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Statins associated with improved mortality among patients with certain histological subtypes of lung cancer

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Abstract

Objectives: To measure the association between statin exposure and mortality in lung cancer patients belonging to different categories of histological subtype.

Materials and methods: A cohort of 19,974 individuals with incident lung cancer between 2007 and 2011 was identified using the SEER-Medicare linked database. Statin exposure both pre- and post-diagnosis was analyzed to identify a possible association with cancer-specific mortality in patients stratified by histological subtype. Intention-to-treat analyses and time-dependent Cox regression models were used to calculate hazard ratios and 95% confidence intervals (95% CIs) corresponding to statin exposure both pre- and post-diagnosis, respectively.

Results: Overall baseline statin exposure was associated with a decrease in mortality risk for squamous-cell carcinoma patients (HR = 0.89, 95%CI = 0.82–0.96) and adenocarcinoma patients (HR = 0.87, 95%CI = 0.82–0.94), but not among those with small-cell lung cancer. Post-diagnostic statin exposure was associated with prolonged survival in squamous-cell carcinoma patients (HR = 0.68, 95%CI = 0.59–0.79) and adenocarcinoma patients (HR = 0.78, 95%CI = 0.68–0.89) in a dose-dependent manner.

Conclusion: There is consistent evidence indicating that baseline or post-diagnostic exposure to simvastatin and atorvastatin is associated with extended survival in non-small-cell lung cancer subtypes. These results warrant further randomized clinical trials to evaluate subtype-specific effects of certain statins in patient cohorts with characteristics similar to those examined in this study.

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Conflict of interest

The authors declare no conflict of interest

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Keywords

Statins; lung cancer; histological subtypes; survival analysis; SEER-Medicare; squamous-cell carcinoma; adenocarcinoma; small-cell lung cancer; retrospective cohort study

Introduction

Lung cancer is the deadliest cancer in the United States, with only 18% of patients surviving longer than 5 years after diagnosis. As a result, extensive clinical investigations are currently under way to identify novel drug candidates that can improve the prognosis of lung cancer patients. In recent years, a class of 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitors called statins have garnered widespread attention for their possible therapeutic activity in several cancer types, including lung cancer [1]. A potential mechanism by which these medications exhibit anti-tumor properties is broadly downregulation of members of the STAT pathway (i.e. STAT4) [2] which affect tumor growth and angiogenesis [3]. Therefore, modulation of the STAT pathway by exposure to statins could affect overall survival, and the effects of specific statins on STAT pathway genes may vary. Thus, analyzing the overall impact of statin use on cancer risk is noteworthy, but more precise analysis according to the specific statin being taken could be more beneficial for understanding its effects on lung cancer growth. Several observational studies have been conducted to evaluate the possible effects of statins on lung cancer mortality. In a nationwide study of Danish patients diagnosed with cancer between 1995 and 2007, pre-diagnostic statin exposure was associated with a 13% decrease in lung cancer mortality risk. However, this study did not analyze post-diagnostic statin exposure in a dose-response manner and did not evaluate the association in different histological subtypes of lung cancer [4]. Cardwell et al. investigated statin exposure in a collection of linked English health registries and found an association similar to that of the Danish study, but they did not incorporate stage information and subtype information into their analyses [5]. Lastly, in a study focusing on stage IV non-small-cell lung cancer, Lin et al. found a decrease in mortality risk of 22–26% among patients who had been exposed to statins prior to diagnosis using the SEER-Medicare registry consisting of patients diagnosed between 2007 and 2009 [6]. However, this study was limited to non-small-cell lung cancer patients, and information was collected only within a 2-year time frame. Furthermore, the study focused mainly on baseline exposure of statins and did not evaluate post-diagnostic statin exposure in a dose-response manner. In summary, these studies have not placed enough emphasis on subtype-specific effects. Several main subtypes exist, including non-small-cell lung cancers (consisting of squamous-cell carcinomas and adenocarcinomas) and small-cell lung cancers. These subtypes exhibit varied disease etiologies and molecular heterogeneity, making it essential to account for these subtypes when carrying out epidemiological analyses [7]. Furthermore, some of these studies do not analyze both pre- and post-diagnostic exposure or do not adjust for stage.

In light of these observational studies, two major randomized prospective clinical trials have been performed to determine whether statin exposure leads to survival benefits among lung cancer patients. The first study, called LUNGSTAR, investigated the association between

pravastatin use and mortality risk in 846 small-cell lung cancer patients and found no association [8]. Another study consisting of 106 patients carried out by Han et al. compared the mortality risk between advanced non-small-cell lung cancer patients receiving gefitinib and simvastatin polytherapy with those receiving gefitinib monotherapy [9]. They found no association among the entire study cohort but did find that simvastatin improved chemotherapy response rate and extended progression-free survival among patients with wild-type EGFR tumors [9]. These studies demonstrate that histological subtype and the molecular characteristics of lung tumors must be considered when evaluating associations between exposure and mortality.

