中山醫學大學 102 學年度碩士班入學招生考試試題

公共衛生學系碩士班（甲組）

考試科目：流行病學 **時間：80 分鐘**

※請注意本試題共（ 4 ）張，如發現頁數不足，應當場請求補齊，否則缺頁部份概以零分計算。 第（ 1 ）頁

本試題共三大題，總分 100 分。（本科目可攜帶依考選部核定通過之國家考試計算器）

一、 根據所附來自 Journal of Clinical Oncology 2012 文章回答下列問題：(76%)

（一） 請寫出本研究目的 (3%)

（二） 本研究的暴露(exposure)為何? 疾病的發生(Outcome)是那一種疾病? (6%)

（三） 本研究是那一種研究設計? 這種設計有何優缺點? (10%)

（四） 本研究考慮了那些社會人口學特徵的潛在干擾因子(potential confounders)? (4%)

（五） 流行病學中干擾因子需符合那三個要件? 調整干擾因子的方法有那些? (18%)

（六） 請說明本研究主要是用何種方法調整本研究的干擾因子? (4%)

（七） 本研究中最主要是使用那一種集中趨勢測量(measure of central tendency)? 使用那一種分散性的測量(measure of dispersion)? 並解釋本研究所使用的集中趨勢測量與分散性測量的統計意義。(8%)

（八） 本研究 Table 2 的 incidence rate (per 10^5)的 95% CI 有(300.0 to 340.2)，也有(61.8 to 306.4)，(1)這兩個中的那一個信賴區間的標準誤差(standard error, SE)比較大? (2)造成信賴區間寬度比較大的原因你認為是什麼? (3)其中(61.8 to 306.4)這個信賴區間是否達到統計顯著意義? 它的 P-value >0.05 或<0.05? (6%)

（九） 本研究 Table 2 的 HR(Hazard Ratio)是一種相對危險性指標，類似 OR(Odds Ratio)或 RR(Rate Ratio)指標，兩個 95% CI 分別是 (0.54 to 1.78)及 (0.08 to 0.59)，請分別判定這兩個信賴區間是否顯著? 其 P-value 是>0.05 或<0.05?。(4%)

（十） 流行病學中，因果關係的判定準則有那些? 本研究主要應用了那些判定準則? (10%)

（十一） 請寫出本研究結論。(3%)

二、 在迴歸模式中進行年齡(age)調整時可以使用三種方法進行處理，(一) age 以連續變項放入模式中 (二) age 分成若干層，例如設成四層(<30, 30-45, 45-60, 60 以上)，再設成數個啞變數(dummy variable)來表達上述四個年齡層後放入模式；(三)將上述四個年齡層用一個新變項，並以值 1, 2, 3, 4 依序代表四個年齡層後放入模式。請說明上述三種處理方法各有何假設與優缺點? 請寫出第二種處理方式的啞變數來代表上述四個年齡層(以<30 當參考組)。(16%)

三、 請比較統計學中的標準機差(standard Deviation, SD)與標準誤差(standard error, SE)的意義與差異? (8%)

(2)

流行病学試題第一大題文章(共6頁)
連同試題共7頁
第一大題共11小題，部份題目的答案
可在文章中找到。

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INTRODUCTION

3-Hydroxy-3-methylglutary– coenzyme A reduc-tase inhibitors, commonly referred to as statins, have therapeutic and primary and secondary pre-ventative effects in cardiovascular disease and stroke.[1-4] Recently, there has been emerging inter-est in use as anticancer agents based on preclinical evidence of their antiproliferative, proapoptotic, anti-invasive, and radiosensitizing properties.[5,6] Inhibition of 3-hydroxy-3-methylglutaryl–coenzyme A reductase by statins interferes with the rate-limiting step of the mevalonate pathway,[7] leading to reduced levels of mevalonate and its downstream products[8,9]; thus, statins may reduce tumor initia-tion, growth, and metastasis. In fact, statins have demonstrated growth-inhibiting activity in cancer cell lines and preclinical tumor models in animals.[10-14] Observational studies have raised the possibility that statin use may decrease overall risk of cancer and risk of specific cancers.[15-18] In contrast, meta-analyses of randomized trials have consis-tently shown no effect of statins on cancer inci-dence or cancer mortality.[1,19-22] In addition, few epidemiologic studies have investigated the asso-ciation between statin use and risk of hepatocel-lular carcinoma (HCC).

