Statins Are Associated With a Reduced Risk of Gastric 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 gastric 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 gastric cancer for the period between 2005 and 2008. The controls were matched to cases by age, sex, and index date. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were estimated by using multiple logistic regression.**

RESULTS: **We examined 337 gastric cancer cases and 1,348 controls. We found that ever-use of any statin was associated with a significant decrease in gastric cancer risk (OR = 0.68, 95% CI = 0.49–0.95). Compared with no use of statins, the adjusted ORs were 0.90 (95% CI = 0.60–1.36) for the group having been prescribed statins with cumulative defined daily doses (DDDs) < 134.25 and 0.49 (95% CI = 0.30–0.79) for the group with cumulative statin use of ≥134.25 DDDs. Also, there was a significant trend toward decreasing gastric cancer risk with increasing cumulative dose (χ^2 for linear trend = 7.42, P = 0.006).**

CONCLUSIONS: **The results of this study are the first to suggest that statins may reduce the risk of gastric 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). The extensive evidence has led to a widespread use of these drugs.

Rodent studies indicate that statins are carcinogenic (4). In contrast, several recent studies of human cancer cell lines and animal tumor models indicate 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 (19–28). The reasons for the varying results are unclear but may relate to methodological issues, including heterogeneous patient populations, small sample size, variable durations of statin exposure, and short follow-up periods (29).

Statins are well recognized as relatively safe drugs, although adverse effects include hepatotoxicity and myopathy at low incidence (30). Only three epidemiological studies have investigated the association between statin use and the risk of gastric cancer. All three studies reported a statistically nonsignificant inverse association between statin use and gastric cancer risk (15,16,23). As a large number of people utilize statins on a long-term basis, and as epidemiological evidence for a link between statin use and the risk of gastric cancer is limited, we undertook the present study in Taiwan to determine whether statin use is associated with a decreased risk of gastric cancer.

METHODS

Data source

The National Health Insurance (NHI) program, which provides compulsory universal health insurance, was implemented in Taiwan on 1 March 1995. Under the NHI, 99% of the island's

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population (23.12 million in 2009) receives all forms of health-care services including outpatient services, inpatient 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 National Health Research Institute (NHRI) 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 relation between the use of statins and the risk of gastric 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).

Because the identification numbers of all individuals in the NHRI databases were encrypted to protect the privacy of the 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 gastric cancer (International Classification of Diseases, 9th revision, Clinical Modification (ICD-9-CM) Code 151) 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 (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). We identified four control patients per case patient. Control patients were matched to the 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 gastric cancer) of their matched case. Under the conditions of detecting an odds ratio (OR) of 0.5 with 80% power at the 5% significance level, 20% of the population aged ≥50 years are statin users, and that a control-to-case of 4 is planned, the minimum number of cases required was estimated to be 169.

Exposure to statins

Information on all statin prescription 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 (39) were used to quantify the usage of statins. Cumulative DDD was estimated as the sum of dispensed DDDs of any statins (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 predictive factors for gastric cancer, including *Helicobacter pylori* eradication (40) and gastric, duodenal, and peptic ulcers (41), recorded between 1 January 1996 and the index date. In addition, we also obtained prescription data for medications for aspirin, nonsteroidal antiinflammatory drugs, proton pump inhibitors, and other lipid-lowering drugs (including fibrate, niacin, bile-acid binding resins, and miscellaneous) that could potentially 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 prior to index date. Furthermore, the number of hospitalizations 1 year before index date were 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, the 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), and users of doses equal to or below the median and above the median based on the distribution of use among controls. The ORs and their 95% confidence intervals (CIs) were calculated using patients with no exposure as the reference. The Wald χ^2 test for linear trend was performed by entering statin exposures as a three-level ordinal variable (with the values 0–2) in the logistic regression model. 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

Records from 337 gastric cancer cases and 1,348 selected matched controls are included in the analyses of gastric cancer risk. **Table 1** presents the distribution of demographic characteristics and selected medical conditions of the gastric cancer cases and controls. Cases had a significantly higher rate of gastric and peptic ulcers. However, the case group had a significantly lower rate of use of nonsteroidal antiinflammatory drugs. There was no significant difference between cases and controls in *H. pylori* eradication, aspirin use, and use of other lipid-lowering drugs.

