LIVER

Statin Use and the Risk of Liver Cancer: A Population-Based Case–Control Study

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OBJECTIVES: **Experimental studies have shown that statins have potential protective effects against cancer. The aim of this study was to investigate whether the use of statins was associated with liver cancer risk.**

METHODS: **We conducted a population-based case–control study in Taiwan. Data were retrospectively collected from the Taiwan National Health Insurance Research Database. Cases consisted of all patients who were aged ≥50 years and had a first-time diagnosis of liver cancer for the period between 2005 and 2008. Controls were pair matched to cases by age, sex, and index date. Adjusted odds ratios (ORs) and 95% CIs (95% confidence intervals) were estimated using multiple logistic regression.**

RESULTS: **We examined 1,166 liver cancer cases and 1,166 controls. Compared with the group with no use of statins, the adjusted ORs were 0.62 (95% CI = 0.42–0.91) for the group having been prescribed statins below 215.4 defined daily dose (DDD) and 0.63 (95% CI = 0.37–1.06) for the group with cumulative statin use ≥215.4 DDD. The ORs for the group with cumulative statin use ≥215.4 DDD were not statistically significant, but this may be due to the relatively small number of subjects.**

CONCLUSIONS: **The results of this study suggest that statins may reduce the risk of liver cancer.**

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INTRODUCTION

Statins are inhibitors of 3-hydroxy-3-methyl glutaryl coenzyme A reductase, which is a key enzyme in the rate-limiting step in cholesterol synthesis (1). Statins are commonly used as cholesterol-lowering medications and have shown effectiveness in the primary and secondary prevention of heart attack and stroke (2,3). Extensive evidence has led to widespread use of these drugs.

Rodent studies have indicated that statins are carcinogenic (4). In contrast, several recent studies of human cancer cell lines and animal tumor models have indicated that statins may have chemopreventive properties through the arresting of cell-cycle progression (5), inducing apoptosis (1,6), suppressing angiogenesis (7,8), and inhibiting tumor growth and metastasis (9,10). Results of meta-analysis and observational studies revealed either no association (11–18) or even a decreased cancer incidence (19–26). The reasons for the varying results are unclear, but may relate to methodological issues, including small sample size and short follow-up periods (27).

Statins are generally well tolerated and have a safe side-effect profile, with the most concerning adverse effects being hepatotoxicity and myotoxicity (28). Few epidemiological studies have investigated the association between statin use and risk of liver cancer. One clinical trial of death due to hepatocellular carcinoma noted a suppression of tumor cell growth and extended survival time with the use of pravastatin (29). In a population-based cohort study conducted in Denmark, no statistically significant elevated risk was observed for liver cancer, which was based on a small number (five cases), among users of statins (27). A recent nested case–control study found that statin use is associated with a significant reduction in the risk of hepatocellular carcinoma among patients with diabetes (30).

As a large number of people use statins on a long-term basis, and because epidemiological evidence for a link between statin use and risk of liver cancer is limited, we undertook this study in Taiwan to determine whether statin use is associated with a decreased risk of liver cancer.

METHODS

Data source

The NHI (National Health Insurance) program, which provides compulsory universal health insurance, was implemented in

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Taiwan on 1 March 1995. Under the NHI program, 98% of the island's population receives all forms of health-care services, including outpatient services, in-patient care, Chinese medicine, dental care, childbirth, physical therapy, preventive health care, home care, and rehabilitation for chronic mental illness. In cooperation with the Bureau of NHI, the NHRI (National Health Research Institute) of Taiwan randomly sampled a representative database of 1,000,000 subjects from the entire NHI enrollees using a systematic sampling method for research purposes. There were no statistically significant differences in age, gender, and health-care costs between the sample group and all enrollees, as reported by the NHRI. This data set (from January 1996 to December 2008) includes all claim data for these 1,000,000 subjects, and offers a good opportunity to explore the relationship between the use of statins and the risk of liver cancer. These databases have previously been used for epidemiological research, and information on prescription use, diagnoses, and hospitalizations has been shown to be of high quality (31–33).

As the identification numbers of all individuals in the NHRI databases were encrypted to protect the privacy of individuals, this study was exempt from full review by the Institution Review Board.

Identification of cases and controls

Cases consisted of all patients who were aged ≥50 years and had a first-time diagnosis of liver cancer (International Classification of Diseases, 9th revision, Clinical Modification (ICD-9-CM) Code 155) over a 4-year period, from 1 January 2005 to 31 December 2008, and who had no previous diagnosis of cancer.