This study was a retrospective cohort analysis of five statins within three major lung cancer histological subtypes: squamous-cell carcinoma, adenocarcinoma, and small-cell lung cancer. We investigated stage-specific associations between exposure and mortality risk within patients with non-small-cell lung cancer subtypes. This study expands on previous reports by using a substantially larger SEER-Medicare cohort to carry out comprehensive subtype-specific, statin-specific, and exposure-specific (pre- or post-diagnosis) analyses [6].

Materials and methods

Data source

All data used in this study were derived from the National Cancer Institute's SEER program linked to Medicare claims [10]. At the time of these analyses, SEER captured incident cancer cases (2007–2011) from 18 population-based registries which contain health records for approximately 26% of the United States population [10]. The SEER program records standardized information on patient demographics, clinical status, and vital status in the Patient Entitlement and Diagnosis Summary File (PEDSF). Individuals documented within SEER registries are linked to Medicare data from the time of eligibility until last follow-up using an algorithm with a 93% match rate [10]. This study used Medicare beneficiary information (Denominator File), inpatient data (MedPAR), outpatient data (Outpatient Claims), physician visit data (Carrier Claims), and prescription data (Part D) to carry out the analyses [10].

Study cohort

The SEER-Medicare registry contains documentation for 235,357 Medicare beneficiaries age ≥ 65 diagnosed with lung cancer between 2007 and 2011. To select a study cohort, several exclusion criteria were used to remove patients not qualified for this study. The complete criteria and the resulting number of patients removed from the study are shown in Figure 1. All patients were observed until death or date of last study follow-up (January 1, 2014). After selecting qualified individuals, we derived a final study cohort of 19,974 Medicare beneficiaries diagnosed with lung cancer between 2007 and 2011.

Statin exposure and primary outcome

The Part D Drug Event File provides detailed longitudinal information on each patient's prescription, including date of prescription, duration of each prescription, and the dosage prescribed. From these data, baseline and post-diagnostic statin use was extracted for all

patients in the study cohort. Exposure information corresponding to three lipophilic and two hydrophilic statins—atorvastatin, simvastatin, lovastatin, pravastatin, and rosuvastatin—was analyzed. Overall statin exposure (any statin versus no statins) and statin-specific exposure (type of statin versus no statins) were considered in the analysis. It was assumed that patients maintained statin use throughout the duration of the prescription. Baseline statin users included patients who had any evidence of statin prescription within 1 year prior to diagnosis. Post-diagnostic users included patients who received a statin prescription any time between diagnosis and the last follow-up. Patients who initiated statin use after diagnosis were considered non-users until the time of their first prescription when they transitioned into users. Representing statin exposure as a time-varying variable eliminates immortal time bias by properly reassigning users' unexposed person-times [11]. Furthermore, post-diagnostic statin exposure was lagged by 1 month to account for end-of-life effects and remove possible reverse causation [12]. The primary outcome was lung-cancer-specific mortality calculated as time from diagnosis to last follow-up (December 31, 2014) using the PEDSF file.

Evaluation of other covariates

This study focused on three major histological subtypes of lung cancer, including squamous-cell carcinoma, adenocarcinoma, and small-cell lung cancer. Subtype information and clinicopathological covariates—including stage, grade, age, sex, and race—were extracted from the PEDSF file. Comorbid conditions that existed 12 months prior to diagnosis were extracted from the MedPAR, NCH, and outpatient claims files. Comorbid conditions were considered if they had more than two claims records that appeared more than 30 days apart in the NCH or outpatient files [13, 14]. The Deyo adaptation of the Charlson comorbidity index was calculated for each patient using ICD-9-CM or Healthcare Common Procedure Coding System (HCPCS) codes using the 2000 version of the Comorbidity SAS macro [15,16]. Myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, chronic obstructive pulmonary disease (COPD), dementia, paralysis, diabetes, chronic renal failure, liver disease, ulcer, rheumatoid arthritis, and AIDS were used to calculate the Charlson index. COPD was used as a proxy for smoking status [17] since this information was not available in SEER-Medicare. To estimate the income of each patient, the mean household income corresponding to the patient's zip code at time of diagnosis was used as a socioeconomic indicator. Receipt of chemotherapy (HCPCS: J9000:J999, Q0083–Q0085) or radiation therapy (HCPCS: 77401–77499, 77750–77799, 90256, G0256, G0261) within 6 months after diagnosis was determined for each patient based on the NCH file. Differences in the distribution of clinical or demographic variables between users and non-users within each subtype were evaluated using a chi-squared test for categorical variables and a two-sided t-test for continuous or ordinal variables.

