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BRIEF ARTICLE

# Statin use and the risk of colorectal cancer: A population-based case-control study

Meng-Hsuan Cheng, Hui-Fen Chiu, Shu-Chen Ho, Shang-Shyue Tsai, Trong-Neng Wu, Chun-Yuh Yang

Meng-Hsuan Cheng, Division of Pulmonary and Critical Medicine, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung 80708, Taiwan, China
Meng-Hsuan Cheng, Graduate Institute of Medicine, Kaohsiung Medical University, Kaohsiung 80708, Taiwan, China
Meng-Hsuan Cheng, Department of Internal Medicine, Ping-Tung Hospital, Department of Health, Executive Yuan, Ping-Tung 90054, Taiwan, China
Hui-Fen Chiu, Institute of Pharmacology, College of Medicine, Kaohsiung Medical University, Kaohsiung 80708, Taiwan, China
Shu-Chen Ho, Institute of Occupational Safety and Health, College of Health Sciences, Kaohsiung Medical University, Kaohsiung 80708, Taiwan, China
Shang-Shyue Tsai, Department of Healthcare Administration, I-Shou University, Kaohsiung 80708, Taiwan, China
Trong-Neng Wu, Department of Public Health, China Medical University, Taichung 40402, Taiwan, China
Trong-Neng Wu, Division of Environmental Health and Occupational Medicine, National Health Research Institute, Miaoli 10694, Taiwan, China
Chun-Yuh Yang, Faculty of Public Health, College of Health Sciences, Kaohsiung Medical University, Kaohsiung 80708, Taiwan, China
Chun-Yuh Yang, Division of Environmental Health and Occupational Medicine, National Health Research Institute, Miaoli 10694, Taiwan, China
Author contributions: Cheng MH wrote the manuscript; Ho SC performed the statistical analysis; Chiu HF, Tsai SS and Wu TN provided essential insight into the interpretation of the results; Yang CY contributed to the study design and interpretation of the data and had full access to all the data in the study and took responsibility for the integrity of the data and accuracy of the data analysis.
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Correspondence to: Chun-Yuh Yang, PhD, MPH, Faculty of Public Health, Kaohsiung Medical University, 100 Shih-Chuan 1st RD, Kaohsiung 80708, Taiwan, China. chunyuh@kmu.edu.tw
Telephone: +886-7-3121101 Fax: +886-7-3110811
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## Abstract

**AIM:** To investigate whether the use of statins is associated with colorectal 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 older and had a first-time diagnosis of colorectal cancer between the period 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 using multiple logistic regression.

**RESULTS:** We examined 1156 colorectal cancer cases and 4624 controls. The unadjusted ORs for any statin prescription was 1.10 (95% CI = 0.94-1.30) and the adjusted OR was 1.09 (95% CI = 0.91-1.30). When statin use was categorized by cumulative dose, the adjusted ORs were 0.99 (95% CI = 0.78-1.27) for the group with cumulative statin use below 105 defined daily doses (DDDs); 1.07 (95% CI = 0.78-1.49) for the group with cumulative statin use between 106 and 298.66 DDDs; and 1.30 (95% CI = 0.96-1.75) for the group with cumulative statin use of 298.66 DDDs or more compared with nonusers.

**CONCLUSION:** This study does not provide support for a protective effect of statins against colorectal cancer.



**Key words:** Case-control study; Colorectal cancer; Pharmacoepidemiology; Statins

**Peer reviewer:** Pascal Gervaz, PhD, Department of Surgery, University Hospital Geneva, 4, Rue Gabrielle Perret Gentile, Geneva 1211, Switzerland

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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 in this field has led to widespread use of these drugs.

Rodent studies indicate that statins are carcinogenic[4]. In contrast, several recent studies on human cancer cell lines and animal tumor models indicate that statins may have chemopreventive properties through the arrest of cell cycle progression[5], induction of apoptosis[1,6], suppression of angiogenesis[7,8], and inhibition of tumor growth and metastasis[9]. Results of a meta-analysis and observational studies revealed either no association[10-17] or a decrease in cancer incidence[18-26]. The reasons for the varying results are unclear but may be related to methodological issues, including small sample size and short follow-up periods[27].

Several epidemiologic studies have investigated the association between statin use and risk of colorectal cancer and the results have been inconsistent. Ten studies reported no statistically significant association between statin use and colorectal cancer risk[10,12,15,17,20-21,27-30]. However, three recent case-control studies reported that statin use is associated with a significant reduction in the risk of colorectal cancer[22,31-32].

Since large numbers of people utilize statins on a long-term basis, and because epidemiologic data linking statin use and risk of colorectal cancer are conflicting, we undertook the present study in Taiwan to evaluate the association between statin use and colorectal 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 can receive 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, gender, and healthcare costs between the sample group and all enrollees, as reported by the NHRI. This dataset (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 colorectal 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[33-35].

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 older and had a first-time diagnosis of colorectal cancer (International Classification of Diseases, 9th revision, Clinical Modification Code 153-154) over a 4-year period, from January 1, 2005 to December 31, 2008, and who had no previous diagnosis of cancer.