Controls comprised patients who were admitted to the hospital for diagnoses that were unrelated to statin use, including orthopedic conditions, trauma (excluding wrist and hip fractures), and other conditions (such as acute infection, hernia, kidney stones, cholecystitis) (13,34). Wrist and hip fractures were excluded because previous studies have reported a reduced risk of osteoporosis among statin users (35–38). Control patients were pair matched to cases by sex, year of birth, and index date, and they were without a previous cancer diagnosis. For controls, the index date (date of hospital admission) was within the same month of the index date (date of first-time diagnosis of liver cancer) of their matched cases.

Exposure to statins

Information on all statin prescriptions was extracted from the NHRI prescription database. We collected the date of prescription, the daily dose, and the number of days supplied. The defined daily doses (DDDs) recommended by the WHO (World Health Organization) (39) were used to quantify usage of statins. Cumulative DDD was estimated as the sum of dispensed DDD of any statins (namely lovastatin, pravastatin, rosuvastatin, fluvastatin, simvastatin, or atorvastatin) from 1 January 1996 to the index date.

Potential confounders

For all individuals in the study population, we obtained potential confounders that are documented risk factors for liver cancer, including hepatitis B virus (HBV) infection (codes 070.22, 070.23, 070.32, 070.33, V02.61), hepatitis C virus (HCV) infection (codes 070.41, 070.44, 070.51, 070.54, V02.62), cirrhosis (codes 571.2, 571.5, 571.6), alcoholic liver disease (codes 571.0, 571.1, 571.3), and diabetes (30), recorded between 1 January 1996 and the index date. In addition, we also obtained prescription data for nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, and other lipid-lowering drugs (including fibrate, niacin, bile acid-binding resins, and miscellaneous), medications that potentially could confound the association between statin use and cancer risk. We defined users of the above-mentioned medications as patients with at least one prescription over 1 year before the index date. Furthermore, the number of hospitalizations 1 year before the index date was treated as confounders.

Statistics

For comparisons of proportions, χ^2 statistics were used. A conditional logistic regression model was used to estimate the relative magnitude in relation to the use of statins. Exposure was defined as patients who received at least one prescription for a statin at any time between 1 January 1996 and the index date. In the analysis, subjects were categorized into one of the three statin exposure categories: nonusers (subjects with no prescription for any statins at any time between 1 January 1996 and the index date), users of doses equal to or below the median (≤215.4), and users of doses above the median based on the distribution of use among controls. Odd ratios (ORs) and their 95% CIs (95% confidence intervals) were calculated using patients with no exposure as the reference. Analyses were performed using the SAS statistical package (version 8.02, SAS Institute, Cary, NC). All statistical tests were two sided. Values of $P < 0.05$ were considered statistically significant.

RESULTS

A total of 1,227 liver cancer cases with completed records were collected for the period 2005–2008. Of the 1,227 cases ascertained, no controls could be found for 61 of the cases.

Records from 1,166 liver cancer cases and 1,166 selected matched controls are included in the analyses of liver cancer risk. **Table 1** presents the distribution of demographic characteristics and selected medical conditions of liver cancer cases and controls. The liver cancer case group had a significantly higher rate of HBV, HCV, cirrhosis, alcoholic liver disease, and diabetes. However, the case group had a significantly lower rate of use of statins and other lipid-lowering drugs.

The relationship between the use of statins and liver cancer is shown in **Table 2**. Ever-use of any statin was associated with a reduced risk of liver cancer (OR = 0.53, 95% CI = 0.41–0.69). When statin users were stratified by the cumulative quantity of statin doses, statin use was statistically significantly associated with a decreased crude OR for liver cancer risk. Adjustments for possible confounders (namely matching variables and use of other lipid-lowering drugs, HBV, HCV, cirrhosis, alcoholic liver disease, diabetes, and number of hospitalizations) only slightly alter the OR (the inverse association was somewhat weaker). Compared with