Statistical analyses

Overall exposure to any statin or to a specific statin was evaluated separately for squamous-cell carcinoma, adenocarcinoma, and small-cell lung cancer. For the statin-specific analysis, any-users of atorvastatin, simvastatin, lovastatin, pravastatin, or rosuvastatin were compared to non-users of any statin. Two models—which input baseline or post-diagnostic statin

exposure as independent variables, respectively—were used to evaluate the association between statin prescription and lung cancer mortality risk.

The first model used an intention-to-treat approach by stratifying patients into baseline exposed or unexposed groups determined by whether they had evidence of statin prescription 1 year prior to lung cancer diagnosis [18]. Namely, patients prescribed statins within the 1-year time frame were considered users, and never-users or patients only prescribed statins >1 year prior to or after diagnosis were considered unexposed. After stratifying patients into exposed and unexposed groups, a multivariable Cox proportional hazards regression model was used to calculate hazard ratios (HRs) and 95% confidence intervals (95% CIs) [19].

The second model incorporated longitudinal prescription information that had been documented between diagnosis and last follow-up to perform a dose–response analysis that measured the association between increasing post-diagnostic exposure and cancer-specific mortality. We implemented a time-varying multivariable Cox proportional hazards regression model using cumulative months of use as the independent variable and cancer-specific mortality risk as the dependent variable [11,19]. Post-diagnostic exposure was lagged by 1 month to remove potential reverse causation and end-of-life effects [12]. Exposed patients were further stratified into short-term users and long-term users using median cumulative months of use as the cutoff. Specifically, the cutoffs were 300 days, 330 days, and 180 days for squamous-cell carcinoma, adenocarcinoma, and small-cell lung cancer patients, respectively. HRs and 95% CIs were calculated to compare the mortality risk between short-term or long-term users, and unexposed patients.

Stage-specific analysis in squamous-cell carcinoma and adenocarcinoma was performed using the intention-to-treat baseline exposure model. Statin exposure status was defined as prescription of simvastatin, atorvastatin, or pravastatin in the year prior to diagnosis. Patients with stage I, II, or III lung cancer were categorized as having early-stage regional or localized tumors, whereas patients with stage IV lung cancer were categorized as having late-stage distant or metastatic lung cancer.

All Cox proportional hazards models included stage, grade, Charlson comorbidity, receipt of chemotherapy, receipt of radiation therapy, COPD status, age, gender, income, and race as additional covariates to correct for potential confounding. These covariates were also used to calculate propensity scores that estimate how likely patients are to receive statin prescription based on their characteristics. These scores were used to match baseline users to a group of non-users using ‘optimal’ matching. Two-sided P values were used to evaluate the significance of the hazard ratios; $P < 0.05$ was considered statistically significant. The R programming language and SAS 9.4 were used to perform all statistical analyses.

Results

Patient characteristics at baseline

Among the 19,974 individuals with an incident lung cancer, the major histological subtypes were: 7,621 (38%) squamous-cell carcinoma, 10,374 (52%) adenocarcinoma, and 1,979

(10%) small-cell lung cancer; 3,622 (18%) of the cohort were identified as statin users (Table 1). Across all subtypes there were significant differences in gender, race, income, Charlson index, and history of COPD. Users were more likely to be female ($P < 0.001$), have lower income ($P < 0.001$), have more comorbid conditions ($P < 0.001$), and be diagnosed with COPD ($P < 0.001$). There were slight but significant differences in tumor stage and grade distributions between users and non-users among adenocarcinoma and small-cell carcinoma patients.

Overall statin exposure and mortality

Patients with squamous-cell carcinoma exposed to statins at baseline exhibited an 11% decrease in mortality risk compared to non-users (HR = 0.89, 95%CI = 0.82–0.96). Adenocarcinoma patients exposed at baseline exhibited a 13% decrease in mortality risk (HR = 0.87, 95%CI = 0.82–0.94) compared to non-users. Small-cell carcinoma patients exposed at baseline exhibited a non-significant increase in mortality risk (HR = 1.05, 95%CI = 0.92–1.20) compared to non-users (Table 2).

When evaluating post-diagnostic exposure, long-term statin users with squamous-cell carcinoma exhibited a 32% decrease in mortality risk (HR = 0.68, 95%CI = 0.59–0.79). Among patients with adenocarcinoma, long-term statin exposure was associated with a 22% decrease in mortality risk (HR = 0.78, 95%CI = 0.68–0.89). Long-term users with small-cell carcinoma exhibited a non-significant increase in mortality risk (HR = 1.16, 95%CI = 0.93–1.43) (Table 3). We also investigated the relationship between baseline and post-diagnostic use by including both variables in a Cox regression model and stratifying patients on baseline use. In this analysis, we found that post-diagnostic ever use was more strongly associated with survival in patients who had no history of baseline use (Appendix A1 & A2).