Controls comprised patients who were admitted to 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)[12,36]. Wrist and hip fractures were excluded because previous studies have reported a reduced risk of osteoporosis among statin users[37-40]. We identified four control patients per case patient. Control patients were matched to the cases by sex, year of birth, and index date and 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 colorectal cancer) of their matched case.

### Exposure to statins

Information on all statin prescriptions was extracted from the NHRI prescription database. We collected the date of prescription, the daily dose, the number of days supplied. The defined daily doses (DDDs) recommended by the WHO[41] were used to quantify use of statins. 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 identified variables which might confound the associations between statin use and colorectal cancer, including diabetes mellitus, cholecystectomy, liver disease, colorectal polyps, and inflammatory bowel disease, recorded between January 1, 1996, and the index date. In addition, we also obtained

**Table 1 Demographic characteristics of colorectal cancer cases and controls**

| Variable | Cases ($n$ = 1156) | Controls ($n$ = 4624) | Odds ratio (95% CI) |
|---|---|---|---|
| Age, yr (mean ± SD) | 68.34 ± 10.40 | 69.29 ± 10.40 | - |
| Female (%) | 447 (38.67) | 1788 (38.67) | - |
| No. of hospitalizations | 0.29 ± 0.93 | 0.26 ± 0.74 | $P$ = 0.23 |
| Diabetes (%) | 422 (36.51) | 1560 (33.74) | 1.13 (0.99-1.29) |
| Cholecystectomy (%) | 21 (1.82) | 105 (2.27) | 0.80 (0.50-1.28) |
| Liver disease (%) | 422 (36.51) | 1861 (40.25) | 0.85 (0.75-0.98) |
| Colorectal polyps (%) | 56 (4.84) | 76 (1.64) | 3.05 (2.14-4.33) |
| Inflammatory bowel disease (%) | 82 (7.09) | 315 (6.81) | 1.04 (0.81-1.34) |
| Colonoscopy (%) | 153 (13.24) | 42 (0.91) | 16.64 (11.75-23.57) |
| FOBT (%) | 152 (13.15) | 216 (4.67) | 3.09 (2.48-3.84) |
| NSAID (%) | 636 (55.02) | 2767 (59.84) | 0.82 (0.72-0.93) |
| Use of other lipid-lowering drugs (%) | 31 (2.68) | 180 (3.89) | 0.68 (0.46-1.00) |

FOBT: Fecal occult blood testing; NSAID: Non-steroidal anti-inflammatory drug; CI: Confidence interval.

prescription data for other lipid-lowering drugs (including fibrate, niacin, bile-acid binding resins, and miscellaneous medications) and non-steroidal anti-inflammatory drugs (NSAIDs) that could potentially confound the association between statin use and the risk of colorectal cancer. We defined users of the above-mentioned medications as patients with at least one prescription over one year prior to the index date. Furthermore, colonoscopy, fecal occult blood testing (FOBT), and number of hospitalizations one year before the index date were treated as confounders.

### *Statistical analysis*

For comparisons of proportions, chi-square 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 January 1, 1996 and the index date. In the analysis, the subjects were categorized into one of four statin exposure categories: nonusers (subjects with no prescription for any statins at any time between January 1, 1996 and the index date), low (the lowest 50th percentile; ≤ 105 DDDs); medium (50th-75th percentile; 106-298.66 DDDs); and high (above the 75th percentile; > 298.66 DDDs) based on the distribution of use among controls. Odd ratios (ORs) 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). All statistical tests were two-sided. Values of $P < 0.05$ were considered statistically significant.

## RESULTS

Records from 1156 colorectal cancer cases and 4624 selected matched controls were included in the analyses.

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

| | Cases ($n$)/ controls ($n$) | Crude OR (95% CI) | Adjusted OR (95% CI)[1] |
|---|---|---|---|
| Overall | | | |
| No statin use | 914/3727 | 1.00 | 1.00 |
| Any statin use | 242/897 | 1.10 (0.94-1.30) | 1.09 (0.91-1.30) |
| Cumulative use | | | |
| 0 | 914/3727 | 1.00 | 1.00 |
| 1-105 DDD | 112/451 | 1.02 (0.82-1.27) | 0.99 (0.78-1.27) |
| 106-298.66 DDD | 60/221 | 1.11 (0.83-1.49) | 1.07 (0.78-1.49) |
| > 298.66 DDD | 70/225 | 1.27 (0.96-1.68) | 1.30 (0.96-1.75) |

OR: Odds ratio; CI: Confidence interval; DDD: Defined daily dose. [1]Adjusted for matching variable, diabetes, number of hospitalizations, cholecystectomy, liver disease, colorectal polyps, inflammatory bowel disease, colonoscopy, fecal occult blood testing, non-steroidal anti-inflammatory drugs and use of other lipid-lowering drugs.

Table 1 shows the distribution of demographic characteristics and selected medical conditions of the cancer cases and controls. The mean age was 68.34 years for cancer cases and 68.81 years for the controls. Case subjects were more likely to have had preventive services (screening colonoscopy and FOBT). The case group had a significantly higher rate of colorectal polyps than control patients. Use of other lipid-lowering drugs and NSAIDs were not significantly different between cases and controls.

