Research Article

Cancer Epidemiology, Biomarkers & Prevention

Statin Use and Survival from Lung Cancer: A Population-Based Cohort Study

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Abstract

Background: Preclinical evidence from lung cancer cell lines and animal models suggest that statins could have anticancer properties. We investigated whether statin users had reduced risk of cancer-specific mortality in a population-based cohort of lung cancer patients.

Methods: Newly diagnosed lung cancer patients, from 1998 to 2009, were identified from English cancer registry data and linked to the UK Clinical Practice Research Datalink, providing prescription records, and to Office of National Statistics mortality data up to 2012. Cox regression models were used to calculate HRs for cancer-specific mortality and 95% confidence intervals (CI) by statin use before and after diagnosis, and to adjust these HRs for potential confounders.

Results: In 3,638 lung cancer patients, there was some evidence that statin use after diagnosis was associated with reduced lung cancer–specific mortality (adjusted HR, 0.89; 95% CI, 0.78–1.02; $P = 0.09$). Associations were more marked after 12 prescriptions (adjusted HR, 0.81; 95% CI, 0.67–0.98; $P = 0.03$) and when lipophilic statins were investigated (adjusted HR, 0.81; 95% CI, 0.70–0.94; $P = 0.01$), but were attenuated in some sensitivity analyses. Furthermore, in 11,051 lung cancer patients, statin use before diagnosis was associated with reduced lung cancer–specific mortality (adjusted HR, 0.88; 95% CI, 0.83–0.93; $P < 0.001$).

Conclusions: There was some evidence that lung cancer patients who used statins, and particularly simvastatin, had reduced rates of cancer-specific mortality.

Impact: These findings should first be confirmed in observational studies, but provide some support for conducting randomized controlled trials of simvastatin as adjuvant cancer therapy in lung cancer patients. *Cancer Epidemiol Biomarkers Prev; 24(5); 833–41.* ©*2015 AACR.*

Introduction

Statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) are primarily used for primary and secondary prevention of coronary heart disease (1). In recent decades the potential anticancer properties of statins have received much attention (2–4). Preclinical studies have proposed a number of relevant biologic mechanisms, including inhibition of cell proliferation, stimulation of anticancer immune surveillance, and interruption of oncogenic signaling (2). In humans, epidemiologic studies have shown reductions in cancer recurrence or cancer-specific mortality at a number of cancer sites, including breast (5), prostate (6), and colorectal (7).

The preclinical evidence for the effect of statins on lung cancer appears promising. *In vitro* studies have shown reduced proliferation (8, 9), reduced migration (10), and increased apoptosis (9) in lung cancer cell lines treated with simvastatin, and an *in vivo* study (10), using a mouse model, demonstrated reduced tumor growth and bone metastases after simvastatin treatment. Despite this preclinical evidence, few studies in humans have investigated the association between statin use and survival in lung cancer patients. A recent Danish study (11) observed some evidence of a weak reduction in cancer-specific mortality in individuals who used statins before lung cancer diagnosis (HR, 0.87; 95% CI, 0.83–0.92). However, this study did not report findings for statins used after diagnosis, the time period when clinical intervention is possible, nor did it report results for lung cancer by statin type or evidence of dose response associations. A phase III randomized clinical trial has also been conducted in 846 small-cell lung cancer patients, which compared chemotherapy and pravastatin with chemotherapy alone (12). Although the final trial report has not yet been published, the results were presented at the World Conference on Lung Cancer, Sydney, and a significant protective effect was not observed (13). It is worth noting that this trial only investigated pravastatin and included only patients with small-cell lung cancer. Consequently, there remains a need to investigate the association between statin use and survival after lung cancer diagnosis, particularly for simvastatin because of the considerable supportive preclinical evidence.

Therefore, we investigated the effect of statin use, both before and after cancer diagnosis, on cancer-specific mortality in a large population-based cohort of lung cancer patients.

Materials and Methods

Data source

This study is based upon linkages between the National Cancer Data Repository (NCDR), the UK Clinical Practice Research Datalink (CPRD), and the Office of National Statistics (ONS) death registration data. NCDR data, available for England,

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included all patients identified by cancer registries, containing date and site of primary cancer diagnosis, and treatment data. The CPRD includes general practice records and contains demographic information, clinical diagnoses, and prescription data of documented high quality (14–16). CPRD is the world's largest computerized database of longitudinal patient records comprising approximately 7% of the UK population. ONS death registration data provided date and cause of death. Linkages between data sources were conducted using a deterministic algorithm based upon NHS number, gender, date of birth, and postcode. Ethical approval for all observational research using CPRD data has been obtained from a multicenter research ethics committee.

Cohort selection

A cohort of newly diagnosed lung cancer patients was identified from cancer registry recorded primary diagnosis of lung cancer (ICD code C34 Malignant neoplasm of bronchus and lung) between 1998 and 2009, from NCDR. Cohort members with previous NCDR cancer diagnosis, apart from *in situ* neoplasms and nonmelanoma skin cancers, were excluded. This cohort was linked to CPRD and ONS death registration data. Deaths were identified from ONS with coverage up to January 2012 with lung cancer–specific deaths defined as those with underlying cause of death ICD code C34.