Recent studies have shown the safety and poten-tial therapeutic applications of statins in patients with knownliverdisease,[23,24] althoughthemostconcerning adverseeffectsofstatinsarehepatotoxicityandmyo-toxicity.[25,26] A recent population-based case-control study in Taiwan showed that statins were associated with a reduction in the risk of liver cancer,[27] but no statistically significant effects were found in a Danish study.[16] One clinical trial showed that pravastatin suppressed tumor cell growth and extended survival time in patients with advanced HCC.[28] A nested

case-control study found that statin use was associated with a significant reduction in the risk of HCC among patients with diabetes.[29]

Carriers of hepatitis B virus (HBV) infection have a substantial risk of HCC and liver-related death compared with individuals not infected with HBV.[30-33] Because the connection between statin use and risk of HCC is unclear, our study investigated whether statin use is associated with the reduction of HCC incidence in HBV-infected patients.

PATIENTS AND METHODS

Data Sources

The sampling cohort data set was obtained from the Taiwanese National Health Insurance (NHI) research database. The NHI program provides compulsory universal health insurance, implemented on March 1, 1995, that covers all forms of health care services in 98% of the island's population. In cooperation with the Bureau of NHI, the National Health Research Institute (NHRI) of Taiwan randomly sampled a representative database of 1,000,000 patients from the year 2005 registry of all NHI enrollees using a systematic sampling method for research purposes, as the Longitudinal Health Insurance Database. There were no statistically significant differences in age, sex, or health care costs between the sample group and all enrollees, as reported by the NHRI. We used databases for admissions and outpatient visits of the sample cohort, both of which included information on patient characteristics, including sex, date of birth, date of admission, date of discharge, dates of visits, and up to five discharge diagnoses or three outpatient visit diagnoses (by International Classification of Diseases, Ninth Revision [ICD-9] classification).[34] The data files also contained information on patient prescriptions, including the names of prescribed drugs, dosage, duration, and total expenditure. These databases have previously been used for epidemiologic research, and information on prescription use, diagnoses, and hospitalizations is of high quality.[27,35-37]

With strict confidentiality guidelines being closely followed in accordance with personal electronic data protection regulations, the NHRI of Taiwan anonymized and maintained the NHI reimbursement data as files suitable for research.[38] In addition, this study was approved by the Ethics Review Board at the National Taiwan University College of Public Health.

Identification of Study Sample

We conducted a population-based cohort study in which all patients older than 18 years who had a first-time diagnosis of HBV infection (ICD-9 codes 070.2, 070.3, and V02.61) without hepatitis C virus (HCV) infection (ICD-9 codes 070.7, 070.41, 070.44, 070.51, 070.54, and V02.62) between January 1, 1997, and December 31, 2008, formed the study cohort (N = 33,413). Because liver diseases are an important health problem in Taiwan, the government pays close attention to this health issue and makes the guideline for diagnosis.[39]

Patients with HCC (ICD-9 code 155.0) were identified in the admission files, with the first-time diagnosis date as the index date. The American Association for the Study of Liver Diseases Practice Guidelines were recommended by the Bureau of NHI for the diagnosis of HCC.[40] We deliberately included only patients with admission for HCC to increase the validity of the diagnosis. We limited eligible patients to those who were newly diagnosed between January 1, 1999, and December 31, 2008, to allow for more than 2 years of prior exposure with complete admission, outpatient visit, and drug data; thus, 36 individuals were excluded from the analysis because they had previously diagnosed HCC.

Exposure to Statins

We identified patients who filled prescriptions for statins in the inpatient and ambulatory care order files between January 1, 1997, and 365 days before the index date for HCC. We collected the dates of prescriptions, the daily dose, the number of days supplied, and the number of pills per prescription. In accordance with the Anatomic Therapeutic Chemical Classification System of drugs, we selected simvastatin, lovastatin, atorvastatin, fluvastatin, pravastatin, and rosuvastatin as the major study drugs of interest.