The relationship between the use of statins and gastric cancer is shown in **Table 2**. A total of 16.6% of the cases and 22.1% of the controls had used any quantity of at least one prescription for a statin. Ever-use of any statin was associated with a decreased crude ORs for gastric cancer risk (OR = 0.70, 95% CI = 0.51–0.96). Adjustments for possible confounders (matching variables, number of hospitalization, *H. pylori* eradication, gastric ulcer, peptic ulcer, duodenal ulcer, and use of aspirin, nonsteroidal antiinflammatory drug, and other lipid-lowering drugs) only slightly altered the ORs; patients who received any prescriptions of statins had a

Table 1. Demographic characteristics of gastric cancer cases and controls

Variable	Cases (*n*=337)	Controls (*n*=1,348)	OR (95% CI)
Age (mean±s.d.)	69.64±10.18	69.51±10.07	*P*=0.82
No. of hospitalizations	0.35±0.86	0.50±1.14	*P*=0.01
HP eradication (%)	46 (13.65)	216 (16.02)	0.83 (0.59–1.17)
Gastric ulcer (%)	138 (40.95)	326 (24.18)	2.17 (1.69–2.79)
Peptic ulcer (%)	203 (60.24)	594 (44.07)	1.92 (1.51–2.45)
Duodenal ulcer (%)	53 (15.73)	227 (16.84)	0.92 (0.67–1.28)
Aspirin (%)	31 (9.20)	130 (9.64)	0.95 (0.63–1.43)
NSAIDs (%)	171 (50.74)	794 (58.90)	0.72 (0.57–0.91)
Use of other lipid-lowering drugs (%)	9 (2.67)	48 (3.56)	0.74 (0.36–1.53)

CI, confidence interval; HP, *Helicobacter pylori*; NSAID, nonsteroidal antiinflammatory drug; OR, odds ratio.

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

	No. of cases/no. of controls	Crude OR (95% CI)	Adjusted OR[a] (95% CI)
Overall			
No statin use	281/1,050	1.00	1.00
Any statin use	56/298	0.70 (0.51–0.96)	0.68 (0.49–0.95)
Cumulative use			
0	281/1,050	1.00	1.00
≤134.25 DDD	36/149	0.89 (0.60–1.32)	0.90 (0.60–1.36)
>134.25 DDD	20/149	0.51 (0.31–0.82)	0.49 (0.30–0.79)
	P for trend	χ^2=7.16, *P*=0.007	χ^2=7.42, *P*=0.006

CI, confidence interval; DDD, defined daily dose; OR, odds ratio.
[a]Adjusted for matching variable, number of hospitalization, Helicobacter pylori eradication, gastric ulcer, peptic ulcer, duodenal ulcer, and use of aspirin, nonsteroidal antiinflammatory drug (NSAID), and other lipid-lowering drugs.

32% decrease in the risk of gastric cancer compared with nonusers (adjusted OR=0.68, 95% CI=0.49–0.95).

When statin use was categorized by cumulative dose, the adjusted ORs were 0.90 (95% CI=0.60–1.36) for the group with cumulative statin use <134.25 DDDs and 0.49 (95% CI=0.30–0.79) for the group with cumulative statin use of ≥134.25 DDDs compared with nonusers. Also, there was a significant trend toward decreasing gastric cancer risk with increasing cumulative dose (χ^2 for linear trend=7.42, *P*=0.006).

DISCUSSION

In this population-based case–control study, ever-use of any statin was associated with a 32% decrease in gastric cancer risk. We also found that there was a significant trend toward decreasing gastric cancer risk with increasing cumulative dose after controlling for potential confounders.

