Statins Dose-Dependently Exert Significant Chemopreventive Effects Against Various Cancers in Chronic Obstructive Pulmonary Disease Patients: A Population-Based Cohort Study

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Abstract

PURPOSE: Chronic obstructive pulmonary disease (COPD) is associated with an increased cancer risk. We evaluated the chemopreventive effect of statins against all cancers in COPD patients and identified the statin with the strongest chemopreventive effect.

PATIENTS AND METHODS: All patients diagnosed with COPD at health care facilities in Taiwan (n = 116,017) from January 1, 2001, to December 31, 2012, were recruited. Each patient was followed to assess the following protective and risk factors for all cancers: age; sex; comorbidities (diabetes, hypertension, dyslipidemia) and the Charlson comorbidity index (CCI); urbanization level; monthly income; and nonstatin drug use. The index date of statins use was the date of COPD confirmation. Propensity scores (PSs) were derived using a logistic regression model to estimate the effect of statins by considering the covariates predicting intervention (statins) receipt. To examine the dose–response relationship, we categorized statin use into four groups (<28 [statin nonusers], 28–90, 91–365, and >365 cumulative defined daily dose).

RESULTS: After PS adjustment for age, sex, CCI, diabetes, hypertension, dyslipidemia, urbanization level, and monthly income, we analyzed the all-cancer risk. The adjusted hazard ratios (aHRs) for the all-cancer risk were lower among statin users than among statin nonusers (aHR = 0.46, 95% confidence interval: 0.43 to 0.50). The aHRs for the all-cancer risk were lower among patients using rosuvastatin, simvastatin, atorvastatin, pravastatin, and fluvastatin than among statin nonusers (aHRs = 0.42, 0.55, 0.59, 0.66, and 0.78, respectively). Sensitivity analysis indicated that statins dose-dependently reduced the all-cancer risk.

CONCLUSION: Statins dose-dependently exert a significant chemopreventive effect against various cancers in COPD patients. In particular, rosuvastatin has the strongest chemopreventive effect.

Key words: statin; COPD; cancer.
Introduction

Chronic obstructive pulmonary disease (COPD) is a common respiratory condition characterized by airflow limitation [1] and airway and systemic inflammation. [2] Inflammation alone or combined with other factors influences cancer risk in humans [3]; the most common link between inflammation and cancer risk in COPD patients is aberrant inflammation and immunity. [4] COPD is primarily caused by smoking. However, COPD has been independently associated with an increased risk of lung cancer and is probably associated with the inflammation and scarring accompanying COPD development. [5, 6] In COPD patients, oxidized low-density lipoprotein (LDL) levels are high and are associated with lung function, inflammation, and oxidative stress. [7]

Lipid metabolism disorders are risk factors for several cancers. [8-10] In COPD patients, a common potential mechanism by which major risk factors such as smoking, hyperlipidemia, obesity, and hypertension lead to chronic diseases is systemic inflammation. [11, 12] A meta-analysis of 28 case-control studies and 17 observational cohort studies revealed an increased lung cancer risk associated with an affected relative risk of 1.8 [13]. Taken together, COPD patients are at a high risk of cancers throughout their lives.

Statin therapy has various effects that may contribute to reducing the cancer risk, such as anti-inflammatory, antioxidant, and antiplatelet effects as well as lipid modification. [14-17] Reduced monocyte adhesion to the endothelium, reduced oxidative stress modification of LDLs, and increased mobilization and differentiation of endothelial progenitor cells also are potential benefits of lipid-lowering therapy. [18, 19] Thus, statins can be chemopreventive agents for COPD patients with chronic systemic inflammation and hyperlipidemia. Some meta-analyses of randomized trials have consistently revealed that statins do not affect cancer incidence and cancer mortality; however, this may be because of the selection of study populations that are not at a high cancer risk. [20, 21]

In this study, we evaluated the chemopreventive effects of statins against all cancers in COPD patients, who are at a high risk of cancer because of chronic systemic inflammation, hyperlipidemia, and higher oxidative stress. In addition, we investigated the dose-dependence of this chemopreventive effect and evaluated the potential of anticancer effects of different types of statins.