The defined daily dose (DDD) recommended by the WHO is a unit for measuring a prescribed amount of drug; it is the assumed average maintenance dose per day of a drug consumed for its main indication in adults. By using the following formula, we could compare any statins based on the same standard: (total amount of drug)/(amount of drug in a DDD) = number of DDDs.[41] Cumulative DDD (cDDD), which indicates the exposed duration, was estimated as the sum of dispensed DDD of any statins to compare their use to the risk of HCC. We collected similar information on nonstatin lipid-lowering medications (cholestyramine, colestipol, colextran, niceritrol, nicofuranose, acipimox, probucol, and ezetimibe). To examine the dose-effect relationship, we categorized the statins into four groups in each cohort (< 28, 28 to 90, 91 to 365, and > 365 cDDDs) because the duration of the refill card was 3 months. Patients who used statins for less than 28 cDDDs were defined as statin nonusers.

Potential Confounders

We identified in a systematic way any liver disease as a potential confounder defined by the following diagnoses recorded between January 1, 1997, and the HCC index date: alcohol-related disease (ICD-9 codes 291, 303.0, 303.9, 305.0, 571.0, 571.1, 571.2, and 571.3) and cirrhosis (ICD-9 codes 571.2, 571.5, 571.6, 572.2, 572.3, 572.4, 572.8, and 573.0) with diabetes (ICD-9 code 250). The prescriptions of medications that potentially could confound the association between statin use and cancer risk were also identified, such as anti-HBV treatment (interferon, lamivudine, entecavir, adefovir dipivoxil, and telbivudine), aspirin, angiotensin-converting enzyme (ACE) inhibitors (captopril, enalapril, lisinopril, perindopril, ramipril, quinapril, benazepril, cilazapril, and fosinopril), and triglyceride-lowering medications (bezafibrate, clofibrate, etofibrate, fenofibrate, gemfibrozil, and simfibrate). We also considered sociodemographic characteristics (age, sex, income, and level of urbanization) in the modeling. Urbanization levels in Taiwan are divided into four strata according to the Taiwan National Health Research Institute publications, with level 1 referring to the most urbanized communities and level 4 referring to the least urbanized communities.

Statistical Analyses

We used the Kaplan-Meier method to estimate HCC cumulative incidences. The log-rank test was performed to examine differences in the risk for HCC in the cohort. Finally, Cox proportional hazards models were used to compute the 10-year hazard ratios (HRs) accompanying 95% CIs after adjustment for the variables mentioned. Two-tailed $P = .05$ was considered significant. Deceased patients (with death date in the admission file) and those from the beneficiaries register who were lost to follow-up were censored.[33,42,43] In multivariable analyses, we evaluated linear trends in risk by treating statin use as a continuous variable after assigning a score to each exposure level so that the P value was calculated for trend to confirm the dose-response relationship. All of these analyses were conducted using SAS statistical software (version 9.2; SAS Institute, Cary, NC).

Sensitivity Analyses

Many agents have shown positive results in chemoprevention.[44,45] To examine potential effect modifiers, we conducted analyses stratified by groups with and without use of anti-HBV treatment, ACE inhibitors, aspirin, and triglyceride-lowering medication. These sensitivity analyses were applied to evaluate the difference and consistency between the statins and the risk of HCC.

RESULTS

A total of 33,413 HBV-infected patients were included as the study cohort, of whom 8.3% had used statins (≥ 28 cDDDs). Table 1 lists the demographic characteristics, medical conditions, and medication use of patients.

There were 1,021 HCCs in the HBV-infected cohort during the follow-up period of 328,946 person-years; the overall incidence rate was 310.4 HCCs per 100,000 person-years. The incidence rates of

Table 1. Patient Demographics and Clinical Characteristics of the HBV-Infected Cohort