Exposure data

Statins were determined from GP prescribing records (from CPRD) based upon the Statins section of the British National Formulary (Section 2.12; ref. 17). A quantity of 28 tablets (the most common pack size prescribed) was assumed for approximately 1% of prescriptions where quantity was missing or assumed incorrect. The daily defined doses (DDD) in each prescription were calculated by multiplying the quantity by the strength (in mg) and dividing by the mg in a DDD from the World Health Organization (18). In the main analysis of stains after diagnosis, the exposure window for statin use was from lung cancer diagnosis to death or end of follow-up, but was subject to a lag (described later). In the main analysis of statins before diagnosis the exposure window was from 1 year before lung cancer diagnosis to the date of lung cancer diagnosis. Statins were analyzed individually and grouped by type into liphophilic statins (including simvastatin, fluvastatin, and cerivastatin) and hydrophilic statins (including atorvastatin, pravastatin, and rosuvastatin).

Covariates

Data available from NCDR included histology, surgery, chemotherapy, and radiotherapy in the 6 months after diagnosis. Cancer registry recorded histology codes (International Classification of Diseases for Oncology, Third edition) were used to identify small-cell lung cancer patients. Smoking, alcohol, and body mass index (BMI) were determined from the closest GP record before lung cancer diagnosis (values more than 10 years before diagnosis were ignored). Comorbidities were determined before diagnosis from GP diagnosis codes using comorbidities comprising a recent adaptation of the Charlson index (19). CPRD provided deprivation based upon postcode of residence using the 2004 index of multiple deprivation for England (20). Low-dose aspirin, beta-blocker use, and bisphosphonate use were determined from GP prescription records to allow for adjustment, because of potential associations with cancer-specific mortality.

Statistical analysis

In analyses of statin use after lung cancer diagnosis, deaths in the first year after diagnosis were removed as it seemed unlikely that statin use after diagnosis could influence such deaths. Consequently, patients were followed from 1 year after lung cancer diagnosis to death, end of registration with the general practice, last date of data collection from general practice or end of ONS follow-up. Time-dependent Cox regression models were used to calculate HRs for lung cancer–specific death and 95% confidence intervals (95% CI). Statin use was defined as a time varying covariate (21) with patients initially considered nonusers, and then users after a lag of 6 months after their first statin prescription. A lag is recommended (22) and was used to remove prescriptions in the 6 months before death as these may reflect increased contact with medical professionals or end of life care. In sensitivity analyses the duration of this lag was varied. Dose–response analyses were conducted with individuals considered nonusers before 6 months after first use, a short-term user between 6 months after first use and 6 months after the 12th prescription (or 365th DDD) and a longer-term user after this time. Adjusted analyses were conducted by including potential confounders in the cox regression models. Analyses were conducted by number of prescriptions, number of DDDs, and type of statin and repeated for all-cause mortality (which does not require classification of the cause of death). Subgroup analyses were conducted by gender, type of lung cancer (i.e., small-cell vs. non–small cell) and prediagnostic statin use. Tests for interactions were performed using interaction terms within the Cox regression models. Sensitivity analyses were conducted increasing the lag to 1 year, additionally adjusting for smoking, BMI, bisphosphonate use, and lung cancer type. A simplified analysis was conducted comparing statin users with nonusers in the first year after lung cancer diagnosis in individuals alive 1 year after diagnosis, thus controlling for immortal time bias (23) without requiring time varying covariates. A nested case–control analysis of the cohort was also conducted in which cases who died due to lung cancer were matched on gender, age (in 5 years), and year of diagnosis (in 2 years) to five risk-set controls who lived at least as long after their lung cancer diagnosis. The exposure period was from lung cancer diagnosis until 6 months before lung cancer–specific death in cases and for a period of identical duration from diagnosis in matched controls. Conditional logistic regression was then used to calculate corresponding ORs, and 95% CIs, for statin use in the exposure period adjusting for potential confounders.

In analyses of statin use before cancer diagnosis, lung cancer patients were followed from diagnosis to death or censoring (as defined previously). Deaths in the first year after diagnosis were not excluded. Cox regression models were used to calculate HRs and 95% CIs for stain use based upon prescriptions in the year before diagnosis (restricted to individuals with at least 1 year of records before diagnosis). Adjusted analysis were conducted, including only potential confounders recorded before diagnosis, to avoid overadjustment (such as age, year, gender, comorbidities, deprivation, aspirin, and beta-blocker user in the year before diagnosis; refs. 24, 25). Analyses were conducted by statin type, number of prescriptions and number of DDDs. Subgroup analyses were conducted by gender. Sensitivity analyses were conducted additionally adjusting for BMI, bisphosphonate use, and smoking before diagnosis and defining statin use as a prescription from 2 years to 6 months before diagnosis (restricted to individuals with at least 2 years of records before diagnosis).

Results

Patient cohort

A total of 14,689 lung cancer patients were diagnosed in NCDR with linked CPRD data. The analysis of statin use after lung cancer contained 3,638 patients, because 11,051 were excluded with less than 1 year of follow-up (10,265 of whom had died), with average follow-up of 3 years (maximum 14 years). The analysis of statin use before lung cancer contained 13,398 patients, because 1,291 were excluded with less than 1 year of records before diagnosis, with average follow-up of 1 year (maximum 14 years).