Patients and Methods

The National Health Insurance (NHI) program, established in 1995, currently provides comprehensive health insurance coverage to 98% of the more than 23 million people in Taiwan. We used data from the NHI Research Database (NHIRD). Distributions of age, sex, and health care costs in the NHIRD and among NHI enrollees do not differ significantly. Data that can be used to identify patients or care providers, including the names of medical institutions and physicians, are encrypted before being sent to the National Health Research Institutes for inclusion in the NHIRD. The institutes further encrypt the data before releasing the database to researchers. Theoretically, the NHIRD data alone is insufficient to identify any individual. All researchers using the NHIRD and its data subsets must sign a written agreement declaring that they have no intention of attempting to obtain information that could potentially violate the privacy of patients or care providers. [22]

Our study cohort comprised all patients diagnosed with COPD (according to International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] codes) at health care facilities in Taiwan (n = 116,017) between January 1, 2001, and December 31, 2012. We excluded patients without a subsequent outpatient visit, emergency department visit, or inpatient hospitalization for COPD within 12 months of the first presentation (n = 48,212); these patients were considered to not have COPD (Fig 1). We also excluded 15,436 patients aged younger than 40 years (n = 52,369) and had any cancer-related inpatient or outpatient diagnoses before the index date (n = 5,353) or had been prescribed any statins within 6 months before the index date (n = 3,214).

Our final study cohort contained 43,802 patients diagnosed with COPD in Taiwan over the 11-year period; of these, 10,086 used statins and 33,716 did not (Table 1). Each patient was followed to assess the risk and protective factors for all cancers. In addition, we considered factors such as demographic characteristics (age and sex); comorbidities (diabetes, hypertension, dyslipidemia) and the Charlson comorbidity index (CCI); urbanization level; monthly income; and the use of nonstatin lipid-lowering drugs, metformin, aspirin, and angiotensin-converting enzyme inhibitor (ACEI). The index date of statin use was the date of COPD confirmation. Because we aimed to evaluate the preventive effects of statin use in COPD patients having a high all-cancer risk, the primary endpoint was the all-cancer risk and the secondary endpoints were the differential benefits of various doses and types of statins. The defined daily dose (DDD)—recommended by the World Health Organization—is a measure of the prescribed drug.
amount. DDD is the assumed average maintenance dose per day of a drug consumed for its main indication in adults. [23] To examine the dose–response relationship, we categorized statin use into four groups in each cohort (<28, 28–90, 91–365, and >365 cumulative DDDs [cDDDs]) because the duration of the refill card was 3 months. Patients receiving <28 cDDDs were defined as statin nonusers (Tables 2–4). [24] Furthermore, to examine the preventive effect of different types of statins, we categorized statin use into different individual statin use groups in each cohort (Table 3).

Propensity scores (PSs) were derived using a logistic regression model to estimate the effect of statins by accounting for the covariates predicting receiving the intervention (statins). This method is commonly used in observational studies to reduce selection bias. [25] The covariates in the main model were PS adjusted for age, sex, CCI, diabetes, hypertension, dyslipidemia, urbanization level, and monthly income in New Taiwan dollars (NT$0, NT$1–21,000, NT$21,000–33,300; and ≥NT$33,301; Table 2). The endpoint for both statin users and nonusers was the diagnosis of all cancers (ICD-9-CM 140–209) with a subsequent outpatient visit, emergency department visit, or inpatient hospitalization for any cancer within 12 months of diagnosis; the nonusers were used as the reference arm. The cumulative incidence of any cancer in the two groups was estimated using the Kaplan-Meier method.