Table 1. Demographic characteristics of liver cancer cases and controls

Variable	Cases (*n*=1,166)	Controls (*n*=1,166)	OR (95% CI)	*P*-value
Age (mean±s.d.)	66.08±9.76	65.92±9.65	—	0.684
Female sex (%)	363 (31.13)	363 (31.13)	—	—
No. of hospitalizations	0.53±1.05	0.42±0.96	—	0.007
HBV (%)	279 (23.93)	62 (5.32)	5.60 (4.20–7.48)	<0.001
HCV (%)	293 (25.13)	41 (3.52)	9.21 (6.54–12.92)	<0.001
Cirrhosis (%)	459 (39.37)	57 (4.89)	12.63 (9.44–16.90)	<0.001
Alcoholic liver disease (%)	68 (5.83)	29 (2.49)	2.43 (1.56–3.78)	<0.001
Diabetes (%)	476 (40.82)	398 (34.13)	1.33 (1.13–1.58)	<0.001
Coronary heart disease (%)	415 (35.59)	422 (36.19)	0.97 (0.82–1.15)	0.763
Aspirin (%)	81 (6.95)	81 (6.95)	1.00 (0.73–1.38)	1.000
NSAID (%)	652 (55.92)	720 (61.75)	0.79 (0.67–0.93)	0.004
ACEI (%)	122 (10.46)	132 (11.32)	0.92 (0.71–1.19)	0.506
Statins (%)				
Any statin	117 (10.03)	195 (16.72)	0.53 (0.41–0.69)	<0.001
Lovastatin	32 (2.74)	45 (3.86)	0.70 (0.44–1.11)	0.132
Pravastatin	11 (0.94)	26 (2.23)	0.42 (0.21–0.85)	0.013
Rosuvastatin	16 (1.37)	33 (2.83)	0.48 (0.26–0.87)	0.014
Fluvastatin	23 (1.97)	41 (3.52)	0.55 (0.33–0.93)	0.023
Simvastatin	26 (2.23)	51 (4.37)	0.50 (0.31–0.81)	0.004
Atorvastatin	50 (4.29)	92 (7.89)	0.52 (0.37–0.75)	<0.001
Use of other lipid-lowering drugs (%)	26 (2.23)	46 (3.95)	0.56 (0.34–0.90)	0.017

ACEI, angiotensin-converting enzyme inhibitor; CI, confidence interval; HBV, hepatitis B virus; HCV, hepatitis C virus; NSAID, nonsteroidal anti-inflammation drugs; OR, odds ratio.

no use of statins, the adjusted ORs were 0.62 (95% CI = 0.42–0.91) for the group with cumulative statin use below 215.4 DDD and 0.63 (95% CI = 0.37–1.06) for the group with cumulative statin use ≥215.4 DDD. The ORs for the group with cumulative statin use ≥215.4 DDD was not statistically significant, but this may be due to the relatively small number of subjects. Although the ORs remained below one, risk reduction was not consistently enhanced with increasing cumulative DDD. This lack of a trend in risk reduction with increasing cumulative DDD of statin use may be due to the relatively small amount of variation in cumulative DDD.

DISCUSSION

In this population-based case–control study, we found that statin use below 215.4 DDD in cumulative dose is associated with a 38% risk reduction in liver cancer as compared with individuals who did not use statins after controlling for potential confounders. The risk reduction observed in our study is of similar magnitude to those observed in the study by El-Serag *et al.* (30), which reported a risk reduction with statin use that ranged between 25 and 40%.

We found no consistent trends in risk reduction with having >215.4 DDD. However, there was a trend toward stronger risk reduction with longer and more frequent statin prescriptions in the study by El-Serag *et al.* (30). The relatively small number of users having statin use >215.4 DDD (only 32 cases and 63 controls were examined) in our study did not allow for a comprehensive trend evaluation. The above-mentioned study was conducted among patients with diabetes, which was related to the known higher likelihood of developing hepatocellular carcinoma and to the higher likelihood of using statins to treat commonly found lipid abnormalities (30). Using a study that is restricted to patients with major risk factors in epidemiological study means that the results of the restricted study may not necessarily apply to the portion of the population that was excluded. Whether an inverse dose-response effect only occurs among patients who are already at a higher risk of liver cancer requires further study.

The mechanism by which statin use may decrease liver cancer risk is not well understood. Yet, several potential mechanisms have been investigated, including the following: (i) inhibition of downstream products of the mevalonate pathway, namely primary geranylgeranyl pyrophosphate and farnesyl pyrophosphate (40–42).

Table 2. Associations between statin use and liver cancer risk in a population-based case–control study, Taiwan, 2005–2008

	No. of cases/no. of controls	Crude OR (95% CI)	Adjusted OR (95% CI)[a]
Overall			
No statin use	1,049/971	1.00	1.00
Any statin use	117/195	0.53 (0.41–0.69)	0.62 (0.45–0.83)
Cumulative use			
0	1,049/971	1.00	1.00
≤215.4 DDD	85/132	0.56 (0.42–0.76)	0.62 (0.42–0.91)
>215.4 DDD	32/63	0.47 (0.30–0.72)	0.63 (0.37–1.06)

CI, confidence interval; DDD, defined daily dose; HBV, hepatitis B virus; HCV, hepatitis C virus; OR, odds ratio.

