Statins are associated with a reduced risk of cholangiocarcinoma: a population-based case–control study

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT
- No effective strategies for the prevention of cholangiocarcinoma (CCA) have been developed.
- Statins are cholesterol-lowering agents which possess pleiotropic properties and the use of statins may reduce cancer risk.

WHAT THIS STUDY ADDS
- Statin use is significantly associated with reduced risk of CCA (adjusted OR 0.80, 95% CI 0.71, 0.90).
- The protective relationship between CCA and statins appears to havesome variation among individual statins.

AIMS
Cholangiocarcinoma (CCA) is the second most common primary liver cancer in the world. Due to the lack of effective treatments, the survival rate of CCA is low and it is usually considered difficult to diagnose early. To date, no effective strategies for the prevention of CCA have been developed. Statins are cholesterol-lowering agents which possess pleiotropic properties and the use of statins may reduce cancer risk. The aim of the study was to investigate the effect of statin use on the risk of CCA.

METHODS
We used nationwide insurance data to perform a case–control study including 3174 CCA patients diagnosed in 2002–2011 and 3174 propensity score matched controls. Odds ratios (ORs) and 95% confidence intervals (CI) were calculated to assess the association between CCA risk and statin use by type of statin and dose.

RESULTS
Patients with CCA were slightly younger than controls with mean ages of 67.4 (SD 12.3) and 68.5 (SD 13.2) years ($P = 0.001$), respectively, and had less users of statins (22.7 vs. 26.5%, $P < 0.001$). The overall adjusted OR of statin use associated CCA was 0.80 (95% CI 0.71, 0.90) and lowered for those with longer medications. The OR ranged from 0.65 to 0.77. Stronger dose–response association was seen when using lovastatin.

CONCLUSIONS
Statin use is associated with reduced risk of CCA and there is a dose–response relationship between the use of statins and risk of CCA.

Introduction

Cholangiocarcinoma (CCA) and hepatocellular carcinoma are the major primary liver cancers. CCA is composed of cells resembling those of the bile duct and is the second most common hepatic malignancy, accounting for about 3% of malignancies of the digestive system [1, 2]. CCA and hepatocellular carcinoma are morphologically, genomically and clinically highly heterogeneous with a dismal clinical outcome [3, 4]. CCA is considered difficult to diagnose early, due to the lack of effective treatments and the survival rate is low [1, 5, 6]. The risk of CCA is increased with liver fluke infection, hepatitis B and C virus infection, cirrhosis, alcohol consumption and hepatolithiasis [2, 7, 8]. At present, there are no definite strategies for CCA prevention, and epidemiological data indicate that chemoprevention provides no protective effect against the development of CCA [9, 10].

Statins inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase [11]. Traditionally, they are primarily used as cholesterol-lowering agents, but in recent years additional effects of statins have been revealed, including anti-inflammation, immunomodulation and anti-tumour effects [12–14]. Statins have pleiotropic effects and may exert beneficial effects in the field of cancer chemoprevention [15–17]. Statin use has been reported to have a promising anti-cancer effect with studies showing decreased risk of cancer in hepatocellular carcinoma [18, 19], pancreatic cancer [20, 21], oesophageal cancer [22], gastric cancer [23, 24], colorectal cancer [25, 26] and lung cancer [27, 28]. However, the putative anti-cancer effect of statins remains controversial [29, 30]. To date, the effect of statins on CCA has not been fully elucidated, and statins have not been considered or proved as chemoprevention agents in CCA [10].

Most patients with CCA are diagnosed and treated at an advanced stage, and often these patients are deemed poor candidates for curative surgery. Conventional chemotherapy and radiation therapy have not been shown to be effective in terms of long term survival, and endoscopic treatment with photodynamic therapy combined with stenting has been reported to be effective as a palliative but not curative treatment. There is an urgent need to develop novel chemopreventive and adjuvant strategies for CCA. Studies on statin use and risk of other cancer types, including hepatocellular carcinoma, indicate that the role of statins in chemoprevention for CCA warrants further investigation.

The aim of the present study was to investigate whether individuals taking statins are at reduced risk of CCA using the National Health Insurance Research Database (NHIRD) of Taiwan. Comorbidities including diabetes, cirrhosis, hepatitis infection, inflammatory bowel disease, pancreatic disease and biliary disease were considered as covariates. The dose–response relationship with statins was evaluated in this study.