A time-dependent Cox proportional hazard model was used to calculate the hazard ratios (HRs) of the all-cancer risk in the statin users and nonusers. The HRs were adjusted for age, sex, CCI, diabetes, hypertension, dyslipidemia, urbanization level, and monthly income in the multivariate analysis. A stratified analysis was conducted to evaluate the effect of statin use on age and sex (Table 2). All analyses were conducted using SAS software (Version 9.3; SAS, Cary, NC, USA); two-tailed P < 0.05 was considered significant. In sensitivity analyses, external adjustments are used to improve the understanding of the effects of drugs and other covariates in epidemiological database studies. [26] Hence, in our sensitivity analyses, data were adjusted in different models to estimate the association of all-cancer incidence with age, sex, diabetes, dyslipidemia, hypertension, CCI, anxiety disorder, and the use of nonstatin lipid-lowering drugs, metformin, aspirin, and ACEI. The drug use-stratified models were adjusted for covariates in the main model and for each additional covariate (Table 4).

Results

Our COPD cohort comprised 43,802 patients; of these, 10,086 (30%) used statins and the remaining 33,716
(70%) did not (Table 1). The total follow-up duration was 194,933.6 and 80,239.4 person-years for the statin nonusers and users, respectively. Compared with the statin nonusers, the statin users exhibited a higher prevalence of pre-existing medical comorbidities, such as diabetes, hypertension, and dyslipidemia, and a higher CCI (all $P < 0.001$). In addition, significant differences were observed between the two groups in the distributions of age, sex, monthly income, and urbanization level as well as the use of nonstatin lipid-lowering drug, aspirin, ACEI, and metformin (Table 1). A higher proportion of statin nonusers used nonstatin lipid-lowering drugs, metformin, ACEI, and aspirin for <28 days; however, most statin users used these drugs for >365 days. A lower proportion of statin nonusers had a monthly income of ≥NT$33,301 or resided in urban areas. Table 2 shows the all-cancer risk among the statin nonusers and users. After PS adjustment for age, sex, CCI, diabetes, hypertension, dyslipidemia, and monthly income, we analyzed the all-cancer risk. The adjusted HRs (aHRs) for the all-cancer risk were lower among the statin users, particularly those aged 40–74 years, regardless of sex. Specifically, the aHRs for the all-cancer risk were lower in the statin users than in the statin nonusers for every age group (40–64, 65–74, and ≥75 years; aHRs = 0.43, 0.45, and 0.51, respectively). The statin users also exhibited lower aHRs for the all-cancer risk than the statin nonusers did, after sex stratification (women: aHR = 0.44, 95% CI: 0.40 to 0.50; men: aHR = 0.48, 95% CI: 0.43 to 0.52).

Statins dose-dependently reduced the all-cancer risk in different cDDD subgroups; the main model was PS adjusted for age, sex, CCI, diabetes, hypertension, dyslipidemia, urbanization level, and monthly income (Table 3). Lipophilia statins comprised simvastatin, lovastatin, atorvastatin, and fluvastatin, whereas hydrophilia statins comprised pravastatin and rosuvastatin. Table 3 presents the all-cancer risk reduction demonstrated by lipophilia and hydrophilia statins in patients with COPD along with the doses and responses ($P$ for trend < 0.001). Among individual statins, lovastatin did not reduce the all-cancer risk in patients with COPD significantly. The aHRs for the all-cancer risk in patients using rosuvastatin, simvastatin, atorvastatin, pravastatin, and fluvastatin were lower than those of statin nonusers (aHRs = 0.42, 0.55, 0.59, 0.66 and 0.78, respectively). Our results revealed that individual statins reduced the all-cancer risk at varying efficacies among COPD patients.