Characteristic	All Patients With HBV Infection (N = 33,413)		Patients With Statin Use (≥28 cDDDs; n = 2,785)		Patients Without Statin Use (< 28 cDDDs; n = 30,628)	
	No.	%	No.	%	No.	%
Age, years						
18-29	10,964	32.8	207	7.4	10,757	35.1
30-39	9,904	29.6	587	21.1	9,317	30.4
40-49	7,225	21.6	942	33.8	6,283	20.5
50-59	3,182	9.5	604	21.7	2,578	8.4
≥ 60	2,138	6.4	445	16.0	1,693	5.5
Median	35.6		34.7		46.3	
IQR	27.2-45.1		26.6-43.8		38.9-55.3	
Male	19,442	58.2	1,590	57.1	17,852	58.3
Statin, cDDD*						
< 28	30,628	91.7	—		30,628	100.0
28-90	933	2.8	933	33.5	—	
91-365	1279	3.8	1,279	45.9	—	
> 365	573	1.7	573	20.6	—	
Median*	0		136.7		0	
IQR			63.5-315.0			
Statin used (≥ 28 cDDDs)						
Simvastatin	790	2.4	790	28.4	—	
Lovastatin	765	2.3	765	27.5	—	
Atorvastatin	1,286	3.9	1,286	46.2	—	
Fluvastatin	518	1.6	518	18.6	—	
Pravastatin	352	1.1	352	12.6	—	
Rosuvastatin	435	1.3	435	15.6	—	
Nonstatin lipid-lowering drugs, cDDD						
0	32,818	98.2	2,570	92.3	30,248	98.8
1-27	353	1.1	78	2.8	275	0.9
28-90	117	0.3	63	2.3	54	0.2
91-365	103	0.3	60	2.2	43	0.1
> 365	22	0.1	14	0.5	8	0.0
Median*	84.0					
IQR	42.0-188.0					
Fibrate, cDDD						
0	30,456	91.1	1,618	58.1	28,838	94.2
1-27	923	2.8	222	8.0	701	2.39
28-90	802	2.4	280	10.1	522	1.7
91-365	862	2.6	423	15.2	439	1.4
> 365	370	1.1	242	8.7	128	0.4
Median*	106.8					
IQR	56.0-268.8					
ACE inhibitors, cDDD						
0	27,697	82.9	1,320	47.4	26,377	86.1
1-27	1,389	4.2	220	7.9	1,169	3.8
28-365	2,694	8.1	690	24.8	2,004	6.5
> 365	1,633	4.9	555	19.9	1,078	3.5
Median*	220.5					
IQR	75.0-699.0					
Aspirin, cDDD						
0	26,639	79.7	1,267	45.5	25,372	82.8
1-27	2,552	7.6	211	7.6	2,341	7.6
28-365	2,557	7.7	613	22.0	1,944	6.3
> 365	1,665	5.0	694	24.9	971	3.2
Median*	218.5					
IQR	64.0-750.0					
Anti-HBV treatment						
No treatment	32,636	97.6	2,721	97.7	29,915	97.7
Partial treatment	359	1.1	27	1.0	332	1.1
Complete treatment	418	1.3	37	1.3	381	1.2
Medical diseases						
Hypertension	9,669	28.9	1,973	70.8	7,696	25.1
Hyperlipidemia	12,742	38.1	2,661	95.5	10,081	32.9
Liver cirrhosis	3,580	10.7	323	11.6	3,257	10.6
Diabetes	8,812	26.4	1,725	61.9	7,087	23.1
Biliary stones	4,140	12.4	509	18.3	3,631	11.9
Alcohol-related disease	2,349	7.0	249	8.9	2,100	6.9
Chronic renal injury	1,231	3.7	298	10.7	933	3.0

Abbreviations: ACE, angiotensin-converting enzyme; cDDD, cumulative defined daily dose; HBV, hepatitis B virus; IQR, interquartile range.
*The median prescribed number of every used (≥ 28 cDDDs) study drug in the cohort.

Table 2. Incidence Rate and Crude and Adjusted HRs of HCC Associated With Statin Use During the Follow-Up Period in the HBV-Infected Cohort