Exposure to specific statins

When analyzing baseline users of a specific type of statin, we found that in squamous-cell carcinoma patients, atorvastatin (HR = 0.87, 95%CI = 0.76–0.99) and simvastatin (HR = 0.88, 95%CI = 0.79–0.99) were associated with a 13% and 12% decrease in mortality, respectively. For adenocarcinoma patients, atorvastatin was associated with a 15% decrease in mortality (HR = 0.85, 95%CI = 0.75–0.96) and simvastatin was associated with a 10% decrease in mortality (HR = 0.90, 95%CI = 0.81–0.99). No statin was significantly associated with decreased mortality risk in small-cell carcinoma patients (Table 4).

When considering post-diagnostic exposure to specific statins, squamous-cell carcinoma patients who were long-term users of atorvastatin exhibited a 38% decrease in mortality risk (HR = 0.62, 95%CI = 0.49–0.78), and those who were long-term users of simvastatin exhibited a 34% decrease in mortality risk compared to non-users (HR = 0.66, 95%CI = 0.54–0.80). We also observed that short-term users of rosuvastatin experienced a 29% reduction in mortality risk (HR = 0.71, 95%CI = 0.52–0.97). Among adenocarcinoma patients, long-term users of simvastatin exhibited a 21% decrease in mortality risk (HR = 0.79, 95%CI = 0.66–0.95), long-term users of pravastatin experienced a 48% decrease in mortality risk (HR = 0.52, 95%CI = 0.34–0.81), and long-term users of rosuvastatin exhibited a 41% decrease in mortality risk (HR = 0.59, 95%CI = 0.36–0.95). We also

observed a non-significant but borderline association between long-term use of atorvastatin and reduced mortality risk (HR = 0.83, 95%CI = 0.68–1.01). There was a borderline increase in mortality risk among long-term users of pravastatin with small-cell lung cancer (Table 5).

Statin exposure in different stages of non-small-cell lung cancer

We also investigated the association between baseline statin exposure and survival within different stages of squamous-cell carcinoma and adenocarcinoma. We observed that overall baseline statin use was associated with a 12% decrease in mortality among patients with early-stage squamous cell tumors (HR = 0.88, 95%CI = 0.83–0.94). A similar association was found in early-stage adenocarcinoma patients where baseline statin exposure was associated with a 14% decrease in mortality risk (HR = 0.86, 95%CI = 0.81–0.90). Baseline statin exposure was not significantly associated with decreased mortality rate in late-stage patients with either squamous-cell carcinoma or adenocarcinoma (Appendix A3).

Discussion

In this retrospective cohort study of SEER-Medicare lung cancer patients we investigated subtype-specific associations between baseline or post-diagnostic statin exposure and lung cancer mortality risk. We also performed a stratified analysis within early- and late-stage squamous-cell carcinoma and adenocarcinoma patients. Of importance, we found that baseline and post-diagnostic statin use was associated with significant decreases in mortality risk only among squamous-cell carcinoma and adenocarcinoma patients, but not among small-cell lung cancer patients. When implementing a propensity score matching analysis, we found similar survival associations with baseline exposure (Appendix A4). We also performed a sensitivity analysis by including patients who did not live past 1 month after diagnosis and observed consistent hazard ratios across the three subtypes. Furthermore, significant associations were observed only in early-stage patients and not in late-stage patients, but this may be due to differences in sample size.

The results of this study are consistent with those of a recent phase III clinical trial of pravastatin among patients diagnosed with small-cell lung cancer (LUNGSTAR) [8]. The investigators found that pravastatin exposure provided no survival benefit within a cohort of 846 patients from 91 hospitals in the United Kingdom. However, our study suggests that further investigation into the effects of statins among patients with squamous-cell carcinoma and adenocarcinoma is warranted. This is supported by the fact that small-cell carcinomas differ substantially from non-small-cell carcinomas in their etiology and molecular underpinnings [7,20]. For instance, small-cell carcinomas are strongly associated with smoking status, cardiovascular disease, TP53 mutations, and highly metastatic characteristics [20]. When investigating baseline and post-diagnostic use of statins together, we found that post-diagnostic users with no history of baseline statin use exhibited a stronger association with decreased mortality compared to post-diagnostic users who were exposed at baseline. A possible explanation for this observation is that baseline users tend to have more comorbid conditions. These pre-existing conditions may have progressed after

cancer diagnosis and thus cannot be fully accounted for in our models since we used pre-diagnosis information to calculate the Charlson index.

In addition to overall statin use, we carried out statin-specific analyses and found that simvastatin and atorvastatin were consistently associated with decreased mortality risk in squamous-cell carcinoma and adenocarcinomas when both baseline and post-diagnostic exposures were considered. This observation may be partially due to the high potency of simvastatin and atorvastatin [21]. Post-diagnostic pravastatin and rosuvastatin use was also associated with decreased mortality among adenocarcinoma patients.