In the sensitivity analysis, PS adjustments were made to estimate the associations of age, sex, CCI, diabetes, hypertension, dyslipidemia, urbanization level, monthly income, and nonstatin lipid-lowering drugs, metformin, ACEI, and aspirin use with the incidence of all cancers in different models. Table 4 shows that the effects of statins remained significant in the subgroups of various covariates when the main model was adjusted for PSs. Statins dose-dependently reduced the all-cancer risk in all subgroups and the main model with additional covariates (nonstatin lipid-lowering drugs, metformin, ACEI, and aspirin use). All aHRs indicated that statins dose-dependently induced significant reductions in the all-cancer risk in all subgroups, regardless of comorbidities or drug use ($P < 0.001$). Thus, our data revealed that statins show a dose-dependent chemopreventive effect against all cancers.

### Table 1. Characteristics of the Sample Population.

|                  | Entire cohort (n = 43,802) | Patients using statins (≥28 cDDDs; n = 10,086) | Patients not using statins (<28 cDDDs; n = 33,716) | P<sup>+</sup> |
|------------------|---------------------------|---------------------------------------------|---------------------------------------------|--------------|
|                  | n                         | n (%)                                      | n (%)                                      |              |
| **Age, years (mean ± SD)** |                           |                                             |                                             |              |
| 40–54            | 14,458 (33.01)            | 3,180 (31.53)                              | 11,278 (33.74)                             | <0.001       |
| 55–64            | 9,644 (22.02)             | 2,899 (28.74)                              | 6,745 (20.01)                              | <0.001       |
| 65–74            | 10,455 (23.87)            | 2,777 (27.53)                              | 7,678 (22.77)                              |              |
| ≥75              | 9,245 (21.11)             | 1,230 (12.20)                              | 8,015 (23.77)                              |              |
| **Sex**          |                           |                                             |                                             |              |
| Female           | 19,715 (45.01)            | 5,150 (51.06)                              | 14,565 (43.20)                             | <0.001       |
| Male             | 24,087 (54.99)            | 4,936 (48.94)                              | 19,151 (56.80)                             |              |
| **CCI**          |                           |                                             |                                             |              |
| 0                | 11,279 (25.75)            | 2,586 (26.64)                              | 8,693 (25.78)                              | <0.001       |
| 1                | 12,907 (28.76)            | 3,014 (29.88)                              | 9,893 (28.42)                              |              |
| 2                | 9,075 (20.72)             | 2,195 (21.76)                              | 6,880 (20.41)                              |              |
| ≥3               | 10,851 (24.77)            | 2,291 (22.71)                              | 8,560 (25.39)                              |              |
| **Diabetes**     |                           |                                             |                                             |              |
| No               | 33,491 (76.46)            | 6,819 (67.61)                              | 26,672 (79.11)                             | <0.001       |
| Yes              | 10,311 (23.54)            | 3,267 (32.39)                              | 7,044 (20.89)                              |              |

* Statins dose-dependently reduced the all-cancer risk in different cDDD subgroups; the main model was PS adjusted for age, sex, CCI, diabetes, hypertension, dyslipidemia, urbanization level, and monthly income.

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### Table 2. All-Cancer Risk in Statin Users and Nonusers in the Study Cohort.