Variable	No. of Patients	No. of Person-Years	No. of Patients With HCC	Incidence Rate (per 10^5 person-years)	95% CI	HR				
						Crude HR	95% CI	Adjusted HR*	95% CI	*P* for Trend
All patients	33,413	328,945.8	1,021	310.4	291.9 to 330.0					
Men	19,442	190,432.3	857	450.0	420.9 to 481.2	3.83	3.24 to 4.53	2.66	2.24 to 3.15	< .001
Women	13,971	138,513.5	164	118.4	101.6 to 138.0	—		—		
Total statin use										
Nonuser (< 28 cDDDs)	30,628	301,439.4	963	319.5	299.9 to 340.3	—		—		< .001
User (≥ 28 cDDDs)	2,785	27,506.4	58	210.9	163.0 to 272.7	0.66	0.51 to 0.86	0.47	0.36 to 0.61	
28-90 cDDDs	933	9,213.6	24	260.5	174.6 to 388.6	0.81	0.54 to 1.22	0.66	0.44 to 0.99	
91-365 cDDDs	1,279	12,622.5	25	198.1	133.8 to 293.1	0.62	0.42 to 0.92	0.41	0.27 to 0.61	
> 365 cDDDs	573	5,670.3	9	158.7	82.6 to 305.1	0.50	0.26 to 0.96	0.34	0.18 to 0.67	
Lipophilia statin use†										
Nonuser (< 28 cDDDs)	30,911	304,226.4	972	319.5	300.0 to 340.2	—		—		< .001
User (≥ 28 cDDDs)	2,502	24,719.4	49	198.2	149.8 to 262.3	0.62	0.47 to 0.83	0.44	0.33 to 0.59	
28-90 cDDDs	694	8,835.1	19	215.1	137.2 to 337.2	0.67	0.43 to 1.06	0.57	0.36 to 0.89	
91-365 cDDDs	1,167	11,524.8	24	208.2	139.6 to 310.7	0.65	0.44 to 0.98	0.42	0.28 to 0.63	
> 365 cDDDs	441	4,359.5	6	137.6	61.8 to 306.4	0.43	0.19 to 0.96	0.29	0.13 to 0.66	
Hydrophilia statin use†										
Nonuser (< 28 cDDDs)	32,670	321,608.9	1,006	312.8	294.1 to 332.7	—		—		< .001
User (≥ 28 cDDDs)	743	7,336.9	15	204.4	123.3 to 339.1	0.65	0.39 to 1.09	0.51	0.31 to 0.85	
28-90 cDDDs	310	3,045.6	11	361.2	200.0 to 652.2	1.16	0.64 to 2.09	0.98	0.54 to 1.78	
> 90 cDDDs	433	4,291.3	4	93.2	35.0 to 248.4	0.30	0.11 to 0.79	0.22	0.08 to 0.59	
Individual statin use (≥ 28 cDDDs)‡										
Simvastatin	790	7,794.1	17	218.1	135.6 to 350.9	0.70	0.43 to 1.13	0.53	0.32 to 0.85	
Lovastatin	765	7,564.1	22	290.8	191.5 to 441.7	0.94	0.61 to 1.43	0.60	0.39 to 0.92	
Atorvastatin	1,286	12,711.6	20	157.3	101.5 to 243.9	0.50	0.32 to 0.77	0.37	0.24 to 0.58	
Fluvastatin	518	5,114.9	6	117.3	52.7 to 261.1	0.38	0.17 to 0.84	0.32	0.14 to 0.71	
Pravastatin	352	3,433.1	13	378.7	219.9 to 652.1	1.23	0.71 to 2.13	0.80	0.46 to 1.38	
Rosuvastatin	435	4,340.5	2	46.1	11.5 to 184.2	0.15	0.04 to 0.58	0.14	0.03 to 0.55	

Abbreviations: cDDD, cumulative defined daily dose; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HR, hazard ratio.
*Adjusted for age, sex, income, urbanization, diabetes, and liver cirrhosis.
†Lipophilia statins include simvastatin, lovastatin, atorvastatin, and fluvastatin. Hydrophilia statins include pravastatin and rosuvastatin.
‡The HRs of individual statin users (≥ 28 cDDDs) were compared with those of nonusers (< 28 cDDDs).

HCC were 319.5, 260.5, 198.1, and 158.7 among HBV-infected patients with statin use of less than 28, 28 to 90, 91 to 365, and more than 365 cDDDs, respectively (Table 2). Figure 1 illustrates the results of the Kaplan-Meier method for the cohort. The log-rank test revealed a significant observed difference over the entire Kaplan-Meier curve. The longer the follow-up, the greater the differences are among the four groups.

There was a dose-response relationship between statin use and the risk of HCC (Table 2). The adjusted HRs were 0.66 (95% CI, 0.44 to 0.99), 0.41 (95% CI, 0.27 to 0.61), and 0.34 (95% CI, 0.18 to 0.67) for patients with statin use of 28 to 90, 91 to 365, and more than 365 cDDDs, respectively. There was a trend toward risk reduction with increasing cDDDs of statin use (*P* for trend < .001).