To our knowledge, only three previous studies have examined the association between statin use and the risk of gastric cancer. In a case–control study that was conducted using the General Practice Research Database in United Kingdom, Kaye and Jick (16) reported an OR of 0.4 (95% CI=0.1–1.3) for stomach cancer in relation to current statin use. The British study was based on a small number (only four cases), and therefore had limited statistical power. Graaf *et al.* (23) used a pharmacy database in the Netherlands to define exposure and observed an OR of 0.88 (95% CI=0.36–2.15) for stomach cancer in relation to statin prescriptions. The number of gastric cancer case in our study (*n*=337) is threefold that in the Dutch nested case–control study (*n*=104). The power of the Dutch study was therefore also relatively limited. The inhibitory potency of different statins is not equal. Of the statin-exposed patients, 79.6% patients were prescribed simvastatin. However, the most commonly used statin was atorvastatin in Taiwan. The results of the Dutch study cannot be generalized to the use of other statins because of its relatively high frequency of simvastatin prescription. Recently, Haukka *et al.* (15) used data from Finland to evaluate statin use and also report no association between statin use and stomach cancer risk (relative risk=0.98, 95% CI=0.94–1.02). The Finnish study consisted of 472,481 pairs of individuals and examined 1,667 stomach cancer cases (770 for statin group, 897 in the control group) during 4.2 million person-years of follow-up period. The Finnish study, however, did not adjust for potential confounders such as *H. pylori* eradication, and gastric, duodenal, and peptic ulcers, which were adjusted for in our study. To our knowledge, our present study is the first epidemiological study to report that statin use may have a protective effect against gastric cancer.

The results of our study are consistent with the assumed biological mechanism of statins, although the mechanism whereby statin use may decrease gastric cancer risk is not well understood. Several potential mechanisms have been investigated, including the following. (i) Inhibiting downstream products of the mevalonate pathway, primary geranylgeranyl pyrophosphate (GGPP) and farnesylpyrophophosphate (FPP) (42–44). Derivatives of the mevalonate pathway GGPP and FPP 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 (42–45). Statins interfere with the production of GGPP and FPP and disrupt the growth of malignant cells, eventually leading to apoptosis (1). (ii) Statins inhibit the activation of the proteosome 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 (10,45,46).

To be eligible as a control disease, the control disease must not be associated with gastric cancer and statin exposure. If we included those diseases that were related to statin use as one of the control diseases, the cases and control groups will be forced to be more alike in terms of the proportion of statin use, and thus an underestimate of the association between statin use and the risk of gastric

cancer will result. Therefore, we chose control patients with diagnoses that we judged to be unrelated to statin use. This criterion is required from the methodological point of view and will also minimize the possibility of selection bias. We assessed the exposure to statins measured as the sum of dispensed DDDs of any statin from 1 January 1996 to the index date (cumulative DDDs). Cumulative DDD is a time-dependent variable in which the number of days of supplies of each statin prescription dispensed was summed over time from 1 January 1996 to the index date. The present study attempted to control for this possible bias by choosing controls who had exposure duration similar to the cases. In other words, cases and controls were matched on index date. This is the reason that we select controls from hospitalized patients, rather than a random sample of the 1,000,000 representative NHI enrollees who were free of cancer. One of the strengths of our study is the use of a computerized database, which is population based and is highly representative. Statins were available only on prescription. Because statin use data were obtained from a historical database that collects all prescription information before the date of gastric cancer, the recall bias for statin use was avoided.