In another prospective clinical trial, Han et al. found no difference in mortality risk between patients taking simvastatin with gefitinib and patients receiving only gefitinib prior to stratifying on EGFR mutation status [9]. Our study is in accordance with these findings as we found no survival benefit among patients with late-stage cancer receiving baseline statin prescription. These results imply that statins may be effective only for patients with early-stage non-small-cell lung cancer. However, we note that the sample size for late-stage tumors is substantially smaller than that of early-stage tumors, which may limit the statistical power of the subgroup analysis.

A limitation of this study is the homogeneity of the patient cohort, since the SEER-Medicare registry only provides information for elderly lung cancer patients. As a result, our conclusions may be limited in their generalizability, especially when considering younger populations of lung cancer patients. Another issue is the absence of information on EGFR mutation and smoking status in the registry, both of which are known to be effect modifiers. For instance, simvastatin was found to exhibit survival benefits in EGFR wild-type patients, but not in EGFR mutant patients with advanced non-small-cell lung cancer [9]. Lastly, the observed protective association may be mediated by lowered cholesterol levels which could impact patient survival. However, in a recent study of pancreatic cancer patients recorded in the Kaiser Permanente Southern California cancer registry, cholesterol exposure was found to not mediate the association between statin exposure and decreased mortality risk [22]. Of course, this remains to be demonstrated in lung cancer patients.

Conclusion

In summary, we investigated the association between statin exposure and cancer-specific mortality in three major histological subtypes of lung cancer: squamous-cell carcinoma, adenocarcinoma, and small-cell lung cancer. We analyzed baseline and post-diagnostic statin exposure (overall and by statin type) within each subtype and carried out stage-specific analyses. The results from the baseline and post-diagnostic exposure models consistently identified atorvastatin and simvastatin as potential modulators of improved survival among squamous-cell carcinoma and adenocarcinoma patients. Both models identified an association between overall statin exposure and reduced mortality risk. Based on the results of this study, we conclude that further randomized clinical trials are needed to evaluate subtype-specific effects of statins in cohorts with similar characteristics as examined in this retrospective study. These follow-up studies can validate whether these statins—particularly

simvastatin and atorvastatin—provide the survival benefit in non-small-cell lung cancer as demonstrated here.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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In this study, MU and CC conceived of and designed the study and the statistical methodology. MU and CC acquired, pre-processed and organized the data. MU, TM, TO, CA, and CC contributed to the analysis and interpretation of the results, and writing of the manuscript. The study was supervised by CC

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Highlights

- This study investigates statin use and mortality risk among SEER-Medicare patients
- Patients with squamous-cell carcinoma or adenocarcinoma benefit from using statins
- No significant survival benefit was observed in patients with small-cell carcinoma
- Simvastatin and atorvastatin were most strongly associated with prognosis
- Response to statins may vary according to histological subtype of the lung neoplasm

Figure 1.

Exclusion criteria to derive study cohort. A final cohort of 19974 was selected from a total of 235357 patients from the Surveillance, Epidemiology, and End Results (SEER) Medicare database.

Table 1:

Patient characteristics of study cohort based on baseline exposure

	Squamous-cell carcinoma (n = 7621)			Adenocarcinoma (n = 10374)			Small-cell carcinoma (n = 1979)		
	Users (n = 1376)	Non-users (n = 6245)	P ^a	Users (n = 1921)	Non-users (n = 8453)	P ^a	Users (n = 325)	Non-users (n = 1654)	P ^a
Stage (%)			0.09			0.03			0.03
I	500 (36.3)	2179 (34.9)		819 (42.6)	3299 (39.0)		–	–	
II	114 (8.3)	654 (10.5)		115 (6.0)	565 (6.7)		–	–	
III	406 (29.5)	1855 (29.7)		413 (21.5)	1866 (22.1)		108 (33.2)	524 (31.7)	
IV	356 (25.9)	1557 (24.9)		574 (29.9)	2723 (32.2)		182 (56.0)	941 (56.9)	
Grade (%)			0.50			0.02			0.02
1	40 (2.9)	177 (2.8)		359 (18.7)	1464 (17.3)		–	–	
2	618 (44.9)	2704 (43.3)		807 (42.0)	3335 (39.5)		–	–	
3	698 (50.7)	3292 (52.7)		740 (38.5)	3574 (42.3)		91 (28.0)	478 (28.9)	
4	20 (1.5)	72 (1.2)		15 (0.8)	80 (0.9)		229 (70.5)	1151 (69.6)	
Mean age (SD)	73.9 (5.1)	73.8 (5.3)	0.35	73.9 (5.3)	73.7 (5.5)	0.17	73.9 (5.3)	73.7 (5.5)	0.17
Gender (%)			<0.001			<0.001			<0.001
Female	601 (43.7)	2324 (37.2)		1089 (56.7)	4426 (52.4)		174 (53.5)	830 (50.2)	
Male	775 (56.3)	3921 (62.8)		832 (43.3)	4027 (47.6)		151 (46.5)	824 (49.8)	
Race (%)			<0.001			<0.001			<0.001
White	1165 (84.7)	5440 (87.1)		1586 (82.6)	7398 (87.5)		278 (85.5)	1488 (90.0)	
Black	109 (7.9)	596 (9.5)		124 (6.5)	639 (7.6)	26 (8.0)		126 (7.6)	
Hispanic	23 (1.7)	57 (0.9)		39 (2.0)	90 (1.1)		–	–	
Asian	79 (5.7)	152 (2.4)		172 (9.0)	326 (3.9)		–	–	
Income (SD) ^b	2.04 (0.90)	2.15 (.89)	<0.001	2.33 (1.14)	2.43 (1.10)	<0.001	2.04 (0.87)	2.12 (0.80)	<0.001
Receipt of chemotherapy (%)			0.25			0.06			0.06
No	1156 (84.0)	5325 (85.2)		1551 (80.7)	6981 (82.6)		249 (76.6)	1300 (78.6)	
Yes	220 (16.0)	920 (14.7)		370 (19.3)	1472 (17.4)		76 (23.3)	354 (21.4)	
Receipt of radiation therapy (%)			0.52			0.10			0.10
No	1143 (83.1)	5235 (85.3)		1541 (80.2)	6918 (81.8)		221 (68.0)	1161 (70.2)	
Yes	233 (16.9)	1010 (16.2)		380 (19.8)	1535 (18.2)		104 (32.0)	493 (29.8)	
Mean Charlson index (SD)	0.9 (1.4)	0.4 (1.0)	<0.001	0.6 (1.2)	0.3 (0.9)	<0.001			<0.001
Prior COPD (%)			<0.001			<0.001			<0.001
No	1053 (76.5)	5392 (86.3)		1608 (83.7)	7627 (90.2)		253 (77.8)	1460 (88.3)	
Yes	323 (23.4)	853 (13.7)		313 (16.3)	826 (9.8)		72 (22.2)	194 (11.7)	

SD, Standard deviation; COPD, chronic obstructive pulmonary disease.

^aTwo-sided p values from t test if covariate is continuous, or chi-squared test if covariate is categorical.^bEach unit of income is \$10,000.

Note: To ensure patient anonymity, groups with small n are not directly reported but are used in the analysis.

Table 2:

Multivariable Cox proportional hazards regression for the association between baseline statin exposure and lung cancer mortality risk

Statin exposure	Squamous-cell carcinoma			Adenocarcinoma			Small-cell carcinoma		
	HR	95%CI	P ^a	HR	95%CI	P ^a	HR	95%CI	P ^a
Overall use									
None	1			1			1		
Any	0.89	0.82 to 0.96	0.004	0.87	0.82 to 0.94	<0.001	1.05	0.92 to 1.20	0.49
Stage									
I	1			1			1		
II	2.01	1.78 to 2.26	<0.001	2.7	2.38 to 3.07	<0.001	1.45	1.01 to 2.08	0.04
III	3.97	3.65 to 4.32	<0.001	4.69	4.30 to 5.11	<0.001	2.47	2.00 to 3.10	<0.001
IV	6.89	6.32 to 7.51	<0.001	10.49	9.67 to 11.38	<0.001	4.43	3.55 to 5.54	<0.001
Grade									
1	1			1			1		
2	0.99	0.83 to 1.19	0.94	1.44	1.32 to 1.58	<0.001	2.08	0.79 to 5.52	0.14
3	1.05	0.88 to 1.26	0.56	1.99	1.82 to 2.18	<0.001	1.76	0.78 to 5.52	0.17
4	1.30	0.96 to 1.74	0.09	1.29	0.98 to 1.69	0.07	1.92	0.86 to 4.29	0.11
Age	1.02	1.01 to 1.03	<0.001	1.02	1.02 to 1.03	<0.001	1.02	1.01 to 1.03	<0.001
Gender									
Female	1			1			1		
Male	1.12	1.05 to 1.19	<0.001	1.26	1.20 to 1.33	<0.001	1.21	1.10 to 1.34	<0.001
Race									
White	1			1			1		
Black	0.99	0.90 to 1.09	0.86	1.02	0.92 to 1.12	0.76	1.01	0.84 to 1.22	0.93
Hispanic	1.21	0.91 to 1.59	0.19	0.88	0.69 to 1.11	0.28	1.35	0.81 to 2.25	0.26
Asian	1.07	0.90 to 1.26	0.45	0.74	0.65 to 0.84	<0.001	0.91	0.65 to 1.29	0.60
Income ^b	0.91	0.88 to 0.94	<0.001	0.93	0.90 to 0.95	<0.001	0.93	0.87 to 0.99	0.03
Receipt of chemotherapy	No			1			1		
Yes	0.66	0.60 to 0.71	<0.001	0.65	0.61 to 0.70	<0.001	0.62	0.55 to 0.70	<0.001
Receipt of radiation therapy	No								
No	1			1			1		
Yes	0.77	0.71 to 0.83	<0.001	0.77	0.73 to 0.83	<0.001	0.52	0.47 to 0.58	<0.001
Charlson index	1.03	0.99 to 1.07	0.07	1.06	1.02 to 1.10	0.003	1.03	0.97 to 1.10	0.34
Prior COPD									
No	1			1			1		
Yes	0.98	0.88 to 1.09	0.73	1.22	1.09 to 1.35	<0.001	1.15	0.95 to 1.39	0.14