|                 | Entire cohort *(n = 43,802)* | Patients using statins (n = 10,886) | Patients not using statins (n = 33,716) | \(P^*\) |
|-----------------|-----------------------------|-------------------------------------|----------------------------------------|---------|
|                 | n                           | %                                   | n                                      | %       |         |
| Hypertension    |                             |                                     |                                        |         |
| No              | 22067                       | 50.38                               | 4158                                   | 41.23   | 17909    | 53.12   | <0.001 |
| Yes             | 21735                       | 49.62                               | 5928                                   | 58.77   | 15807    | 46.88   |         |
| Dyslipidemia    |                             |                                     |                                        |         |
| No              | 31731                       | 74.42                               | 5785                                   | 57.36   | 25946    | 76.95   | <0.001 |
| Yes             | 12071                       | 27.56                               | 4301                                   | 42.64   | 7770     | 23.05   |         |
| Nonstatin lipid-lowering drugs |               |                                     |                                        |         |
| <28 days        | 39267                       | 89.65                               | 7212                                   | 71.51   | 32055    | 95.07   | <0.001 |
| 28–365 days     | 3186                        | 7.27                                | 1923                                   | 19.07   | 1263     | 3.75    |         |
| >365 days       | 1349                        | 3.08                                | 951                                    | 9.43    | 398      | 1.18    |         |
| Metformin       |                             |                                     |                                        |         |
| <28 days        | 35961                       | 82.10                               | 6286                                   | 62.32   | 29675    | 88.01   | <0.001 |
| 28–365 days     | 2684                        | 6.13                                | 964                                    | 9.56    | 1720     | 5.10    |         |
| >365 days       | 5157                        | 11.77                               | 2836                                   | 28.12   | 2321     | 6.88    |         |
| Urbanization level |                           |                                     |                                        |         |
| Urban           | 30539                       | 69.72                               | 7208                                   | 71.47   | 23331    | 69.20   | <0.001 |
| Suburban        | 8914                        | 20.35                               | 1920                                   | 19.04   | 6994     | 20.74   |         |
| Rural           | 4349                        | 9.93                                | 958                                    | 9.50    | 3391     | 10.06   |         |
| Monthly income (NT$) |                       |                                     |                                        |         |
| 0              | 3464                        | 7.91                                | 795                                    | 7.88    | 2669     | 7.92    | <0.001 |
| 1–21000        | 15001                       | 34.25                               | 3067                                   | 30.41   | 11934    | 35.40   |         |
| 21000–33300    | 12904                       | 29.46                               | 3165                                   | 31.38   | 9739     | 28.89   |         |
| ≥33300         | 12433                       | 28.38                               | 3059                                   | 30.33   | 9374     | 27.80   |         |

\(^a\) Comparison between statin use and no statin use.

\(^b\) CCI: Charlson comorbidity index.

| No. of patients with any cancer | Incidence rate (per 10^5 person-years) (95% CI) | No. of patients with any cancer | Incidence rate (per 10^5 person-years) (95% CI) | \(aHR^*\) (95% CI) |
|-------------------------------|-----------------------------------------------|--------------------------------|-----------------------------------------------|---------------------|
| Entire cohort                 |                                               |                                |                                               |                     |
| 5279                          | 2708.1                                        | (2635.0, 2781.2)              | 964                                           | 1201.4              | (1125.6, 1277.2) | 0.46(0.43, 0.50)*** |
| Age, 40–64 years\(^a\)       | 2172                                          | 1868.7                        | (1790.1, 1947.3)                             | 449                 | 889.5             | (807.3, 971.8) | 0.43(0.39, 0.48)*** |
| Age, 65–74 years\(^b\)       | 1665                                          | 3732.1                        | (3552.8, 3911.4)                             | 350                 | 1607.1            | (1438.7, 1775.5) | 0.45(0.40, 0.50)*** |
| Age, 75 years\(^c\)          | 1442                                          | 4229.7                        | (4011.4, 4448.0)                             | 165                 | 2066.3            | (1751.1, 2381.6) | 0.51(0.43, 0.60)*** |
| Female\(^d\)                 | 1874                                          | 2144.4                        | (2047.3, 2241.5)                             | 423                 | 1011.3            | (914.9, 1107.6) | 0.44(0.40, 0.50)*** |
| Male\(^e\)                   | 3405                                          | 3166.2                        | (3059.8, 3272.5)                             | 541                 | 1408.5            | (1289.8, 1527.1) | 0.48(0.43, 0.52)*** |

\(^a\) Total follow-up 116228.5 person-year for patients not using statins and 50476.0 for patients using statins.

\(^b\) Total follow-up 44612.9 person-year for patients not using statins and 21778.3 for patients using statins.

\(^c\) Total follow-up 34092.2 person-year for patients not using statins and 7985.1 for patients using statins.

\(^d\) Total follow-up 87389.9 person-year for patients not using statins and 41828.7 for patients using statins.