[a]Adjusted for matching variables, number of hospitalizations, diabetes, HBV infection, HCV infection, cirrhosis, alcoholic liver disease, and use of other lipid-lowering drugs.

Derivatives of the mevalonate pathway, namely geranylgeranyl pyrophosphate and farnesyl pyrophosphate, are important in the activation of a number of cellular proteins, including small guanosine-5′-triphosphate-binding proteins, such as K-ras, N-ras, and the Rho family (40–42). Statins interfere with the production of geranylgeranyl pyrophosphate and farnesyl pyrophosphate and disrupt the growth of malignant cells, eventually leading to apoptosis (1). (ii) Statins inhibit the activation of the proteasome pathway, limiting the breakdown of both p21 and p27, allowing these molecules to exert their growth-inhibitory effects and in turn to retard cancer cell mitosis (43,44). (iii) It has been shown that HCV replication depends in part on geranylgeranylation of a host protein but HCV-RNA replication is disrupted by high concentrations of statins (45). The effect was due to severe depletion of mevalonic acid, which in turn led to low cellular levels of geranylgeranyl pyrophosphate (45).

One of the strengths of our study is the use of a computerized database, which is population based and is highly representative. As we included all patients newly diagnosed with liver cancer from 2005 to 2008, and because the control subjects in this study were selected from a simple random sampling of an insured general population, we can rule out the possibility of selection bias. Statins were available only on prescription. As statin use data were obtained from an historical database that collects all prescription information before the date of liver cancer, therefore the recall bias for statin use was avoided.

Several limitations of this study should be noted. First, although we adjusted for several potential confounders in the statistical analysis, a number of possible confounding variables, including body mass index, smoking, and alcohol use, which are associated with liver cancer 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. Using pharmacy records representing dispensing data rather than usage data might have introduced an overestimation of statin use. However, there is no reason to assume that this would be different for cases and controls. Even if patients did not take all of the statins prescribed, our findings would underestimate the effect of statin use. Third, lovastatin and pravastatin (available in 1990), simvastatin (available in 1992), and fluvastatin (available in April 1996) became available before patient enrollment in the database. Prescriptions for these drugs before 1996 would not be captured in our analysis. This could have underestimated cumulative DDDs and may weaken the observed association. In addition, some exposure misclassification was likely caused by the fact that information on prescription was available only since 1996. However, such misclassification was likely to be nondifferential, which would tend to underestimate rather than overestimate the association. Fourth, we are unable to separately analyze the risks for users of distinct statins because of the relatively small number of statin users. Fifth, our findings may have been confounded by indication for statin use if patients with liver disease (including elevated liver enzymes, alcoholic liver disease, HCV, HBV, and cirrhosis) were less likely to be prescribed statins, which could lead to a spurious inverse association between statin use and liver cancer. We tried to lower the possible effect of confounding by indication by adjusting for liver diseases (including alcoholic liver disease, HCV, HBV, and cirrhosis) in the statistical model and found that the adjustment attenuated the observed inverse association between statin use and liver cancer. Furthermore, we believe that the choice made between statins and other lipid-lowering drugs by treating physicians and their patients was not based on cancer risks. Finally, as with any observational study, residual confounding by unmeasured factors which are different between cases and controls is also possible.

In summary, results of this study demonstrate a 38% risk reduction for liver cancer with statin use below 215.4 DDD as compared with individuals who did not use statins. Given the widespread use of statins, this magnitude of risk reduction would have a substantial public health impact. Our study suggests that statins have a potential role in the chemoprevention of liver cancer. Further and larger studies, particularly prospective randomized trial studies, are necessary to confirm our findings and the value of statins in liver cancer prevention and treatment.

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CONFLICT OF INTEREST

Guarantor of the article: Chun-Yuh Yang, PhD, MPH.

Specific author contributions: Drafting of the manuscript: Hui-Fen Chiu; performed the statistical analysis: Shu-Chen Ho; data interpretation: Chih-Cheng Chen; study concepts and design, acquisition of

data, revised and edited the manuscript: Chun-Yuh Yang.

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Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Experimental studies have shown that statins have potential protective effects against cancer.
- ✓ Very few (only three) studies have investigated the association between statin use and risk of liver cancer, and the results are inconsistent.

WHAT IS NEW HERE

- ✓ Statins are associated with a reduction in the risk of liver cancer.
- ✓ There was no dose–response relationship between statin use and the risk of liver cancer.

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