Patient characteristics by statin use are shown in Table 1. Statin users (before or after diagnosis) were more likely to be diagnosed more recently, be older, be male, have higher BMI, have comorbidities (particularly for cerebrovascular disease, diabetes, and myocardial infarction) and to use aspirin and beta-blockers. Statin users after diagnosis were less likely to have chemotherapy. The associations between statin use and other patient characteristics were less marked. In 3,357 lung cancer patients who lived at least 1 year after diagnosis and who had 1 year of records before diagnosis, 2,223 did not use statins in the year before diagnosis and did not use statins any time after diagnosis, 76 used before but not after, 256 used after but not before, and 802 used before and after.

Statin use after diagnosis

Overall, statin users after diagnosis had an 11% reduction in the rate of lung cancer–specific mortality (adjusted HR, 0.89; 95% CI, 0.78–1.02; $P = 0.09$) compared with statin nonusers after adjustment for confounders, Table 2. Compared with statin nonusers, individuals with 1 to 12 statin prescriptions after diagnosis had a 6% reduction (adjusted HR, 0.94; 95% CI, 0.81–1.09; $P = 0.39$) whereas individuals with more than 12 prescriptions had a 19% reduction (adjusted HR, 0.81; 95% CI, 0.67, 0.98; $P = 0.03$) in the rate of lung cancer–specific mortality. A similar pattern was seen for statin use based upon DDDs. There was some indication that lipophilic statins (adjusted HR, 0.81; 95% CI, 0.70–0.94; $P = 0.01$), particularly simvastatin (adjusted HR, 0.80; 95% CI, 0.69–0.93; $P = 0.003$), appeared to have more protective associations than hydrophilic agents (adjusted HR, 1.00; 95% CI, 0.85–1.18; $P = 0.01$). Similar associations were observed for all-cause mortality. In subgroup analyses (Table 3) there were no marked differences in associations by gender ($P_{interaction} = 0.47$), prediagnostic statin use ($P_{interaction} = 0.49$), or by lung cancer type ($P_{interaction} = 0.12$). The associations were little altered in most sensitivity analyses, but they were attenuated when the lag was increased to 1 year (adjusted HR, 0.92; 95% CI, 0.80–1.05; $P = 0.22$).

Statin use before diagnosis

Overall, statin users before diagnosis had a 12% reduction in rate of lung cancer–specific mortality (adjusted HR, 0.88; 95% CI, 0.83–0.93; P<0.001) compared with statin nonusers following adjustment for confounders, Table 4. The magnitude of the reduction in risk of lung cancer–specific death was similar in patients with 1 to 12 statin prescriptions in the year before diagnosis (adjusted HR, 0.87; 95% CI, 0.82–0.92; $P < 0.001$) and in those with more than 12 prescriptions (adjusted HR, 0.91; 95% CI, 0.84–0.99; $P = 0.02$) compared with statin nonusers. Comparable associations were observed for all-cause mortality. The observed associations were similar by statin type, by gender ($P_{interaction} = 0.10$) and in sensitivity analyses, Table 5.

Discussion

In this large population-based cohort, lung cancer patients who used statins after diagnosis had a nonsignificant 11% reduction in cancer-specific mortality and those who used simvastatin had a 20% reduction in cancer-specific mortality. These associations were apparent when prescriptions in the 6 months before death, which could reflect end of life care, were removed but were attenuated in a sensitivity analysis, which removed prescriptions in the year before death. Lung cancer patients who used statins in the year before diagnosis had a 12% reduction in cancer-specific mortality. This association was little altered in sensitivity analyses.

Although there have not been any epidemiologic studies that have investigated the association between statin use after lung cancer diagnosis and cancer-specific mortality, a recent trial (12, 13) found no protective effect of pravastatin and chemotherapy compared with chemotherapy alone in small-cell lung cancer patients. Our study also found no association between pravastatin use after diagnosis and cancer-specific mortality (adjusted HR, 1.23; 95% CI, 0.85–1.77; $P = 0.27$), but we found some evidence of protective associations for other statins that were not investigated in this trial, such as simvastatin. A similar phase II trial (26) has also been conducted that included 106 advanced (stage IIIb or IV) non–small cell lung cancer patients. This trial observed a weak improvement in survival in a group that received simvastatin plus gefitinib compared with gefitinib only (HR, 0.88; 95% CI, 0.57–1.35: $P = 0.49$), but this was not significant. We observed a slightly more marked, but not inconsistent, inverse association between simvastatin and cancer-specific mortality (adjusted HR, 0.80; 95% CI, 0.69–0.93; $P = 0.003$). Other early-phase trials, though not powered to report upon efficacy, are also in progress (27–30) but contain relatively small numbers.

Statin use before diagnosis and survival of lung cancer patients was investigated in a subgroup of a large Danish epidemiologic study (11). This Danish study demonstrated a weak protective effect of prediagnostic statins on cancer-specific mortality in lung cancer patients (adjusted HR, 0.87; 95% CI, 0.83–0.92) almost identical to our finding (adjusted HR, 0.88; 95%, CI 0.83–0.93), but this study did not report results for different types of statins or dose–response analyses in lung cancer patients.