Sensitivity Analysis

The sensitivity analysis adjustments had little effect on the estimates of the association between statin use and the incidence of HCC by different models. Table 3 also shows that the effects of statins remained significant in the subgroups of male patients or patients older than age 50 years. When the data were stratified according to anti-HBV treatment, ACE inhibitor, and aspirin use and analyzed, we still found the trend in the subgroup analysis, although the HRs of a number of subgroups did not decrease monotonically with increasing statin use. This may have been a result of the relatively small number of patients.

DISCUSSION

This study is the first study, to our knowledge, to document a dose-response relationship between the use of statins in HBV-infected patients and the risk of HCC after controlling for the confounders. This study has a number of strengths. The study population was mainly taken from a computerized database, which is population based and highly representative. Because we included patients newly diagnosed with HCC from 1999 to 2008 from the admission file and because the HBV-infected patients were selected from a simple random sampling of an insured general population, we can rule out the possibility of selection bias.[38] In addition, because the data on statin use were obtained from an historical database that collects all available prescription information before the date of HCC, we can rule out the possibility of recall bias. We conducted sensitivity analyses by stratification to clarify the misclassifications and potential confounders, and the results revealed no significant changes in the HRs of the different

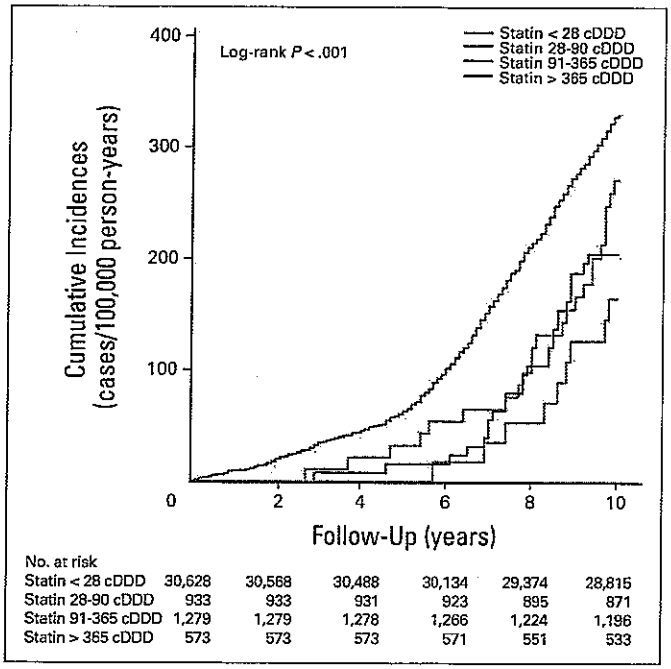

Fig 1. Cumulative incidence of hepatocellular carcinoma by cumulative defined daily dose (cDDD) of statin use during the follow-up period in the cohort infected with hepatitis B virus.

models and subgroups. We allowed a latent period of 1 year before diagnosis. Finally, we examined the association between HCC and the amounts of nonstatin cholesterol-lowering drugs used, which showed no significant associations.[46,47] Thus, we concluded that a dose-response relationship exists between the use of statins and the risk of HCC.

The overall incidence rate of HCC was 310.4 cases per 100,000 person-years in the HBV-infected cohort, which was similar to the incidence rate found by Yang et al[43] of 324.3 among patients who were positive only for hepatitis B surface antigen. The incidence rate of 450.0 in the male HBV-infected patients was also similar to the overall incidence rate for HBV-infected patients found by Yang et al.[43]

We found that statin use of 28 to 90 cDDDs was associated with a 34% risk reduction in HCC compared with nonuse, after controlling for potential confounders in HBV-infected patients. The risk reduction observed in our study was similar to those observed in the studies by El-Serag et al[29] and Chiu et al,[27] which reported a risk reduction with statin use that ranged between 25% and 40%.