HR, hazard ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease.

^aP values from two-sided Cox proportional hazards regression models adjusted for stage, grade, receipt of chemotherapy, receipt of radiation therapy, Charlson comorbidity, prior COPD diagnosis, age, race, gender, and income.

^bEach unit of income is \$10,000

Table 3:

Multivariable Cox proportional hazards regression for the association between post-diagnostic statin exposure and lung cancer mortality risk

Statin exposure ^b	Squamous-cell carcinoma			Adenocarcinoma			Small-cell carcinoma		
	HR	95%CI	P ^a	HR	95%CI	P ^a	HR	95%CI	P ^a
Overall use ^c									
None	1			1			1		
Short-term	0.93	0.85 to 1.01	0.1	1.02	0.94 to 1.11	0.66	0.92	0.84 to 1.09	0.39
Long-term	0.68	0.59 to 0.79	<0.001	0.78	0.68 to 0.89	<0.001	1.16	0.93 to 1.43	0.19
Stage									
I	1			1			1		
II	2.18	1.94 to 2.46	<0.001	2.82	2.48 to 3.20	<0.001	1.64	1.14 to 2.35	0.007
III	4.60	4.26 to 5.03	<0.001	5.22	4.79 to 5.69	<0.001	2.63	2.08 to 3.30	<0.001
IV	9.02	8.28 to 9.81	<0.001	12.90	11.93 to 13.99	<0.001	5.08	4.07 to 6.33	<0.001
Grade									
1	1			1			1		
2	0.98	0.82 to 1.17	0.81	1.46	1.33 to 1.60	<0.001	1.61	0.61 to 4.25	0.34
3	1.04	0.87 to 1.24	0.68	2.14	2.00 to 2.35	<0.001	1.47	0.65 to 3.29	0.36
4	1.33	0.99 to 1.79	0.06	1.40	1.07 to 1.83	0.02	1.57	0.70 to 3.51	0.28
Age	1.03	1.02 to 1.03	<0.001	1.03	1.02 to 1.03	<0.001	1.03	1.01 to 1.04	<0.001
Gender									
Female	1						1		
Male	1.13	1.06 to 1.20	<0.001	1.28	1.21 to 1.35	<0.001	1.21	1.10 to 1.34	<0.001
Race									
White	1			1			1		
Black	0.98	0.89 to 1.08	0.63	1.04	0.94 to 1.15	0.45	0.98	0.81 to 1.18	0.83
Hispanic	1.21	0.91 to 1.59	0.19	0.81	0.65 to 1.04	0.09	1.43	0.85 to 2.40	0.17
Asian	1.03	0.87 to 1.21	0.76	0.70	0.62 to 0.80	<0.001	0.81	0.57 to 1.14	0.22
Income ^d	0.86	0.83 to 0.89	<0.001	0.93	0.90 to 0.95	<0.001	0.95	0.89 to 1.01	0.12
Receipt of chemotherapy									
No	1			1			1		
Yes	0.63	0.58 to 0.68	<0.001	0.60	0.56 to 0.64	<0.001	0.65	0.58 to 0.74	<0.001
Receipt of radiation therapy									
No	1			1			1		
Yes	0.75	0.70 to 0.81	<0.001	0.75	0.70 to 0.80	<0.001	0.56	0.50 to 0.63	<0.001
Charlson index	1.09	1.05 to 1.12	<0.001	1.09	1.04 to 1.13	<0.001	1.04	0.97 to 1.10	0.25
Prior COPD									
No	1			1			1		
Yes	0.91	0.82 to 1.01	0.09	1.20	1.08 to 1.34	<0.001	1.16	0.96 to 1.40	0.11

HR, hazard ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease.

^aP values from two-sided Cox proportional hazards regression models adjusted for stage, grade, receipt of chemotherapy, receipt of radiation therapy, Charlson comorbidity, prior COPD diagnosis, age, race, gender, and income.