\(^e\) Total follow-up 107543.7 person-year for patients not using statins and 38410.7 for patients using statins.

C.I.: confidence interval

HR: adjusted hazard ratio

\(^f\) Main model was adjusted using propensity scores for age, sex, Charlson comorbidity index, diabetes, hypertension, dyslipidemia, urbanization level, and monthly income.
Table 3. Incidence Rate and aHRs of the All-Cancer Risk Associated with Statin Use During the Follow-Up Period in COPD Patients.

| Variable                          | No. of patients | No. of person-years | No. of patients with any cancer | Incidence Rate (per 10^5 person-years) | aHR (95%CI) | P for Trend |
|-----------------------------------|-----------------|---------------------|---------------------------------|----------------------------------------|-------------|-------------|
| Total statin use                  |                 |                     |                                 |                                        |             |             |
| Nonuser (<28 cDDDs)              | 33716           | 194933.6            | 5279                            | 2708.1 (2635.0, 2781.2)                | 1.00        | <0.001      |
| User (>365 cDDDs)                | 10086           | 80239.4             | 964                             | 1201.4 (1125.6, 1277.2)                | 0.46(0.43, 0.50)*** |             |
| 28–90 cDDDs                      | 2346            | 17095.6             | 294                             | 1719.7 (1523.2, 1916.3)                | 0.65(0.58, 0.73)*** |             |
| 91–365 cDDDs                     | 3215            | 24193.1             | 343                             | 1471.8 (1267.7, 1567.8)                | 0.54(0.48, 0.60)*** |             |
| >365 cDDDs                       | 4525            | 38950.7             | 327                             | 839.5 (748.5, 930.5)                  | 0.32(0.29, 0.36)*** |             |
| Lipophilia statin use†            |                 |                     |                                 |                                        |             |             |
| Nonuser (<28 cDDDs)              | 35008           | 204288.0            | 5379                            | 2633.0 (2562.7, 2703.4)                | 1.00        | <0.001      |
| User (>365 cDDDs)                | 8794            | 70885.0             | 864                             | 1218.9 (1137.6, 1300.2)                | 0.57(0.53, 0.61)*** |             |
| 28–90 cDDDs                      | 2296            | 17069.8             | 270                             | 1581.7 (1393.1, 1770.4)                | 0.67(0.59, 0.75)*** |             |
| 91–365 cDDDs                     | 3012            | 23258.7             | 332                             | 1427.4 (1273.9, 1581.0)                | 0.65(0.58, 0.73)*** |             |
| >365 cDDDs                       | 3486            | 30556.4             | 262                             | 857.4 (753.6, 961.3)                  | 0.42(0.37, 0.48)*** |             |
| Hydrophilia statin use‡           |                 |                     |                                 |                                        |             |             |
| Nonuser (<28 cDDDs)              | 39878           | 242812.7            | 5974                            | 2460.3 (2397.9, 2522.7)                | 1.00        | <0.001      |
| User (>365 cDDDs)                | 3924            | 32360.4             | 269                             | 831.3 (731.9, 930.6)                  | 0.48(0.42, 0.55)*** |             |
| 28–90 cDDDs                      | 1122            | 8876.1              | 102                             | 1149.2 (926.1, 1372.2)                | 0.62(0.51, 0.75)*** |             |
| 91–365 cDDDs                     | 1531            | 12432.2             | 94                              | 756.1 (603.2, 909.0)                  | 0.45(0.36, 0.55)*** |             |
| >365 cDDDs                       | 1271            | 11052.0             | 73                              | 660.5 (509.0, 812.0)                  | 0.40(0.31, 0.50)*** |             |
| Individual statin use             |                 |                     |                                 |                                        |             |             |
| Simvastatin                       | 3418            | 28625.0             | 257                             | 899.7 (788.0, 1007.6)                 | 0.55(0.49, 0.63)*** |             |
| Lovastatin                        | 2109            | 18281.5             | 262                             | 1433.1 (1259.6, 1606.7)               | 0.92(0.81, 1.04) |             |
| Atorvastatin                      | 5484            | 44678.1             | 484                             | 1083.3 (966.8, 1179.8)                | 0.59(0.54, 0.65)*** |             |
| Fluvastatin                       | 1510            | 12855.7             | 151                             | 1174.6 (987.2, 1361.9)                | 0.78(0.66, 0.92)*** |             |
| Pravastatin                       | 1501            | 12654.5             | 122                             | 964.1 (793.0, 1135.2)                 | 0.66(0.55, 0.79)*** |             |
| Rosuvastatin                      | 2741            | 22641.7             | 158                             | 697.8 (589.0, 806.6)                  | 0.42(0.36, 0.49)*** |             |