To test the potential dose-response relationship, we summed up the doses of statins and stratified statin use into less than 28, 28 to 90, 91 to 365, and more than 365 cDDDs. We detected a statistically significant inverse trend between the dose and the cumulative incidences of HCC, which was compatible with the results in the previously mentioned studies.[27,29] Therefore, our study was related to the known higher likelihood of developing HCC, and the results suggest that using statins not only treats lipid abnormalities but also reduces the risk of HCC. In a general population study, Chiu et al[27] suggested that statins are associated with a reduced risk of liver cancer without a dose-response relationship after cumulative statin use of $\geq$ 215.4 cDDDs. This may have been a result of the relatively small number of patients.

The mechanism by which statin use may decrease HCC risk is not well understood. Yet, several potential mechanisms have been investigated. One is inhibition of downstream products of the mevalonate pathway, namely primary geranylgeranyl pyrophosphate and farnesyl pyrophosphate.[13,48-50] Statins interfere with the production of geranylgeranyl pyrophosphate and farnesyl pyrophosphate and disrupt the growth of malignant cells, eventually leading to apoptosis.[7] Second, statins inhibit the activation of the proteasome pathway, allowing these molecules to exert their growth-inhibitory effects and retard cancer cell mitosis.[51,52] Third, HCV replication depends in part on geranylgeranylation of a host protein, but HCV-RNA replication is disrupted by high concentrations of statins as a result of severe depletion of mevalonic acid, which in turn leads to low cellular levels of geranylgeranyl pyrophosphate.[53,54,55] Finally, chronic HBV or HCV infection predicts atherosclerosis and increases risk of stroke,[56,57] because of higher serum low-density lipoprotein and total cholesterol levels in HCV-positive individuals.[58,59] Statins may exhibit anti-HBV activity via inhibition of cholesterol synthesis and HBV replication.[60] In addition, accumulating evidence from rat models and a single report in humans suggests that statins may decrease portal hypertension through the nitric oxide pathway.[61-64]

If physicians are less likely to prescribe statins because of their hepatotoxicity, patients with liver disease are less likely to be prescribed statins.[65] We attempted to mitigate the effect of this potential bias even though we recognize that residual confounding effects could have existed. We took several steps to avoid and evaluate possible confounding effects of indication because the population of patients who received statins might have been different from the population that did not in ways that are not related to HCC. First, we examined the effect of statin use in stratified analyses in patients with and without liver disease. The findings indicate significant risk reduction in the HBV-infected group, but there was no statistically significant trend of protective effects with cumulative statin use in the cohort without liver disease (data not shown). Second, we conducted an analysis in which statin use recorded within 1 year before HCC was excluded, assuming that in this time period liver disease is likely to be severe and overt; in these analyses, we found the associations between statin use and HCC to be less strong. The associations lost significance in the adjusted analysis and in some of the stratified analyses of patients with and without liver disease. However, the number of patients with HCC in some of these categories was relatively small. Third, we categorized the HBV-infected patients into two groups, those with and without liver cirrhosis (data not shown). Among the HBV-infected patients with liver cirrhosis, 13.6% took statins, compared with 12.9% of patients without liver cirrhosis ($P = .76$). We found no significant confounding effects of indication for statin use in patients with liver cirrhosis.

In addition to overall statin use, individual statin use also had protective effects after adjustment for the risk of HCC in the HBV-infected cohort, except for pravastatin, which had no statistical significance. This may have been a result of different activities, lipophilicities, and relatively small numbers. Old age and male sex showed greater risk for HCC in the HBV-infected cohort, and statin use had a protective effect in these subgroups of the cohort. Anti-HBV treatment also had beneficial effects on preventing HCC development, which was consistent with the effect of statin use. ACE inhibitors and aspirin also showed mild protective effects on HCC. In addition, there

Table 3. Sensitivity Analysis of Adjusted HRs of Statin Use in Risk Reduction of Hepatocellular Carcinoma During the Follow-Up Period in the HBV-Infected Cohort

