Statin Use and the Risk of Pancreatic Cancer

A Population-Based Case-Control Study

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Objectives: The aim of this study was to investigate whether the use of statins was associated with pancreatic 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 50 years or older and had a first-time diagnosis of pancreatic cancer for the period between 2003 and 2008. The control subjects 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 190 pancreatic cancer cases and 760 control subjects. The unadjusted OR for any statin prescription was 1.07 (95% CI, 0.72–2.06), and the adjusted OR was 0.87 (95% CI, 0.56–1.36). Compared with no use of statins, the adjusted ORs were 1.06 (95% CI, 0.61–1.85) for the group having been prescribed statins with cumulative defined daily doses less than 114.33 and 0.71 (95% CI, 0.39–1.30) for the group with cumulative statin use of 114.33 defined daily doses or more.

Conclusions: This study does not provide support for a beneficial association between usage of statin and pancreatic cancer.

Key Words: pharmacoepidemiology, statins, pancreatic cancer, case-control study

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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 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.[19–27] The reasons for the varying results are unclear but may relate to methodological issues, including small sample size and short follow-up periods.[28]

Statins are generally well tolerated and have a safe side effect profile, with the most concerning adverse effects being hepatotoxicity and myotoxicity.[29] Few epidemiologic studies have investigated the association between statin use and risk of pancreatic cancer. Four studies reported a statistically nonsignificant inverse association between statin use and pancreatic cancer risk.[11,13,18,21] A recent nested case-control study, however, found that statin use is associated with a significant reduction in the risk of pancreatic cancer among half a million veterans.[26]

Because a large number of people use statins on a long-term basis, and because epidemiologic evidence for a link between statin use and risk of pancreatic cancer is limited, we undertook the present study in Taiwan to evaluate the association between statin use and pancreatic cancer risk.

MATERIALS AND METHODS

Data Source

The National Health Insurance (NHI) program, which provides compulsory universal health insurance, was implemented in Taiwan on March 1, 1995. Under the NHI, 98% of the island's population 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 by means of a systematic sampling method for research purposes. There were no statistically significant differences in age, sex, 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 risk of pancreatic cancer. This database has previously been used for epidemiological research, and information on prescription use, diagnoses, and hospitalizations has been shown to be of high quality.[30–32]

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 institutional review board.

Identification of Cases and Control Subjects

Cases consisted of all patients who were aged 50 years or older and had a first-time diagnosis of pancreatic cancer

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This study is based in part on data from the National Health Insurance (NHI) Research Database provided by the Bureau of NHI, Department of Health, and managed by the National Health Research Institute. The interpretation and conclusions contained herein do not represent those of Bureau of NHI, Department of Health, or National Health Research Institute. This study was partly supported by a grant from the National Science Council, Executive Yuan, Taiwan (NSC-96-2628-B-037-039-MY3).

TABLE 1. Demographic Characteristics of Pancreatic Cancer Cases and Control Subjects

Variable	Cases (n = 190)	Control Subjects (n = 760)	OR (95% CI)
Age, mean (SD), y	68.84 (10.41)	68.81 (10.37)	—
Female sex, n (%)	86 (45.26)	344 (45.26)	—
No. of hospitalizations, mean (SD)	0.48 (0.86)	0.27 (0.82)	$P = 0.003$
Diabetes,* n (%)	80 (42.11)	232 (30.53)	1.69 (1.21–2.35)
Chronic pancreatitis, n (%)	10 (5.26)	3 (0.39)	18.84 (4.11–86.35)
Use of other lipid-lowering drugs, n (%)	10 (5.26)	26 (3.42)	1.56 (0.74–3.28)

*Values are expressed as percentage of the presence of underlying comorbidity of diabetes.

(*International Classification of Diseases, Ninth Revision, Clinical Modification* code 157) over a 6-year period, from January 1, 2003, to December 31, 2008, and who had no previous diagnosis of cancer.

Control subjects 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).[13,33] Wrist and hip fractures were excluded because previous studies have reported a reduced risk of osteoporosis among statin users.[34–37] We identified 4 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 control subjects, the index date (date of hospital admission) was within the same month of the index date (date of first-time diagnosis of pancreatic 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 or older is 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 World Health Organization[38] were used to quantify usage of statins. For each year of the study period, the cumulative usage (in milligrams) for each statin was calculated based on all prescription dispensed in that year. The yearly usage was divided with the quantity corresponding to 1 DDD. Cumulative DDDs were estimated as the sum of dispensed DDD of any statins (lovastatin, pravastatin, rosuvastatin, fluvastatin, simvastatin, or atorvastatin) from January 1, 1996, to the index date.

Potential Confounders

For all individuals in the study population, we obtained potential confounders that are documented risk factors for pancreatic cancer, including diabetes mellitus (code 250) and chronic pancreatitis (code 577.1),[39] recorded between January 1, 1996, and index date. In addition, we also obtained prescription data for other lipid-lowering drugs (including fibrate, niacin, bile-acid–binding resins, and miscellaneous) and medications that potentially could confound the association between statin use and cancer risk. We defined users of the previously mentioned medications as patients with at least 1 prescription over 1 year before index date. Furthermore, the number of hospitalizations 1 year before index date was treated as a confounder.

Statistics

For comparisons of proportions, McNemar 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 1 prescription for a statin at any time between January 1, 1996, and the index date. In the analysis, the subjects were categorized into 1 of the 3 statin exposure categories: nonusers (subjects with no prescription for any statins at any time between January 1, 1996, and the index date), users of doses equal to or less than the median, and users of doses greater than the median based on the distribution of use among control subjects. Odds ratios and their 95% confidence intervals (CIs) were calculated using patients with no exposure as the reference. Analyses were performed using the SAS statistical package (version 8.02; SAS Institute Inc, Cary, NC). All statistical tests were 2-sided. $P < 0.05$ was considered statistically significant.