Our study has several strengths and limitations. This is the first study to investigate statin use after diagnosis and lung cancer–specific mortality. The cohort was large with long follow-up of up to 14 years. NCDR and ONS data allowed robust verification of cancer diagnosis and death. Although some misclassification of cause of death is possible, this seems unlikely to bias results particularly as analysis of all-cause mortality produced similar findings. Routinely recorded GP dates of prescriptions were used eliminating the potential for recall bias. However, misclassification of statin use is possible due to over the counter use, but only low-dose 10 mg simvastatin is available over the counter in the UK and only from 2004 (31). Noncompliance may also contribute to misclassification, but associations were also apparent in patients who had 12 or more statin prescriptions in whom noncompliance is of less concern. Furthermore, any misclassification of statin usage is likely to drag associations to the null rather than create spurious associations.

The cause of any reduction in lung cancer–specific mortality in lung cancer patients using statins is unknown. As with all observational studies, it is not possible to rule out residual confounding by unrecorded or incomplete variables. In particular, adjustments

Table 1. Characteristics of lung cancer patients by statin use before and after diagnosis

Characteristics	Statin use in year before diagnosis[a]		Statin use in year after diagnosis[b]		Statin use after diagnosis[b]	
	Ever *n* (%)	Never (%)	User *n* (%)	Nonuser (%)	User *n* (%)	Nonuser (%)
	(*n* = 13,398)		(*n* = 3,638)		(*n* = 3,638)	
Year of diagnosis						
1998–2000	102 (3)	2,204 (22)	24 (3)	618 (22)	79 (7)	563 (22)
2001–2003	451 (14)	2,893 (29)	132 (15)	754 (27)	217 (19)	669 (26)
2004–2006	1,118 (34)	2,650 (26)	279 (32)	690 (25)	347 (31)	622 (25)
2007–2009	1,616 (49)	2,362 (23)	428 (50)	713 (26)	472 (42)	669 (27)
Age at diagnosis						
<50	16 (0)	405 (4)	7 (1)	166 (6)	14 (1)	159 (6)
50–59	230 (7)	1,363 (13)	84 (10)	486 (18)	132 (12)	438 (17)
60–69	966 (29)	2,607 (26)	295 (34)	873 (31)	377 (34)	791 (31)
70–79	1,447 (44)	3,447 (34)	360 (42)	897 (32)	451 (40)	806 (32)
80–89	598 (18)	2,045 (20)	115 (13)	325 (12)	137 (12)	303 (12)
≥90	30 (1)	242 (2)	2 (0)	28 (1)	4 (0)	26 (1)
Gender, males	2,030 (62)	5,886 (58)	541 (63)	1,563 (56)	690 (62)	1,414 (56)
Treatment within 6 months of cancer diagnosis						
Surgery[c]	339 (13)	883 (11)	212 (31)	659 (31)	333 (38)	538 (28)
Chemotherapy	743 (23)	2,287 (23)	267 (31)	993 (36)	324 (29)	936 (37)
Radiotherapy	1,028 (31)	3,197 (32)	319 (37)	1,062 (38)	377 (34)	1,004 (40)
Histology						
Non–small cell	1,901 (58)	5,627 (56)	638 (74)	1,982 (71)	835 (75)	1,785 (71)
Small cell	418 (13)	1,257 (12)	89 (10)	335 (12)	108 (10)	316 (13)
Missing	968 (29)	3,225 (32)	136 (16)	458 (17)	172 (15)	422 (17)
Smoking status before cancer diagnosis						
Non-smoker	372 (11)	1,338 (13)	100 (12)	385 (14)	128 (11)	357 (14)
Ex-smoker	1,688 (51)	3,175 (31)	439 (51)	955 (34)	525 (47)	869 (34)
Current smoker	1,149 (35)	4,305 (43)	295 (34)	1,144 (41)	411 (37)	1,024 (41)
Missing	78 (2)	1,291 (13)	29 (3)	291 (10)	51 (5)	269 (11)
Alcohol consumption before diagnosis						
Never	564 (17)	1,271 (13)	132 (15)	340 (12)	165 (15)	307 (12)
Ever	2,175 (66)	5,709 (56)	586 (68)	1,671 (60)	750 (67)	1,507 (60)
Missing	548 (17)	3,129 (31)	145 (17)	764 (28)	200 (18)	709 (28)
BMI (kg/m^2) before diagnosis, mean (SD)	26.4 (5.0)	24.8 (4.8)	26.8 (4.9)	25.2 (4.7)	26.6 (4.9)	25.1 (4.7)
Underweight (<18.5)	119 (4)	510 (5)	23 (3)	109 (4)	29 (3)	103 (4)
Normal (18.5–25)	1,074 (33)	3,451 (34)	257 (30)	980 (35)	336 (30)	901 (36)
Overweight (25–30)	1,124 (34)	2,244 (22)	296 (34)	722 (26)	378 (34)	640 (25)
Obese (>30)	598 (18)	946 (9)	175 (20)	299 (11)	214 (19)	260 (10)
Missing	372 (11)	2,958 (27)	112 (13)	665 (24)	158 (14)	619 (25)
Deprivation fifth						
1st (least deprived)	552 (17)	1,786 (17)	154 (18)	536 (19)	201 (18)	489 (19)
2nd	638 (19)	1,945 (25)	160 (19)	527 (19)	204 (18)	483 (19)
3rd	648 (20)	2,080 (21)	166 (19)	557 (20)	213 (19)	510 (20)
4th	712 (22)	2,194 (22)	185 (21)	621 (22)	243 (22)	563 (22)
5th (most deprived)	725 (22)	2,070 (20)	195 (23)	528 (19)	251 (23)	472 (19)
Missing	12 (0)	33 (0)	3 (0)	6 (0)	3 (0)	6 (0)
Comorbidity before cancer diagnosis						
Cerebrovascular disease	552 (17)	697 (7)	106 (12)	140 (5)	125 (11)	121 (5)
Chronic pulmonary disease	871 (27)	2,517 (25)	226 (26)	703 (25)	296 (27)	633 (25)
Congestive heart disease	307 (9)	593 (6)	64 (7)	98 (4)	72 (6)	90 (4)
Diabetes	854 (12)	600 (6)	203 (24)	132 (5)	230 (21)	105 (4)
Myocardial infarction	817 (25)	368 (4)	186 (22)	106 (4)	210 (19)	82 (3)
Peptic ulcer disease	263 (8)	743 (7)	58 (7)	188 (7)	79 (7)	167 (7)
Peripheral vascular disease	695 (21)	677 (7)	173 (20)	161 (6)	194 (17)	140 (6)
Renal disease	480 (15)	358 (4)	98 (11)	99 (4)	111 (10)	86 (3)
Other medication use after diagnosis						
Low-dose aspirin use[d]	2,109 (64)	1,770 (18)	550 (64)	620 (22)	710 (64)	460 (18)
Beta-blocker use[d]	1,050 (32)	1,090 (11)	310 (36)	378 (14)	407 (37)	281 (11)