Methods

Data source

The National Health Insurance (NHI) programme of Taiwan is a compulsory health insurance programme, providing comprehensive medical coverage for all residents. Approximately 99% of 23.74 million people enrolled in the programme by 2009 [31]. The National Health Research Institutes (NHRI) has been in charge of managing NHIRD for claims data. Information on inpatient care, ambulatory care, dental care, prescription drugs and costs are available in the NHIRD. Data provided to researchers contained scrambled identification numbers associated with the relevant claims information, which includes the patient gender, date of birth, registry of medical services and medication prescriptions. Similar identification numbers were encrypted to all data files for linking data in accordance with privacy protocols. International Classification of Diseases-9-Clinical Modification (ICD-9-CM) codes were used to define diseases in the database. This study was approved by the Ethics Review Board of the China Medical University (CMU-REC-101-012).

Subject selection

Figure 1 shows the procedure for selecting cases and controls, from two data sets of the NHIRD: 1) Cases were identified from the Registry of Catastrophic Illnesses Patient Database (RCIPD), containing health claims data for catastrophic illnesses from 1997 to 2011. Thirty categories of diseases requiring long term care were registered, including cancer. The insurance programme exempts beneficiaries from some obligations to reduce their financial burden. Cases comprised the CCA patients (ICD-9-CM codes 155.1 and 156.1) aged over 20 years newly diagnosed between 2002 and 2011. The CCA diagnosis date was defined as the index date. 2) Control subjects were identified from the Longitudinal Health Insurance Database 2000 (LHID 2000), a database containing the claims data from 1996 to 2011 for 1 million people randomly sampled from 2000 NHIRD enrolment records. The distribution of gender, age and health care costs of the LHID2000 was similar to that of all insured enrollees, as reported by the NHRI in Taiwan. Individuals with previous cancer (ICD-9-CM code 140-208) or incomplete information in both groups were excluded (Figure 1). The CCA cases and controls were selected at a ratio of 1 : 1 matching on propensity score and the diagnosis date. We used a logistic regression model to calculate the propensity score. The potential confounders to be considered were age, gender, medication with aspirin and metformin, Charlson comorbidity index score and comorbidities of diabetes (ICD-9-CM codes 250), cirrhosis (ICD-9-CM codes 571), chronic pancreatitis (ICD-9-CM codes 577.1), hepatitis B infection (ICD-9-CM codes V02.61, 070.20, 070.22, 070.30, 070.32), hepatitis C infection (ICD-9-CM codes V02.62, 070.41, 070.44, 070.51,070.54), gastric disease
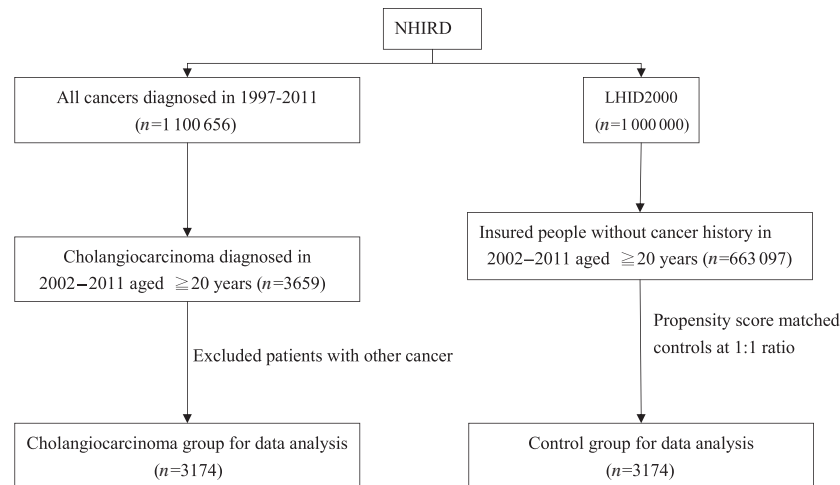
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                                    ┌──────────┐
                                    │  NHIRD   │
                                    └────┬─────┘
                    ┌────────────────────┴────────────────────┐
                    ▼                                          ▼
        ┌──────────────────────────┐              ┌──────────────────────────┐
        │ All cancers diagnosed in │              │        LHID2000           │
        │       1997-2011          │              │     (n=1 000 000)         │
        │     (n=1 100 656)        │              │                           │
        └────────────┬─────────────┘              └────────────┬─────────────┘
                     ▼                                          ▼
        ┌──────────────────────────┐              ┌──────────────────────────┐
        │ Cholangiocarcinoma       │              │ Insured people without    │
        │ diagnosed in             │              │ cancer history in         │
        │ 2002−2011 aged ≧20 years │              │ 2002−2011 aged ≧20 years  │
        │ (n=3659)                 │              │ (n=663 097)               │
        └────────────┬─────────────┘              └────────────┬─────────────┘
             Excluded patients                      Propensity score matched
             with other cancer                      controls at 1:1 ratio
                     ▼                                          ▼
        ┌──────────────────────────┐              ┌──────────────────────────┐
        │ Cholangiocarcinoma group │              │ Control group for data    │
        │ for data analysis        │              │ analysis                  │
        │ (n=3174)                 │              │ (n=3174)                  │
        └──────────────────────────┘              └──────────────────────────┘
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Figure 1