RESULTS

Records from 190 pancreatic cancer cases and 760 selected matched control subjects are included in the analyses of pancreatic cancer risk. Table 1 presents the distribution of demographic characteristics and selected medical conditions of the pancreatic cancer cases and control subjects. The mean ages were 68.84 years for pancreatic cancer cases and 68.81 years for the control subjects. The pancreatic cancer case group had a significantly higher rate of diabetes and chronic pancreatitis. Use of other lipid-lowering drugs was not significantly different between patients and control subjects (5.25% vs 3.42%).

The relationship between the use of statins and pancreatic cancer is shown in Table 2. The prevalent use of any statin was similar in pancreatic cancer cases and control subjects (crude OR, 1.07; 95% CI, 0.72–2.06). After adjustments for possible confounders (matching variables, diabetes, chronic pancreatitis, number of hospitalizations, and use of other lipid-lowering drugs), patients who received any prescriptions of statins had a 13% reduction in risk of pancreatic cancer compared with nonusers (adjusted OR, 0.87; 95% CI, 0.56–1.36). When statin use was categorized by cumulative dose, the adjusted ORs were 1.06 (95% CI, 0.61–1.85) for the group with cumulative statin use less than 114.33 DDDs and 0.71 (95% CI, 0.39–1.30) for the group with cumulative statin use of 114.33 DDDs or more compared with nonusers. No association was found between cumulative statin use and pancreatic cancer risk.

DISCUSSION

In this population-based case-control study, we found that statin drug use was not associated with the risk of pancreatic cancer. Our findings are consistent with 4 recent studies that

TABLE 2. Associations Between Statin use and Pancreatic Cancer Risk in a Population-Based Case-Control Study, Taiwan, 2003–2008

	No. Cases/No. of Control Subjects	Crude OR (95% CI)	Adjusted OR (95% CI)*
Overall			
No statin use	151/613	1.00	1.00
Any statin use	39/147	1.07 (0.72–2.06)	0.88 (0.56–1.36)
Cumulative use			
0	151/613	1.00	1.00
1–114.33 DDD	22/73	1.23 (0.73–2.06)	1.06 (0.61–1.85)
>114.33 DDD	17/74	0.92 (0.53–1.52)	0.71 (0.39–1.30)

*Adjusted for diabetes, chronic pancreatitis, number of hospitalizations, and use of other lipid-lowering drugs.

reported no associations between statin use and overall pancreatic cancer risk.

In a case-control study conducted using the General Practice Research Database in the United Kingdom, Kaye and Jick[11] reported an OR of 0.8 (95% CI, 0.4–1.6) for pancreatic cancer in relation to current statin use. Graaf et al[21] used a pharmacy database in the Netherlands to define exposure and observed a similar OR (OR, 0.89; 95% CI, 0.24–3.34) for pancreatic cancer in relation to statin prescriptions. Data from 3 centers in Philadelphia, New York, and Baltimore in the United States revealed a modest reduction in pancreatic cancer risk (OR, 0.70; 95% CI, 0.3–1.40) associated with regular statin use, but statistical significance was not reached.[13] Recently, Haukka et al[18] used data from Finland to evaluate statin use and also report no association between statin use and pancreatic cancer risk (relative risk, 0.99; 95% CI, 0.95–1.02).

Whereas the findings of our study were consistent with the direction of the association (inverse) reported in 4 observational studies,[11,13,18,21] a study by Khurana et al[26] found a statistically significant and dramatically stronger association (OR, 0.37; 95% CI, 0.30–0.46). There are at least 2 differences between our study and the study of Khurana et al. First, the study population in the study of Khurana et al consists solely of veterans with active access to health care, and thus, they were more likely to be prescribed a statin than the general population. Statin use was present in 33.8% of the study population. For this study, this number was 19.34%. Second, the previously mentioned study was conducted among a study population that was predominantly male (98.5% of the cases are men). Future studies may want to consider examining whether the protective effect occurs only among males.

The results of our study are consistent with the assumed biologic mechanism of statins, although the mechanism whereby statin use may decrease pancreatic cancer risk is not well understood. Several potential mechanisms have been investigated, including the following: (1) inhibiting downstream products of the mevalonate pathway, primary geranylgeranyl pyrophosphate (GGPP) and farnesylpyrophophosphate (FPP).[40–42] 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.[40–43] Statins interfere with the production of GGPP and FPP and disrupt the growth of malignant cells, eventually leading to apoptosis.[1] (2) 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.[10,44,45]

One of the strengths of our study is the use of a computerized database, which is population based and is highly representative. Because we included all patients newly diagnosed with pancreatic cancer from 2003 to 2008, and because the control subjects in this study were selected from a simple random sampling of insured general population, we can rule out the possibility of selection bias. 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 pancreatic cancer, 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 body mass index and smoking, which are associated with pancreatic cancer were not included in our database. Second, we were not able to contact the 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 control subjects. Even if the 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 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, data on the accuracy of discharge diagnoses are not available in Taiwan. Potential inaccurate data in the claims records could lead to possible misclassification. However, there is no reason to assume that this would be different for cases and control subjects. Lastly, as with any observational study, residual confounding by unmeasured factors that are different between cases and control subjects 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.

In summary, the results of this study do not provide support for an association between statin use and pancreatic cancer risk. Given the widespread use of statins, it is prudent public health policy to continue monitoring cancer incidence among

statin users of such a commonly used drug, particularly as durations of use are increasing.[13]

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