Statin Use Is Associated With Improved Prognosis of Colorectal Cancer in Taiwan

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Abstract

We established a population-based cohort of patients who received curative surgery for stage I, II, or III colorectal cancer. Among 17,115 patients included in this study, we found that statin use was an independent predictor for longer cancer-specific survival and overall survival in multivariate analysis after adjusting for other potential prognostic factors. These associations were consistent across subgroups.

Background: Statins are widely used for hyperlipidemia control and might also exhibit anticancer properties. This study explored whether statin use is associated with the prognosis of curatively resected colorectal cancer (CRC). **Materials and Methods:** Using data from the Taiwan Cancer Registry, we established a population-based cohort of patients who received curative surgery for stage I, II, or III CRC. Data related to prescription medications and comorbidities were retrieved from the database of the National Health Insurance program of Taiwan. Statin users were defined as patients who had used statins within 1 year before their cancer diagnosis. Univariate and multivariate analyses were used to compare cancer-specific survival (CSS) and overall survival (OS) between statin users and patients who had never used statins (never users). In the multivariate analysis, we used propensity scores to adjust for age, sex, diagnosis year, physician visits, hospitalization, conjunctive medications, and comorbidities. **Results:** A total of 17,115 patients were enrolled; 2145 (13%) of these patients were statin users, and 14,970 (87%) were never users. After adjusting for other potential prognostic factors, statin use was an independent predictor for longer CSS (hazard ratio [HR], 0.77; 95% confidence interval [CI], 0.68-0.88; $P < .001$) and OS (HR, 0.82; 95% CI, 0.74-0.92; $P < .001$). These associations were consistent across subgroups, including sexes, tumor stages, and age cohorts, and in CRC patients who suffered from diabetes and hypertension. **Conclusion:** Statin use is associated with an improved prognosis of curatively resected CRC.

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Introduction

Statins are inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A reductase. They are the most commonly used medication in the control of hyperlipidemia and are capable of reducing cardiovascular events in high-risk patients.[1-3] Statins might also possess anticancer properties associated with blocking the production of mevalonate, which involves the posttranslational modification of numerous oncogene products.[4,5]

Inflammation is strongly associated with the risk and prognosis of colorectal cancer (CRC).[6,7] Patients with inflammatory bowel disease are at increased risk of CRC.[8,9] Regular use of cyclooxygenase-2 inhibitors has been shown to reduce rectal polyps in patients

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suffering from familial adenomatous polyposis.[10,11] Furthermore, high serum levels of proinflammatory cytokines such as interleukin-6 are associated with less favorable CRC prognosis in patients who undergo curative surgery.[12,13] Statins produce anti-inflammatory effects; therefore, statin use might be associated with improved prognosis of CRC.[14-16]

A population-based study in Denmark showed that statin use is associated with improved prognosis of 13 types of cancer, including colon cancer.[17] Although treatment and tumor stages were adjusted in the multivariate analysis, variables related to early surgery outcomes, such as whether the surgical margin was involved, were not investigated. In addition, data related to conjunctive medications and comorbidities were limited or lacking. Consequently, the prognostic effect of statin use on CRC has yet to be elucidated.

In this study, we investigated whether statin use is associated with an improved prognosis of CRC in a population-based cohort in Taiwan. Using patient records obtained from the national cancer registry and the National Health Insurance (NHI) system in Taiwan, we examined the detailed prescription history of patients who received curative surgery for localized CRC to determine the effect of statin use on CRC prognosis.

Materials and Methods

Data Sources

We established a population-based CRC cohort by searching the Taiwan Cancer Registry database, which is managed by the Bureau of Health Promotion (BHP), Department of Health, Taiwan.[18,19] All major cancer care providers in Taiwan are required to enter patient data into the database, which covers approximately 78% of newly diagnosed cancer patients in Taiwan.[19] Data related to patient demographic characteristics, tumor size, tumor stage, and treatment were also obtained from this database.

National Health Insurance reimbursement data were analyzed to identify comorbidities and the use of various medications, including statins. The NHI program covers more than 98% of the Taiwanese population.[20] Outpatient clinical services and in-patient hospitalization provided by the private and public sectors are included in this unified reimbursement system. Finally, the National Death Registry database was used to identify the dates and causes of patient deaths.

To comply with personal electronic data privacy regulations, personal identities were encrypted and all data were analyzed anonymously. The study protocol was approved by the Research Ethics Committee of the College of Public Health, National Taiwan University. The release of all data used or generated in this study was approved by the Collaboration Center of Health Information Application, Department of Health, Executive Yuan, Taiwan, and the Data Release Review Board of the BHP, respectively.

Study Population

The study cohort comprised patients aged 40 years and older who were newly histologically diagnosed with stage I, II, or III CRC (International Classification of Diseases [ICD] for Oncology, Third Revision codes: C18, C199, C209) and had received curative surgery with uninvolved microscopic margins between January 1, 2004 and December 31, 2008. Patients with multiple primary cancer types, lymphoma, Kaposi sarcoma, or a history of other types of cancer, and those who had received other treatment before curative surgery, were excluded.

Definitions of Statin Usage

In this study, we reviewed the prescription records of all study patients over an observation period spanning from 1 year before the diagnosis of cancer to the date of death or last follow-up (December 31, 2011). Patients who had been prescribed statins within 1 year before the cancer diagnosis were defined as statin users. Patients who did not receive any statins during the entire observation period were defined as never users.

For the statin user group, a detailed statin prescription history was recorded over the observation period. We calculated statin exposure intensity by dividing the cumulative defined daily dose (DDD) of statins by the total number of prescription days in the observation period. The DDD was calculated according to the Anatomical, Therapeutic, and Chemical classification system and the DDD recommended by World Health Organization.[21] Patients were then divided into 4 groups according to their quartiles of statin exposure intensity. In the analysis of statin characteristics, atorvastatin, pravastatin, and rosuvastatin were classified as hydrophilic statins. Simvastatin, lovastatin, and fluvastatin were classified as lipophilic statins.

End Point Definitions

Patients were monitored from the day of cancer diagnosis to the day of death from cancer to determine cancer-specific survival (CSS), or to the day of death from all causes to determine overall survival (OS). Data from patients who survived beyond the study end point (December 31, 2011) and data from patients who died from causes other than those specified were censored.

Definition of Comorbidities

Comorbidities based on the Deyo Charlson Comorbidity Index were considered.[22] We also included hypertension and coronary artery disease for their potential associations with statin use, and liver cirrhosis for its high prevalence and potential prognostic effect. Using the revised mapping algorithm of Quan et al,[23] we screened the NHI claims data for the ICD, Ninth Revision, Clinical Modification diagnosis codes to identify comorbidities. Patients were defined as having a specific comorbidity if it was identified at least twice in the records of outpatient clinics or at least once during hospitalization within 1 year before cancer diagnosis. All comorbidities with a prevalence exceeding 1% were adjusted.

Statistical Analysis

In all statistical testing, 2-sided P values $\leq .05$ were considered statistically significant for all of the analyses performed. SAS statistical software version 9.3 (SAS Institute, Cary, NC) was used for all statistical analyses. The mean and frequency of patient characteristics were compared using 2-sample t tests or the Wilcoxon signed-rank test for continuous variables. The χ^2 test or Fisher exact test was used to compare categorical variables. Patient survival based on the history of statin use was estimated using the Kaplan–Meier method and compared using the log-rank test in univariate analysis.

To adjust for potential confounding factors, a propensity score was derived using logistic regression to model the probability of