[a]Analysis includes lung cancer patients who have more than 1 year of records before diagnosis.
[b]Analysis includes lung cancer patients who live more than 1 year after diagnosis.
[c]Excluding cancer patients from Thames Registry as surgery information not available.
[d]Low-dose aspirin and beta-blocker use ever after diagnosis for statin use after diagnosis columns, low-dose aspirin and beta-blocker use in year before diagnosis for statin use in year before diagnosis column.

for stage were not possible that could influence results for statins after diagnosis, but such adjustments are probably not appropriate for the analysis of statins before diagnosis, as stage may lie on the causal pathway. The observed associations could also be influenced by confounding by indication (32) or the healthy user effect (33), though these biases would assume that statin users

Table 2. Association between statin usage after cancer diagnosis and cancer-specific and all-cause mortality in lung cancer patients

					Cancer-specific mortality				All-cause mortality			
Medication usage after diagnosis	**Cancer-specific mortality**	**All-cause mortality**	**All patients**	**Person years**	**Unadjusted HR (95% CI)**	***P***	**Adjusted[a] HR (95% CI)**	***P***	**Unadjusted HR (95% CI)**	***P***	**Adjusted[a] HR (95% CI)**	***P***
Number of patients					(*n* = 3,638)		(*n* = 2,792)		(*n* = 3,638)		(*n* = 2,792)	
Statin nonuser	1,669	1,962	2,523	4,619	1.00		1.00		1.00		1.00	
Statin user[b]	556	700	1,115	2,135	0.84 (0.76–0.92)	<0.001	0.89 (0.78–1.02)	0.09	0.89 (0.82–0.97)	0.01	0.91 (0.80–1.02)	0.10
Statin user 1 to 11 prescriptions[c]	355	422	535	977	0.84 (0.75–0.94)	0.003	0.94 (0.81–1.09)	0.39	0.88 (0.79–0.98)	0.02	0.95 (0.83–1.09)	0.44
Statin user ≥ 12 prescriptions[c]	201	278	580	1,158	0.84 (0.72–0.97)	0.02	0.81 (0.67–0.98)	0.03	0.91 (0.80–1.04)	0.17	0.84 (0.71–0.99)	0.04
Statin user 1 to 365 DDDs[c]	337	406	493	903	0.90 (0.80–1.01)	0.07	0.94 (0.81–1.09)	0.40	0.95 (0.85–1.06)	0.34	0.96 (0.84–1.10)	0.57
Statin user ≥ 365 DDDs[c]	219	294	622	1,232	0.76 (0.66–0.88)	<0.001	0.82 (0.68–0.98)	0.03	0.82 (0.72–0.93)	0.002	0.83 (0.70–0.97)	0.02
Simvastatin nonuser	1,912	2,227	2,867	5,210	1.00		1.00		1.00		1.00	
Simvastatin user[b]	343	435	771	1,544	0.77 (0.68–0.86)	<0.001	0.80 (0.69–0.93)	0.003	0.80 (0.72–0.89)	<0.001	0.81 (0.71–0.92)	0.001
Simvastatin 1 to 11 prescriptions[c]	220	268	387	777	0.75 (0.65–0.86)	<0.001	0.82 (0.69–0.98)	0.03	0.78 (0.69–0.89)	<0.001	0.84 (0.72–0.98)	0.03
Simvastatin ≥ 12 prescriptions[c]	123	167	384	767	0.80 (0.67–0.97)	0.02	0.76 (0.60–0.95)	0.01	0.84 (0.72–0.99)	0.04	0.75 (0.62–0.91)	0.004
Atorvastatin nonuser	2,083	2,432	3,301	6,126	1.00		1.00		1.00		1.00	
Atorvastatin user[b]	172	230	337	628	0.93 (0.80–1.09)	0.37	0.93 (0.78–1.12)	0.47	1.04 (0.91–1.20)	0.52	1.03 (0.88–1.21)	0.68
Pravastatin nonuser	2,216	2,615	3,564	6,620	1.00		1.00		1.00		1.00	
Pravastatin user[b]	39	47	74	133	1.02 (0.74–1.39)	0.93	1.23 (0.85–1.77)	0.27	1.01 (0.76–1.35)	0.94	1.11 (0.79–1.56)	0.53
Rosuvastatin nonuser	2,237	2,640	3,598	6,668	1.00		1.00		1.00		1.00	
Rosuvastatin user[b]	18	22	40	86	0.93 (0.58–1.47)	0.74	1.15 (0.66–2.01)	0.61	0.89 (0.58–1.35)	0.58	0.87 (0.51–1.48)	0.61
Fluvastatin nonuser	2,246	2,651	3,624	6,726	1.00		1.00		1.00		1.00	
Fluvastatin user[b]	9	11	14	28	1.16 (0.60–2.23)	0.66	0.98 (0.47–2.09)	0.98	1.17 (0.65–2.12)	0.60	1.07 (0.55–2.06)	0.85
Any lipophilic[d] nonuser	1,901	2,214	2,851	1,573	1.00		1.00		1.00		1.00	
Any lipophilic statin user[b]	354	448	787	5,181	0.78 (0.69–0.87)	<0.001	0.81 (0.70–0.94)	0.01	0.81 (0.73–0.90)	<0.001	0.82 (0.72–0.93)	0.002
Any hydrophilic[d] nonuser	2,027	2,367	3,205	5,945	1.00		1.00		1,00		1.00	
Any hydrophilic statin user[b]	228	295	433	809	0.96 (0.84–1.10)	0.54	1.00 (0.85–1.18)	0.97	1.04 (0.92–1.17)	0.54	1.05 (0.91–1.22)	0.49