The flow chart for selecting cholangiocarcinoma cases and non-cholangiocarcinoma controls. NHRID: the National Health Insurance Research Database; LHID 2000: the Longitudinal Health Insurance Database 2000, a database containing the claims data from 1996 to 2011 for 1 million people randomly sampled from 2000 NHRID enrollment records

(ICD-9-CM codes 530-533), haemochromatosis (ICD-9-CM codes 275.0), inflammatory bowel disease (ICD-9-CM codes 556, 555), biliary tract disease (ICD-9-CM codes 751.69, 571.6, 574, 575.0-575.1, 121.0-121.1, 121.3), stroke (ICD-9-CM codes 430-438), CAD (ICD-9-CM codes 410-414), COPD (ICD-9-CM codes 491, 492, 496) and alcohol-related illness (ICD-9-CM codes 291, 303, 305, 571.0, 571.1, 571.2, 571.3, 790.3, A215, and V11.3).

Measurements of statins

The records of statin use were retrieved from ambulatory and inpatient claims data, including the cumulative defined daily dose (DDD) of each type of statin and day prescribed for cases and controls. Statins provided in the insurance programmes were simvastatin (ATC C10AA01), lovastatin (ATC C10AA02), pravastatin (ATC C10AA03), fluvastatin (ATC C10AA04), atorvastatin (ATC C10AA05) and rosuvastatin (ATC C10AA07). We calculated combined doses of all types of statin prescribed for the CCA case group and control group.

Statistical analysis

We compared proportionate distributions of gender, age (≤64 years, 65–74 years, ≥75 years), statin medication history and comorbidities between CCA cases and controls and examined the significance levels using a Chi-square test. The t-test was used to examine differences for continuous variables. The conditional logistic regression analysis was used to calculate odds ratios (ORs) and 95% confidence intervals (95% CIs) for the association between CCA and statin uses. ORs associated with uses of all types of statin together and individual statins were analyzed. Dose–response relationships were also measured. The cumulative DDD for all statins were stratified into quartiles. For each type of statin, the cumulative DDD was partitioned

into two levels by the median dose. All statistical analyses were performed using the SAS statistical package (version 9.2 for Windows; SAS Institute, Inc., Cary, NC, USA).

Results

Demographic data

We identified 3174 CCA cases diagnosed between 2002 and 2011 and 3174 controls of non-CCA patients also between 2002 and 2011. Of the 3174 CCA patients, 40.6% were younger than 64 years old and 50.9% of them were men (Table 1). The mean ages of patients in the CCA and controls groups were 67.4 (±12.3) and 68.5 (± 13.2) years, respectively. Patients with CCA tended to have a lower prevalence of statin use than subjects in the control group (all P values <0.001).

Risk of CCA and association with individual statins

Table 2 shows the ORs of estimated CCA risk based on statin use. Use of a statin was associated with a significantly reduced risk of CCA (OR 0.80, 95% CI 0.71, 0.90). Results that measured for individual statins were all significant, ranging from 0.65 (95% CI 0.52, 0.82) for pravastatin and rosuvastatin to 0.77 (95% CI 0.61, 0.96) for fluvastatin.

CCA risk by cumulative DDD dose of statin

Table 3 shows the dose–response relationship between statin use and CCA risks, compared with non-users. Of all types of statin combined, the OR decreased from 0.86 (95% CI 0.70, 1.05) for those on < 50 cumulative DDD to 0.78 (95% CI 0.66, 0.9) for those on ≥ 150 cumulative DDD. For individual statins, CCA risk was the lowest in patients using ≥80 cumulative DDD of lovastatin (OR 0.55, 95% CI 0.41, 0.73), followed by ≥55 cumulative DDD of pravastatin