The observed associations between the use of statins and colorectal cancer are shown in Table 2. Ever-use of any statins was associated with a slight but not statistically significant increased colorectal cancer risk (adjusted OR = 1.09, 95% CI = 0.91-1.30). When statin use was categorized by cumulative dose, the adjusted ORs were 0.99 (95% CI = 0.78-1.27) for the group with cumulative statin use below 105 DDDs; 1.07 (95% CI = 0.78-1.49) for the group with cumulative statin use between 106 and 298.66 DDDs; and 1.30 (95% CI = 0.96-1.75) for the group with cumulative statin use of 298.66 DDDs or more compared with nonusers. Overall, we found no association between cumulative statin use and colorectal cancer risk. ORs for cancers of the colon and rectum considered separately were similar (data not shown).

## DISCUSSION

In this population-based case-control study, we found that statin drug use was not associated with colorectal cancer risk. Our findings are consistent with ten recent studies which reported no associations between statin use and overall colorectal cancer risk[10,12,15,17,20-21,27-30].

Our results, however, conflict with three recent case-control studies. In a case-control study conducted in Israel, a reduced risk of colorectal cancer was found to be associated with the use of statins for at least 5 years, compared with less than 5 years of use (OR = 0.50, 95% CI = 0.40-0.63)[22]. Another population-based study from Germany showed that statin use was associated

with a 35% (OR = 0.65, 95% CI = 0.43-0.99) colorectal risk reduction occurring within 1-4 years of statin use and no further risk reduction was seen after 5 years or more[31]. Neither study characterized the dose or duration of statins in detail and both studies defined statin use by recall. In a nested case-control study consisting solely of veterans with diabetes, using national databases of the Department of US Veterans Affairs and Medicare-linked files, Hachem *et al*[32] reported an odds ratio 0.91 (95% CI = 0.86-0.96) for colorectal cancer in relation to any statin use. However, there is no clear dose-response or duration-response relationship between filled statin prescriptions and colorectal cancer risk.

Duration of statin use may be important when investigating the chemopreventive effects of statins. We assessed exposure to statins measured as cumulative DDDs. Cumulative DDDs is a time-independent variable in which the daily supplies of each statin prescription dispensed were summed over time from January 1, 1996 to the index date. Because cumulative DDDs and statin duration are highly interrelated, it was not possible to model them together. Similar findings were noted when statin users were stratified by duration (data not shown).

There are at least two differences between our study and the study of Hachem *et al*[32]. First, their study population was limited to mostly male 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 51% of the study population. In our study this number was 19.4%. Second, the above-mentioned study was conducted among patients with diabetes who are known to have a higher likelihood of developing colorectal cancer[42]. Therefore, it is possible that it was easier to show benefit owing to the generally elevated risk in patients with diabetes[32]. Using an epidemiologic study which is restricted to patients with major risk factors means that the results of the restricted study may not necessarily apply to the portion of the population that was excluded. Whether a protective effect only occurs among patients who are already at higher risk of colorectal cancer requires further study. Other studies have reported a possible protective effect of statins in patients with diabetes on lung (adjusted OR = 0.43, 95% CI = 0.38-0.49)[24], pancreatic (adjusted OR = 0.32, 95% CI = 0.23-0.44)[25], and liver cancer (adjusted OR = 0.74, 95% CI = 0.64-0.87)[26].

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 colorectal cancer from 2005 to 2008, and because the control subjects in this study were selected from a simple random sampling of the insured general population, we can rule out the possibility of selection bias. Statins were available only on prescription. Because the data on statin use were obtained from an historical database which collects all prescription information before the date of colorectal cancer, recall bias for statin use was thus 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 family history of colorectal cancer, dietary habits or physical activity, and alcohol and tobacco use, which are associated with colorectal cancer were not included in our database. Second, we were unable 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 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 from 1996. Such misclassification, however, was likely to be non-differential, which would tend to underestimate rather than overestimate the association. Fourth, we were unable to analyze the risks for users of distinct statins separately due to 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 controls. Lastly, as with any observational study, residual confounding by unmeasured factors which 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.

In summary, the results of this study do not provide support for an association between statin use and colorectal cancer risk. Given the widespread use of statins, it is prudent public health policy to continue monitoring cancer incidence among statin users, particularly as the duration of use is increasing[12].

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## COMMENTS

### Background

Experimental studies have shown that statins have potential protective effects against cancer. Several epidemiologic studies have investigated the association between statin use and risk of colorectal cancer, and the results are inconsistent.

### Research frontiers

This study was undertaken to examine the relationship between statin use and the risk of colorectal cancer.

### Applications

Statins are widely used cholesterol-lowering drugs, and the duration of use is increasing. Further and larger studies are needed to determine the long-term effects of statin use on cancer development and to clarify whether statins are truly effective for cancer chemoprevention.

### Peer review

This is a nice population-based study which strength is the fact that Taiwan National Health Insurance research program provides extensive data of one million patients. The methodology and statistical analysis is adequate and altogether the authors provide convincing evidence that statin use does not protect against the risk of colorectal cancer.

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