1 Main model was adjusted using propensity scores for age, sex, Charlson comorbidity index, diabetes, hypertension, dyslipidemia, urbanization level, and monthly income.
2 Lipophilia statins included simvastatin, lovastatin, atorvastatin, and fluvastatin. Hydrophilia statins include pravastatin and rosvastatin.
3 HRs for individual statins were compared between users (>28 cDDDs) and nonusers (<28 cDDDs).

Table 4. Sensitivity Analysis of aHRs of Statin Use for Reduction of the All-Cancer Risk.

| Main model† | Additional covariates‡ | Statin use | aHR (95% CI) | P for Trend |
|-------------|------------------------|------------|--------------|-------------|
| <28 cDDDs   | 28–90 cDDDs            | 91–365 cDDDs | >365 cDDDs   |             |
| 1.00        | 0.65(0.58, 0.73)***    | 0.54(0.48, 0.60)*** | 0.32(0.29, 0.36)*** | <0.001      |

1 Main model includes simvastatin, lovastatin, atorvastatin, and fluvastatin. Hydrophilia statins are pravastatin and rosvastatin.
2 Additional covariates include age, sex, Charlson comorbidity index, diabetes, hypertension, dyslipidemia, and urbanization level.
3 P for Trend
Discussion

Recently, interest in the function of systemic inflammation in COPD has been increasing.[27-31] Epidemiological studies have shown that elevated levels of systemic inflammatory markers, particularly C-reactive protein (CRP), interleukin 6, and fibrinogen, predict poor outcomes in COPD, including accelerated lung function loss, stronger infective exacerbation propensity, and higher mortality.[32-34] The prevalence of smoking is considerably high among COPD patients: 54%–77% among mild COPD patients and 38%–51% among severe COPD patients.[35-38] A 25-year follow-up study of a general population in the Danish Death Register revealed that 92% of the COPD patients have a current or past history of smoking.[39] Smoking reduces the serum high-density lipoprotein (HDL)-cholesterol levels and impairs HDL function by reducing its antioxidant and anti-inflammatory capacity and impeding the cellular cholesterol efflux.[40, 41] Statins reduce CRP levels, independent of their effects on lipids,[42, 43] thus potentially preventing cancers among COPD patients with systemic inflammation and lipid disorder.

Cancers are the leading causes of death in Taiwan.[44] Age is a major risk factor for sporadic cancer. In this study, the strongest chemopreventive effect against all cancers was observed in COPD patients aged 40–75 years (Table 2). Thus, in Taiwan, statins may have favorable chemopreventive effects in COPD patients at higher all-cancer risk owing to their age. After sex stratification, the aHRs in statin users were lower than statin nonusers (women: aHR = 0.55, 95% CI: 0.42 to 0.72; men: aHR = 0.44, 95% CI: 0.31 to 0.61; P for Trend <0.001). A similar effect of reduction in the all-cancer risk was observed among COPD patients, regardless of their sex.