Table 1

Baseline characteristics compared between cholangiocarcinoma and control groups

	Control n = 3174		CCA n = 3174		
	n	%	n	%	P value
Age group (years)					0.001
≤64	1183	37.3	1289	40.6	
65–74	880	27.7	933	29.4	
≥75	1111	35.0	952	30.0	
Mean (SD) (years)*	68.5	13.2	67.4	12.3	0.001
Gender					0.78
Female	1548	48.8	1559	49.1	
Male	1626	51.2	1615	50.9	
Medications					
Statin	840	26.5	720	22.7	<0.001
Aspirin	1515	47.7	1534	48.3	0.63
Metformin	714	22.5	732	23.1	0.59
CCI score‡					0.15
0	1510	47.6	1596	50.3	
1	967	30.5	898	28.3	
2	350	11.0	350	11.0	
3 or more	347	10.9	330	10.4	
Baseline co-morbidities					
Diabetes	767	24.2	772	24.3	0.88
Cirrhosis	1826	57.5	1818	57.3	0.84
Chronic pancreatitis†	35	1.10	34	1.07	0.90
Hepatitis B infection	569	17.9	537	16.9	0.29
Hepatitis C infection	320	10.1	323	10.2	0.90
Gastric disease	2152	67.8	2124	66.9	0.45
Haemochromatosis†	1	0.03	1	0.03	0.99
Inflammatory bowel disease	94	2.96	94	2.96	0.99
Biliary tract disease	1267	39.9	1303	41.1	0.36
Stroke	371	11.7	346	10.9	0.32
CAD	999	31.5	1021	32.2	0.55
COPD	686	21.6	713	22.5	0.41
Alcohol-related illness	263	8.29	271	8.54	0.72

Chi-square test, *t-test and †Fisher-exact test comparing subjects with and without CCA. Data are presented as the number of subjects in each group, with percentages given in parentheses. CCA cholangiocarcinoma ‡CCI score, Charlson comorbidity index score.

(OR 0.64, 95% CI 0.44, 0.94), ≥80 cumulative DDD of simvastatin (OR 0.74, 95% CI 0.56, 0.98) and ≥65 cumulative DDD of atorvastatin (OR 0.78, 95% CI 0.62, 0.98). Compared with non-statin users, CCA risk was the lowest in patients using <300 cumulative DDD of fluvastatin (OR 0.68, 95% CI 0.47, 0.99). Fluvastatin was also associated with significant reduction in odds of CCA in <300 cumulative DDD (OR 0.68, 95% CI 0.47, 0.99).

Discussion

This population-based nationwide study demonstrated a dose–response protective relationship between the use

Table 2

Odds ratio and 95% confidence intervals of cholangiocarcinoma associated with statin uses

Variable	Cases/Controls 3174/3174	OR	(95% CI)
Medications	n1/n2		
All statins	720/840	0.80	(0.71, 0.90)***
Individual statin			
Simvastatin	262/368	0.68	(0.57, 0.80)***
Lovastatin	244/337	0.69	(0.58, 0.83)***
Pravastatin	131/197	0.65	(0.52, 0.82)***
Fluvastatin	143/183	0.77	(0.61, 0.96)*
Atorvastatin	357/489	0.69	(0.60, 0.80)***
Rosuvastatin	141/210	0.65	(0.52, 0.82)***

n, number of persons on the medicine. **$P < 0.01$, ***$P < 0.001$

Table 3

Odds ratio and 95% confidence intervals of cholangiocarcinoma associated with cumulative DDD dose of statin uses

Non-use of statins	Case numbers/ control numbers 2454/2334	Odds ratio 1.00	(95% CI) (reference)
All statins*			
<50 DDD	210/227	0.86	(0.70, 1.05)
50 − 149 DDD	157/187	0.79	(0.64, 0.99)*
≥ 150 DDD	353/426	0.78	(0.66, 0.91)**
P for trend		<0.001	
Simvastatin†			
<80 DDD	131/163	0.76	(0.58, 0.99)*
≥80 DDD	118/148	0.74	(0.56, 0.98)*
Lovastatin†			
<80 DDD	136/160	0.74	(0.57, 0.96)*
≥80 DDD	107/162	0.55	(0.41, 0.73)***
Pravastatin†			
<55 DDD	62/77	0.72	(0.48, 1.08)
≥55 DDD	64/90	0.64	(0.44, 0.94)*
Fluvastatin†			
<300 DDD	64/89	0.68	(0.47, 0.99)*
≥300 DDD	73/71	1.22	(0.81, 1.84)
Atorvastatin†			
<65 DDD	165/196	0.84	(0.66, 1.08)
≥65 DDD	164/199	0.78	(0.62, 0.98)*
Rosuvastatin†			
<35 DDD	68/63	1.01	(0.66, 1.56)
≥35 DDD	57/74	0.75	(0.50, 1.12)

*The cumulative DDD dose is partitioned into three segments for the first quartile, second quartile and third and fourth quartiles combined. †The cumulative DDD dose is partitioned into two segments by median. *$P < 0.05$, **$P < 0.01$

of statins and odds of CCA. Overall, the CCA risk reduced by 20% based on measuring all statins combined. ORs measured by the cumulative DDD of individual statins also showed lowered risk of CCA for most subgroups of

individual statins. The stronger dose related reduction in CCA risk is more likely for those who have taken lovastatin and pravastatin. The beneficial association was also seen for those on simvastatin, lovastatin and fluvastatin. Our results demonstrated an important role of statin use associated with the reduced risk of CCA.