Model	Statin Use					
	28-90 cDDDs		91-365 cDDDs		> 365 cDDDs	
	HR	95% CI	HR	95% CI	HR	95% CI
Main model*	0.66	0.44 to 0.99	0.41	0.27 to 0.61	0.34	0.18 to 0.67
Additional covariates†						
Main model + Nonstatin lipid-lowering drug	0.66	0.44 to 0.99	0.44	0.28 to 0.62	0.36	0.19 to 0.70
Main model + fibrate	0.75	0.50 to 1.14	0.47	0.31 to 0.70	0.40	0.21 to 0.77
Main model + ACE inhibitor	0.71	0.47 to 1.06	0.46	0.31 to 0.68	0.38	0.20 to 0.74
Main model + aspirin	0.71	0.47 to 1.06	0.48	0.32 to 0.72	0.41	0.21 to 0.80
Main model + anti-HBV treatment	0.67	0.45 to 1.01	0.41	0.28 to 0.62	0.34	0.18 to 0.66
Subgroup effects						
Age, years						
18-49	0.52	0.26 to 1.05	0.69	0.39 to 1.19	0.16	0.02 to 1.17
≥ 50	0.76	0.46 to 1.25	0.31	0.17 to 0.55	0.42	0.21 to 0.85
Sex						
Male	0.68	0.44 to 1.07	0.49	0.32 to 0.74	0.33	0.16 to 0.69
Female	0.55	0.20 to 1.50	0.14	0.03 to 0.56	0.48	0.12 to 1.96
ACE inhibitors, cDDDs						
0-27	0.66	0.39 to 1.12	0.52	0.31 to 0.89	0.38	0.14 to 1.02
28-365	1.25	0.63 to 2.50	0.28	0.10 to 0.75	0.47	0.11 to 1.91
> 365	0.21	0.03 to 1.53	0.47	0.21 to 1.02	0.29	0.09 to 0.94
Aspirin, cDDDs						
0-27	0.55	0.32 to 0.96	0.44	0.24 to 0.79	0.10	0.01 to 0.73
28-365	1.17	0.53 to 2.61	0.55	0.26 to 1.14	0.37	0.05 to 2.64
> 365	0.63	0.22 to 1.78	0.46	0.19 to 1.07	0.65	0.29 to 1.43
Anti-HBV treatment						
No	0.68	0.45 to 1.03	0.40	0.27 to 0.60	0.34	0.18 to 0.66
Yes‡	0.50	0.06 to 4.50	—		—	

Abbreviations: ACE, angiotensin-converting enzyme; cDDD, cumulative defined daily dose; HBV, hepatitis B virus; HR, hazard ratio.
*Main model is adjusted for age, sex, urbanization, income, diabetes, and liver cirrhosis.
†The models were adjusted for covariates in the main model as well as each additional listed covariate.
‡The statins were divided into only two categories of use (0 to 27 and ≥ 28 cDDDs) in the anti-HBV treatment subgroup.

was a protective trend against the risk of HCC with a higher economic status in the HBV-infected cohort. To consider the time-varying exposure, we also analyzed the subgroups of statin users (data no shown). HR was calculated using time-varying multivariable Cox regression in the statin user cohort, and the starting time was evaluated from the first prescription date of statins. Within the subgroups of statin users, we still found the dose-response effect. We separated liver metastasis (ICD-9 code 197.7) from other diseases for the sensitivity analysis for the subgroup of patients with liver metastasis in the HBV-infected cohort. There were 133 patients with metastatic liver cancer, and we excluded 34 patients with the diagnosis of both metastatic liver cancer and HCC. The results showed that statin use had no effect on reducing the risk for liver metastasis of other cancers except HCC in HBV-infected patients.

Potential limitations of this study should be noted. First, several unmeasured confounders, including body mass index, smoking, alcohol intake, and other over-the-counter drug use, which are associated with HCC, were not included in our database. Second, we were unable to contact patients directly about their use of statins because of anonymization of their identification number. We presumed that all prescribed medications were actually taken by patients as prescribed, which may overestimate the actual ingested dosage, because some degree of noncompliance is always expected. Third, because we included only patients admitted for HCC, undoubtedly, our estimates are more conservative than they could have been with different criteria. Thus, because the data on drug prescription were not complete in 1996, we included statin use after 1997 so that the use of these drugs before 1997 would not be captured in our analysis. This could have underestimated the cDDD and dose-response effects. Finally, although there was an increasing trend of the differential lost-to-follow-up patients in these groups, the effect of the trend in censoring patients was little.

In conclusion, statin use may reduce the risk for HCC in HBV-infected patients in a dose-dependent manner. Further mechanistic research is needed.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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