In this study, statins reduced the all-cancer risk in COPD patients with dose-dependently regardless of lipophilia or hydrophilia statin use. This is the first article to estimate the dose-dependent chemopreventive effect of statins against all cancers in COPD patients. Hydrophilia statins (aHR = 0.45, 95% CI: 0.36 to 0.55) appeared to have a stronger potential anticancer effect because their moderate dose (91–365 cDDDs) could more sufficiently reduce cancer incidence compared with lipophilia statins (aHR = 0.59, 95% CI: 0.45 to 0.79). On estimating the chemopreventive effects of individual statins against all cancers, we observed the following: the aHRs for all-cancer risk was observed among COPD patients, regardless of their sex.

| Statin use | Statin lipid lowering drugs | Nonstatin lipid-lowering drugs |
|-----------|----------------------------|--------------------------------|
| 91–365 cDDDs | aHR (95% CI) | aHR (95% CI) |
| >365 days | 0.32 (0.28, 0.37)** | 0.65 (0.54, 0.76)** |
| 28–90 cDDDs | 0.60 (0.50, 0.66)** | 0.38 (0.27, 0.49)** |
| <28 cDDDs | 0.81 (0.64, 1.02) | 0.51 (0.34, 0.73)** |

*p < 0.05 **p < 0.01 ***p < 0.001
aHR: adjusted hazard ratio
CCI: Charlson comorbidity index
Models were adjusted for covariates in the main model as well as each additional listed covariate.
with the potency of for lowering LDL levels. These outcomes can indicate a statin ideal for further clinical studies

A higher proportion of statins nonuser used nonstatin lipid-lowering drugs, metformin, and aspirin for <28 cDDD; however, most statin users used these for ≥28 cDDD. If moderate to high cDDDs (28–365 or >365 cDDDs) of aspirin, metformin, and ACEI are used, the chemopreventive effect of statins against the all cancer risk will be masked (Table 4). If statin dose is increased to >365 cDDDs, the aHRs of statins for reducing all-cancer risk in COPD patients were significant in our sensitivity analysis. These outcomes might explain the independent chemopreventive effect of aspirin, metformin, ACEI, nonstatin lipid-lowering drugs, and statins.[48, 49] However, the anticancer effects of statins, associated with anti-inflammatory, antioxidant, antiplatelet, and lipid modification effects, cannot be replaced by aspirin, metformin, ACEI, and nonstatin lipid-lowering drug use.[14-16] This is also the first study to propose that statins exerts dose-response and chemopreventive effects against all cancers in COPD patients.

However, this study has potential limitations. The bias of additional risk factors associated with COPD and all cancers, including a personal or family history of sporadic cancers, obesity, alcohol use, physical activity, and smoking, could not be eliminated. A large-scale randomized trial with a suitable regimen in well-selected patients comparing standard approaches is required for obtaining this crucial information. However, methodological concerns may obscure the precise relationship between these factors and cancer risk. In our study, we used PSs to match age, sex, the CCI, diabetes, hypertension, dyslipidemia, urbanization levels, and monthly income. The urbanization level and monthly income are invalidated alternatives for lifestyle factors and the environmental level. Moreover, the diagnoses of all cancers and other comorbidities were completely dependent on the ICD-9-CM codes. Nevertheless, the NHI Administration randomly reviews medical records and interviews patients to validate diagnoses, and hospitals with outlier diagnoses and practices may be audited and subsequently penalized heavily if malpractice and discrepancies are discovered. Another limitation of this study is that information on several unmeasured confounders, such as body mass index, smoking, alcohol use, and other over-the-counter drug use—which are associated with cancers—is unavailable in the NHIRD. However, considering the magnitude and significance of the observed effects, it is unlikely that these limitations have compromised the results. Finally, because our study is not a prospective randomized blinded study, a cause–effect relationship could not be established. The findings of this study suggest that statins dose-dependently exert a significant chemopreventive effect against all cancers in COPD patients. Additional randomized studies are required to verify these findings.

Conclusions

Statins dose-dependently exert a significant chemopreventive effect against all cancers in COPD patients; in particular, rosuvastatin has the strongest chemopreventive effect.

Competing Interests

The authors have declared that no competing interest exists.

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