To the best of our knowledge, this is the first study demonstrating a protective relationship of statin use on CCA in a dose-dependent manner. The data were obtained from a large computerized database so the studied population was sufficient in size and highly representative. CCA patients and controls were selected by matching propensity score and diagnosis date to reduce bias. As the data on statin use were collected from a computerized database containing all available prescription information, the potential for bias with regard to medication was minimized. The statin prescriptions were required to be in accordance with national health insurance regulations with a definite diagnosis of increased serum lipid profiles.

The use of cholesterol-lowering agents has increased as part of the effort to improve nutrition, lifestyle habits and health care. Prolonged control of LDL cholesterol with statin treatment may be warranted in all patients at high risk of any type of major vascular event [32]. Besides their cholesterol-lowering effect, statins also exhibit pleiotropic properties including anti-inflammation, immunomodulation and anti-tumour effects [12, 13, 17]. In addition, statin use could reduce the risk of cancer [14, 17], and this effect has been demonstated in multiple organ systems, including the digestive system [18, 23, 25, 26, 33], respiratory system [27, 28], haematological system [34] and genitourinary system [35], as well as in breast [36] and skin tissues.

Whether statins reduce the risk of various cancers is controversial [29, 30, 37, 38] particularly with regard to the duration of statin use. Short term use of statins may not reduce cancer risk [16]. Our study did show a nonsignificant protection relationship on CCA for those on all statins of < 50 cumulative DDD. However, studies on cholesterol-reducing strategies suggest that the long term use of statins is recommended to protect against vascular events [32]. Thus, it appears that long term statin use may not be a cause for concern. However, a definitive baseline duration of statin use for cancer prevention or anti-cancer effect has not been established. In addition to the use of statins in cancer prevention, the combined treatment of statins and chemotherapy agents could be a promising new strategy for the treatment of certain tumour types [16].

The mechanism of statin use for reducing cancer risk is not well understood. Interestingly, the risk of cancer may be related to increased serum lipid concentrations or the pleiotropic properties of statins or both [37]. The mechanism by which lower cholesterol confers health benefits may involve its effects on membrane lipid organization possibly resulting in various molecular effects that might be effective for preventing and treating the

progression of malignant tumours [39]. Most of the molecular mechanisms reported in the literature involve the effect of statins on inhibition of cell proliferation and stimulation of apoptosis, and these results have also been demonstrated in cholangiocytes [40, 41].

There are several potential limitations to the present study. First, because this study was a retrospective cohort study based on computerized data, most of patients were presumed to comply with their prescribed medications. However, the true compliance rates among patients taking statins could not be evaluated. Second, unmeasured confounding factors, such as body mass index, smoking, alcohol intake, drug history and parasite infection, which may be associated with the effects of drugs and CCA, were not included in our database. Third, as this was a retrospective study, a definite diagnosis of CCA was not possible for all patients. However, experts must review the certificate for CCA with the aid of imaging or pathological results. Fourth, there was likely a range of variance in the registration of diagnosis of CCA as well as co-morbid diseases, but the effect of variance would be limited.

In conclusion, statin use may associated with reduced risk of CCA by 20% in this population-based nationwide study. The dose-dependent relationship between the use of statins and risk of CCA demonstrates a benefit of long term usage. However, the role of statin use for reducing cancer risk in chemoprevention, and its synergic effect with chemotherapy, as well as the baseline recommended duration of statin use require further study. The long term effect of statins on the incidence of CCA and other cancers also warrants further research.

Competing Interests

All authors state that they have no conflicts of interest.

Contributors

Conception and design: Yen-Chun Peng, Cheng-Li Lin, Chia-Hung Kao; Administrative support: Chia-Hung Kao; Collection and assembly of data: Yen-Chun Peng, Cheng-Li Lin, Chia-Hung Kao; Data analysis and interpretation: Yen-Chun Peng, Cheng-Li Lin, Chia-Hung Kao; Manuscript writing: All authors; Final approval of manuscript: All authors.

Financial support

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