[a]Adjusted for year of diagnosis, age at diagnosis, gender, radiotherapy within 6 months, chemotherapy within 6 months, surgery within 6 months, comorbidities (before diagnosis, including cerebrovascular disease, chronic pulmonary disease, congestive heart disease, diabetes, myocardial infarction, peptic ulcer disease, peripheral vascular disease, and renal disease), other medication use (after diagnosis, as time varying covariates, specifically low-dose aspirin and beta-blockers), and deprivation (in fifths).

[b]Medication use modeled as a time-varying covariate with an individual considered a nonuser before 6 months after first medication usage, and a user after this time, excludes deaths in the year after cancer diagnosis.

[c]Medication use modeled as a time-varying covariate with an individual considered a nonuser before 6 months after first medication usage, a user of 0 to 12 prescriptions from 6 months after first prescription to 6 months after 12th prescription (or 365th DDD), and a greater user after this time, excludes deaths in the year after cancer diagnosis.

[d]Lipophilic statins include simvastatin, fluvastatin, cerivastatin; hydrophilic statins include atorvastatin, pravastatin, and rosuvastatin.

Table 3. Sensitivity analyses for association between statin use and cancer-specific mortality in lung cancer patients

	Cancer-specific mortality	All patients	Person years	User vs. nonuser		1-11 prescriptions vs. none		≥ 12 prescriptions vs. none	
				Adjusted HR[a] (95% CI)	*P*	Adjusted HR[a] (95% CI)	*P*	Adjusted HR[a] (95% CI)	*P*
Main analysis: Statin user versus nonuser after diagnosis	1,735	2,792	5,227	0.89 (0.78–1.02)	0.09	0.94 (0.81–1.09)	0.39	0.81 (0.67–0.98)	0.03
Subgroup analyses: Statin user versus nonuser after diagnosis, restricted to:									
Males	1,007	1,620	2,928	0.94 (0.79–1.12)	0.62	0.99 (0.82–1.21)	0.96	0.85 (0.66–1.09)	0.19
Females	728	1,172	2,299	0.83 (0.67–1.03)	0.09	0.86 (0.68–1.10)	0.23	0.78 (0.58–1.06)	0.11
Prediagnosis statin nonusers[b]	1,222	1,912	3,691	0.78 (0.60–1.02)	0.07	0.64 (0.45–0.91)	0.01	1.06 (0.72–1.57)	0.77
Prediagnosis statin users[b]	402	697	1,132	0.76 (0.54–1.07)	0.12	0.83 (0.59–1.17)	0.29	0.63 (0.42–0.93)	0.02
Small-cell lung cancer	268	338	489	0.66 (0.44–0.99)	0.05	0.64 (0.41–0.99)	0.05	0.74 (0.41–1.36)	0.33
Non–small cell lung cancer	1,163	1,995	4,090	0.93 (0.79–1.09)	0.38	1.01 (0.84–1.21)	0.90	0.80 (0.64–1.01)	0.06
Sensitivity analyses: Statin user versus nonuser after diagnosis									
Increasing lag to 1 year	1,735	2,792	5,227	0.92 (0.80–1.05)	0.23	0.92 (0.80–1.07)	0.30	0.90 (0.72–1.14)	0.39
Increasing lag to 1 year (simvastatin only)	1,735	2,792	5,227	0.86 (0.74–1.00)	0.06	0.84 (0.71–1.00)	0.05	0.91 (0.70–1.19)	0.50
Additionally adjusting for smoking before diagnosis	1,584	2,564	4,760	0.90 (0.78–1.03)	0.12	0.95 (0.82–1.11)	0.52	0.82 (0.66–0.97)	0.03
Additionally adjusting for BMI before diagnosis	1,340	2,206	4,154	0.93 (0.80–1.08)	0.34	0.98 (0.83–1.15)	0.80	0.85 (0.68–1.04)	0.12
Additionally adjusting for small cell/non–small cell	1,431	2,333	4,579	0.86 (0.75–1.00)	0.05	0.92 (0.78–1.09)	0.32	0.77 (0.62–0.95)	0.02
Additionally adjusting for bisphosphonate use[c]	1,735	2,792	5,227	0.89 (0.78–1.02)	0.09	0.94 (0.81–1.09)	0.40	0.81 (0.67–0.98)	0.03
Based upon first year after diagnosis[d]	1,735	2,792	5,227	0.90 (0.78–1.03)	0.13	0.97 (0.83–1.12)	0.66	0.75 (0.60–0.93)	0.01
Nested case–control analysis[e]	1,705			0.92 (0.79–1.07)	0.27	0.98 (0.82–1.15)	0.77	0.81 (0.65–1.01)	0.06