^bCumulative months of statin exposure treated as a time-varying covariate.

^cMedian cumulative months of use was used to categorize patients into short- and long-term users. Squamous-cell carcinoma (short-term: 90–300 days, long-term: >300 days), adenocarcinoma (short-term: 90–330 days, long-term: >330 days), small-cell carcinoma (short-term: 90–189 days, long-term: >189 days).

^dEach unit of income is \$10,000.

Table 4:

Adjusted hazard ratios (95% CIs) for baseline exposure to specific statins and mortality

Statin exposure	Squamous-cell carcinoma			Adenocarcinoma			Small-cell carcinoma		
	HR	95%CI	P ^a	HR	95%CI	P ^a	HR	95%CI	P ^a
Overall use									
None	1			1			1		
Any	0.89	0.82 to 0.96	0.004	0.87	0.82 to 0.94	<0.001	1.05	0.92 to 1.20	0.49
Atorvastatin									
None	1			1			1		
Any	0.87	0.76 to 0.99	0.04	0.85	0.75 to 0.96	0.007	0.94	0.77 to 1.16	0.58
Simvastatin									
None	1			1			1		
Any	0.88	0.79 to 0.99	0.03	0.90	0.81 to 0.99	0.03	1.09	0.90 to 1.31	0.37
Lovastatin									
None	1			1			1		
Any	1.20	0.95 to 1.50	0.12	1.15	0.93 to 1.41	0.207	0.77	0.48 to 1.23	0.27
Pravastatin									
None	1			1			1		
Any	0.95	0.76 to 1.18	0.14	0.63	0.66 to 1.02	0.07	1.13	0.78 to 1.63	0.52
Rosuvastatin									
None	1			1			1		
Any	0.93	0.73 to 1.18	0.55	0.97	0.78 to 1.21	0.81	1.09	0.75 to 1.58	0.65

HR, hazard ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease.

^aP values from two-sided Cox proportional hazards regression models adjusted for stage, grade, receipt of chemotherapy, receipt of radiation therapy, Charlson comorbidity, prior COPD diagnosis, age, gender, race, and income.

Table 5:

Adjusted hazard ratios (95% CIs) for post-diagnosis exposure to specific statins and mortality

Statin exposure ^b	Squamous-cell carcinoma			Adenocarcinoma			Small-cell carcinoma		
	HR	95%CI	P ^a	HR	95%CI	P ^a	HR	95%CI	P ^a
Overall use									
None	1			1			1		
Short-term	0.93	0.85 to 1.01	0.1	1.02	0.94 to 1.11	0.65	0.92	0.77 to 1.11	0.39
Long-term	0.68	0.59 to 0.79	<0.001	0.76	0.67 to 0.87	<0.001	1.16	0.93 to 1.43	0.19
Atorvastatin									
None	1			1			1		
Short-term	0.89	0.76 to 1.04	0.14	0.98	0.85 to 1.13	0.77	0.90	0.66 to 1.21	0.47
Long-term	0.62	0.49 to 0.78	<0.001	0.83	0.68 to 1.01	0.07	1.24	0.86 to 1.78	0.25
Simvastatin									
None	1			1			1		
Short-term	1.02	0.90 to 1.16	0.72	1.08	0.96 to 1.20	0.19	1.05	0.82 to 1.36	0.68
Long-term	0.66	0.54 to 0.80	<0.001	0.79	0.66 to 0.95	0.01	1.02	0.76 to 1.37	0.91
Lovastatin									
None	1			1			1		
Short-term	0.79	0.58 to 1.07	0.13	1.08	0.83 to 1.42	0.57	0.91	0.50 to 1.66	0.76
Long-term	0.89	0.56 to 1.41	0.61	0.89	0.56 to 1.39	0.60	0.45	0.14 to 1.40	0.17
Pravastatin									
None	1			1			1		
Short-term	0.84	0.65 to 1.07	0.15	1.01	0.80 to 1.27	0.92	0.66	0.34 to 1.29	0.23
Long-term	0.75	0.49 to 1.14	0.17	0.52	0.34 to 0.81	0.004	1.87	1.00 to 3.51	0.05
Rosuvastatin									
None	1			1			1		
Short-term	0.71	0.52 to 0.97	0.03	1.00	0.77 to 1.30	0.99	0.92	0.52 to 1.63	0.78
Long-term	0.82	0.56 to 1.20	0.31	0.59	0.36 to 0.95	0.03	1.18	0.43 to 3.22	0.75

HR, hazard ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease.

^a P values from two-sided Cox proportional hazards regression models adjusted for stage, grade, receipt of chemotherapy, receipt of radiation therapy, Charlson comorbidity, prior COPD diagnosis, age, race, gender, and income.^b Cumulative months of statin exposure treated as a time-varying covariate.