Several limitations of the present study should be noted. First, although we adjusted for several potential confounders in the statistical analysis, a number of possible confounding variables, including smoking, alcohol use, diet, and occupation that are associated with gastric cancer, were not included in our database. Second, we were not able to contact the patients directly regarding 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 the patients did not take all of the statins prescribed, our findings would underestimate the effect of statin use. Third, lovastain and pravastatin (available in 1990), Simvastatin (available in 1992), and Fluvastatin (available in April, 1996) became available prior to patient enrollment in the database. Prescriptions for these drugs prior to 1996 would not be captured in our analysis. This could have underestimated the 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. Such misclassification, however, 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 cases and the relatively small number of statin users. Fifth, diagnoses of gastric cancer or any other comorbid medical conditions and prescription information that rely on administrative claims data may be less accurate than those obtained according to standardized criteria, and misclassification is possible. However, this misclassification is likely to be nondifferential (i.e., there is no reason to assume that this would be different for cases and controls) and therefore would tend to underestimate rather than overestimate the true association. Sixth, *H. pylori* infection is associated with gastric cancer development (47). There is no information available on this variable for an individual study subject and, hence, it could not be adjusted for directly in the analysis. However, there is no reason to believe that there would be any correlation between this variable and the use of statin. Furthermore, we found that gastric and peptic ulcers were more prevalent in the case group, whereas controls had a higher rate of *H. pylori* eradication (although not statistically significant). These features are consistent with previous findings (40,41) and increase the internal validity of our study. Seventh, we did not have information on the socioeconomic status of our study subjects. However, confounding by socioeconomic status is minimal because the NHI system in Taiwan has comprehensive coverage and allows patients to visit any clinic or hospital freely without referral by a general practitioner, and patients only need to pay a small co-payment (the co-payment for prescription is ~10% of the cost of the drugs dispensed). People in Taiwan have nearly no barriers to medical service in terms of accessibility and costs (48). Finally, as with any observational study, residual confounding by unmeasured factors that are different between cases and controls is also possible. However, the confounding effect of medical attention could be corrected for by introducing the number of hospitalizations into the conditional logistic regression model.

Numerous observational studies of various designs have demonstrated a positive association between the presence of anti-*H. pylori* antibodies and the risk of stomach cancer. The *H. pylori* infection appears to be the strongest and the most important risk factor for gastric cancer, especially for noncardia cancer (49). Although the ultimate proof of causality is still missing, a recent meta-analysis (50) showed that the pooled relative risk of developing gastric cancer after *H. pylori* eradication was 0.56 (95% CI = 0.4–0.8). These data were considered to be very suggestive that *H. pylori* eradication would protect against the development of gastric cancer (49). Efforts to improve the treatment of gastric cancer have had limited success. Population screening and treatment of *H. pylori* infection is likely to become the first target in future prevention strategies, particularly in high gastric cancer risk countries (49) such as Taiwan.

In summary, our study demonstrates that ever-use of any statin was associated with a 32% risk reduction for gastric cancer. There was also a trend toward stronger risk reduction with more statin prescriptions. Given the widespread use of statins, this magnitude of risk reduction would have a substantial public health impact. This study is the first to suggest that statins have a potential role in chemoprevention of gastric cancer. Further and larger studies, particularly prospective randomized trial studies, are necessary to confirm our findings and the value of statins in gastric cancer prevention and treatment.

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CONFLICT OF INTEREST

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

Specific author contributions: Hui-Fen Chiu: drafting of the manuscript; Shu-Chen Ho: performed the statistical analysis; Chih-Ching Chang and Trong-Neng Wu: interpretation of the data; Chun-Yuh Yang: study concepts and design, acquisition of the data revised, and edited the manuscript. All authors approved the final draft submitted.

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Potential competing interests: None.

Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Experimental studies have shown that statins have potential protective effects against cancer.
- ✓ Only three studies have investigated the association between statin use and the risk of gastric cancer.
- ✓ All three studies reported a statistically nonsignificant inverse association between statin use and gastric cancer risk.

WHAT IS NEW HERE

- ✓ Statins are associated with a reduction in the risk of gastric cancer.
- ✓ There was a dose-response relationship between statin use and the risk of gastric cancer.

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