[a]Except where otherwise stated, all analyses of post-diagnostic statin use adjusted for year of diagnosis, age at diagnosis, gender, surgery within 6 months of diagnosis, radiotherapy within 6 months, chemotherapy within 6 months, comorbidities (before diagnosis, including cerebrovascular disease, chronic pulmonary disease, congestive heart disease, diabetes, myocardial infarction, peptic ulcer disease, peripheral vascular disease, and renal disease), other medication use (after diagnosis, as time varying covariates, specifically low-dose aspirin and beta-blockers), and deprivation (in fifths).

[b]Based upon statin use in the year before diagnosis, restricted to individuals with 1 year of records before lung cancer diagnosis.

[c]Contains all confounders in [a] along with bisphosphonate use after diagnosis (as a time-varying covariate).

[d]Simplified analysis, not requiring time-varying covariate use, comparing statin users with statin nonusers in the first year after diagnosis in individuals living more than 1 year after cancer diagnosis, adjusted for all confounders in [a] but other medication use also restricted to first year after diagnosis.

[e]Estimate and 95% CIs are for adjusted OR, 25% (433/1,705) of cancer-specific deaths used statins compared with 29% (2,388/8,150) of risk-set controls (not dying from cancer), matched on age at diagnosis, year of diagnosis, gender, and adjusted for all other confounders in [a].

Table 4. Association between statin usage in the year before diagnosis and cancer-specific death in lung cancer patients

					Cancer-specific mortality				All-cause mortality			
Medication usage in year before diagnosis	**Cancer-specific mortality**	**All-cause mortality**	**All patients**	**Person years**	**Unadjusted HR (95% CI)**	***P***	**Adjusted[a] HR (95% CI)**	***P***	**Unadjusted HR (95% CI)**	***P***	**Adjusted[a] HR (95% CI)**	***P***
Number of patients					(*n* = 13,398)		(*n* = 13,353)		(*n* = 13,398)		(*n* = 13,353)	
Statin nonuser	8,064	8,926	10,111	9430	1.00		1.00		1.00		1.00	
Statin user	2,558	2,898	3,287	3,077	0.94 (0.90–0.98)	0.007	0.88 (0.83–0.93)	<0.001	0.97 (0.93–1.01)	0.10	0.89 (0.85–0.94)	<0.001
Statin user 1 to 11 prescriptions	1780	2,011	2,290	2,235	0.92 (0.87–0.96)	0.001	0.87 (0.82–0.92)	<0.001	0.94 (0.89–0.98)	0.01	0.88 (0.83–0.93)	<0.001
Statin user ≥ 12 prescriptions	778	887	997	841	1.00 (0.93–1.08)	0.93	0.91 (0.84–0.99)	0.02	1.04 (0.97–1.11)	0.29	0.92 (0.85–1.00)	0.04
Statin user 1 to 365 DDDs	1,737	1,981	2,235	2,110	0.94 (0.89–0.99)	0.02	0.88 (0.83–0.93)	<0.001	0.97 (0.93–1.02)	0.27	0.89 (0.84–0.95)	<0.001
Statin user ≥ 365 DDDs	821	917	1,052	967	0.94 (0.87–1.01)	0.08	0.89 (0.82–0.96)	0.004	0.95 (0.89–1.02)	0.14	0.88 (0.82–0.95)	0.002
Simvastatin nonuser	8,977	9,966	11,265	10,499	1.00		1.00		1.00		1.00	
Simvastatin user	1,645	1,858	2,133	2,008	0.95 (0.90–1.00)	0.05	0.92 (0.86–0.97)	0.004	0.97 (0.92–1.02)	0.18	0.92 (0.87–0.97)	0.003
Atorvastatin nonuser	9,832	10,922	12,392	11,549	1.00		1.00		1.00		1.00	
Atorvastatin user	790	902	1,006	958	0.93 (0.87–1.00)	0.06	0.91 (0.85–0.99)	0.02	0.96 (0.90–1.03)	0.28	0.93 (0.87–1.00)	0.05
Pravastatin nonuser	10,468	11,643	13,200	12,332	1.00		1.00		1.00		1.00	
Pravastatin user	154	181	198	174	0.99 (0.84–1.16)	0.88	0.96 (0.82–1.12)	0.60	1.05 (0.90–1.21)	0.54	1.00 (0.86–1.16)	0.96
Rosuvastatin nonuser	10,555	11,750	13,310	12,418	1.00		1.00		1.00		1.00	
Rosuvastatin user	67	74	88	89	0.83 (0.66–1.06)	0.14	0.82 (0.65–1.05)	0.11	0.83 (0.66–1.05)	0.12	0.81 (0.64–1.02)	0.07
Fluvastatin nonuser	10,575	11,771	13,341	12,464	1.00		1.00		1.00		1.00	
Fluvastatin user	47	53	57	43	1.03 (0.78–1.38)	0.82	1.01 (0.76–1.35)	0.93	1.06 (0.81–1.39)	0.68	1.03 (0.78–1.35)	0.85
Any lipophilic[b] nonuser	8,922	9,904	11,200	10,455	1.00		1.00		1.00		1.00	
Any lipophilic statin user	1,700	1,920	2,198	2,052	0.95 (0.91–1.00)	0.07	0.92 (0.87–0.98)	0.01	0.97 (0.93–1.02)	0.25	0.92 (0.87–0.98)	0.01
Any hydrophilic[b] nonuser	9,631	10,690	12,129	11,302	1.00		1.00		1.00		1.00	
Any hydrophilic statin user	991	1,134	1,269	1,205	0.93 (0.87–0.99)	0.02	0.90 (0.84–0.96)	0.003	0.96 (0.90–1.02)	0.17	0.92 (0.86–0.98)	0.01

