	(0.41–0.82)	0.94	(0.61–1.44)
≥48 mg	18/141	0.49	(0.30–0.80)	0.48	(0.24–0.96)
P for trend		<0.0001		0.06	
Atorvastatin					
<10 mg	45/280	0.61	(0.45–0.84)	0.96	(0.64–1.42)
≥10 mg	56/477	0.45	(0.34–0.59)	0.56	(0.38–0.81)
P for trend		<0.0001		0.004	
Pravastatin					
<20 mg	23/129	0.68	(0.44–1.06)	1.01	(0.57–1.79)
≥20 mg	9/57	0.60	(0.30–1.22)	0.86	(0.34–2.19)
P for trend		0.03		0.81	
Rosuvastatin					
<10 mg	14/90	0.59	(0.34–1.04)	0.70	(0.33–1.49)
≥10 mg	13/84	0.59	(0.33–1.06)	0.57	(0.25–1.31)
P for trend		0.02		0.11	

[a] Adjusted for age, sex, diabetes mellitus, cirrhosis, alcoholic liver damage, non-alcoholic fatty liver disease, hepatitis B infection, hepatitis C infection, thiazolidinediones, treatments for Hepatitis B, treatments for Hepatitis C, and non-statins lipid-lower drugs

disease can partially explain the low prevalence of this disease. Second, in Taiwan, more than 90 % of patients with HCC are related to Hepatitis B or Hepatitis C infection [10]. We selected the subjects without HCC as controls. Thus, it is why the prevalence rates of Hepatitis B or Hepatitis C infection and cirrhosis were much lower in control group than the case group (5.02 vs. 66.1 % in viral hepatitis, and 1.29 vs. 52.4 % in cirrhosis). In Table 3, however, the adjusted OR for HCC in subjects prescribed for statins was 0.78 (95 % CI 0.62–0.99) among patients without chronic liver diseases, as compared with those not on statins. This means that statins still have protective effect among patients without chronic liver diseases. Third, the corresponding figures for median (interquartile) exposure were 5 (2–16) months in patients with HCC and 8 (3–21) months in the control group. These figures indicate that about half of subjects in the two groups had prescription of statins for more than half a year, but median exposure of the other half of subjects was less than a year. Whether a medication can lead to a reduction in HCC risk with an exposure for less than a year needs further prospective trials to validate our findings. Forth, the proportion of patients receiving antiviral drugs was very low in our analysis. Initially, the National health Insurance Program of Taiwan did not allow reimbursement of antiviral drugs. The patients received antiviral drugs only at their own expense. Thus, this database could not include these treatment records. After 2006, the national health insurance program allowed reimbursement with restrictions; only those simultaneously with ALT ≥80 IU/ml and high level of virus loading could be reimbursed for use of antiviral drugs. Thus, data on the treatments for hepatitis B and hepatitis C were underestimated. However, the confounding of treatments for Hepatitis B and C might have been partially taken into account in the models adjusted for history of hepatitis B and hepatitis C. Fifth, due to the inherent limitation of this database, it is difficult to make sure whether the patients were adherent to statin use. Last, we could not exclude the possibility of the potential misclassification of HCC, an inherent limitation in the secondary analysis using claims data. The misclassification is likely to be at a similar extent between the exposure groups.

Conclusion

This study demonstrates that statins use correlates with overall 28 % decreased risk of HCC. Statins use reduces 22 % risk of HCC for those without chronic liver diseases and particularly reduces 59 % risk for those with chronic liver diseases. Individual statins, including simvastatin, lovastatin and atorvastatin, are associated with reduced risk of HCC.

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Conflict of interest The authors disclose no conflicts of interest.

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