[a]Adjusted for year of diagnosis, age at diagnosis, gender, comorbidities (before diagnosis, including cerebrovascular disease, chronic pulmonary disease, congestive heart disease, diabetes, myocardial infarction, peptic ulcer disease, peripheral vascular disease, renal disease), other medication use (in year before diagnosis, specifically low-dose aspirin and beta-blockers), and deprivation (in fifths).
[b]Lipophilic statins include simvastatin, fluvastatin, and cerivastatin; hydrophilic statins include atorvastatin, pravastatin, and rosuvastatin.

Table 5. Sensitivity analyses for association between statin use and cancer-specific mortality in lung cancer patients

	Cancer-specific mortality	All patients	Person years	Unadjusted HR (95% CI)	*P*	Adjusted[a] HR (95% CI)	*P*
Main analysis: Prediagnostic statin use[b]	10,622	13,398	12,507	0.94 (0.90–0.98)	0.007	0.88 (0.83–0.93)	<0.001
Subgroup analyses							
Male	6,292	7,918	7,115	0.91 (0.86–0.96)	0.001	0.87 (0.80–0.93)	<0.001
Female	4,330	5,480	5,391	0.99 (0.92–1.06)	0.80	0.91 (0.83–0.99)	0.02
Sensitivity analyses							
Smoking before diagnosis available (and adjusted for)	9,519	9,519	11,329	0.96 (0.92–1.00)	0.07	0.89 (0.84–0.95)	<0.001
BMI before diagnosis available (and adjusted for)	7,959	10,040	9,783	0.98 (0.93–1.03)	0.42	0.92 (0.87–0.98)	0.01
Additionally adjusting for bisphosphonate use[c]	10,622	13,398	12,507	0.94 (0.90–0.98)	0.007	0.88 (0.83–0.93)	<0.001
Statin use between 2 years and 6 months before diagnosis[d]	9,733	12,260	11,437	0.93 (0.89–0.98)	0.01	0.87 (0.82–0.92)	<0.001

[a]Except where otherwise stated, adjusted for year of diagnosis, age at diagnosis, gender, comorbidities (before diagnosis, including cerebrovascular disease, chronic pulmonary disease, congestive heart disease, diabetes, myocardial infarction, peptic ulcer disease, peripheral vascular disease, and renal disease), other medication use (in year before diagnosis, specifically low-dose aspirin and beta-blockers), and deprivation (in fifths).
[b]Based upon use in the year before diagnosis, restricted to individuals with 1 year of records before lung cancer diagnosis.
[c]Contains all confounders in [a] along with bisphosphonate use in year before diagnosis.
[d]Restricted to individuals with 2 years of records before diagnosis, removing prescriptions in the 6 months before lung cancer diagnosis as these could reflect increased medical care due to early symptoms.

were healthier, but in our cohort statin users had higher BMI and more comorbidities. The observed associations are consistent with the preclinical evidence for anticancer properties of statins from lung cancer cell lines (8–10) and mouse models (10). These results require confirmation in further large epidemiologic studies, particularly those with complete stage data, which could inform the decision to conduct a trial of simvastatin in lung cancer patients.

In conclusion, in this large population-based lung cancer cohort, there were weak inverse associations between statin usage and time to cancer-specific death. These associations could be causal or could reflect residual confounding or other biases.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

The funders had no role in the study design; collection, analysis, and interpretation of data; writing of the article; or the decision to submit for publication. The interpretation and conclusions contained in this study are those of the authors alone.

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Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): Ú. Mc Menamin
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