Post-Diagnosis Statin Use and Survival Among Patients with Cancer

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Abstract

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Statins are widely used cholesterol-lowering medications. Evidence from preclinical and observational studies suggest that statins use may improve cancer survival in patients with cancer, while findings from clinical trials have been mixed. The aim of this study was to evaluate the association between post-diagnosis statin use and cancer outcomes in seven common cancers. In this retrospective cohort study, we identified all individuals aged 66 years or older who were newly diagnosed with breast cancer, prostate cancer, colorectal cancer, lung cancer, bladder cancer, pancreatic cancer or non-Hodgkin lymphoma (NHL) from 2008 through 2017 from the linked SEER-Medicare database. Statin use was assessed based on prescription fills from the Medicare Part D Prescription Drug Event data. We used multivariable Cox regression models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the association of post-diagnosis statin use with cancer-specific mortality for all seven cancers and with cancer recurrence for breast cancer. Statin use post-diagnosis was associated with a reduction in cancer-specific mortality risk in breast cancer (HR=0.85, 95% CI: 0.75–0.96), lung cancer (HR=0.81, 95% CI: 0.74–0.88) and pancreatic cancer (HR=0.72, 95% CI: 0.59–0.87). No

significant association with risk of breast cancer recurrence, or with risk of cancer-specific mortality in prostate cancer, colorectal cancer, bladder cancer, or NHL was observed. We found evidence that suggests enhanced cancer survival associated with statin use after cancer diagnosis in patients with breast cancer, lung cancer and pancreatic cancer. These findings should be confirmed in large randomized trials of statins in patients with these cancers.

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Chapter 1. Use of statins and risks of adverse cancer outcomes in women with breast cancer

Abstract

Background: Preclinical evidence suggests improved breast cancer survival associated with statin use, but findings from clinical trials and observational studies are conflicting and remain inconclusive. The objective of this study was to assess the association between statin use after cancer diagnosis and cancer outcomes among breast cancer patients.

Methods: In this retrospective cohort study, women aged ≥66 years who were diagnosed with localized and regional stage breast cancer from 2008 through 2017 were identified from the SEER-Medicare database. Statin use was ascertained from Medicare Part D pharmacy claims data. Multivariable Cox proportional hazards models were used to estimate the association between post-diagnosis statin use and risks of breast cancer recurrence and breast cancer-specific mortality.

Results: Statin use post-diagnosis was not associated with recurrence risk (hazard ratio [HR]=1.05, 95% confidence interval [CI]: 0.91–1.21), but was associated with a reduced risk of cancer-specific mortality (HR=0.85, 95% CI: 0.75–0.96). Stratified analyses revealed that the reduction was more pronounced in women with hormone receptor-positive (HR+)/human epidermal growth factor receptor 2-negative (HER2-) negative breast cancer (HR=0.71, 95% CI: 0.57–0.88).

Conclusions: Our findings suggest that post-diagnosis statin use is associated with improved cancer-specific survival in women with breast cancer and should be confirmed in randomized trials of statin therapy in breast cancer patients.

Introduction

Statins are widely used prescription medications to reduce blood cholesterol.[1] Aside from their role in improving cardiovascular outcomes, statins also exhibit antitumor properties in *in vitro* studies. Statins can suppress tumor cell survival by inducing apoptosis, inhibiting cell proliferation, and reducing invasiveness and metastasis.[2-4] Statins may elicit synergistic effects in chemotherapy through similar mechanisms.[5] Furthermore, lipophilic statins have been shown to exert greater anti-cancer effects in breast cancer cells than hydrophilic statins.[6, 7]

The *in vitro* evidence is supported by findings from observational studies that suggest that statin use is associated with improved cancer-specific survival for multiple cancers [8-11] including breast cancer[12]. Several prior cohort studies further suggest that the protective association with cancer survival seen in patients with breast cancer may be more pronounced among those taking lipophilic statins,[13, 14] while a reduction in recurrence risk among breast cancer patients has also been observed among users of lipophilic, but not hydrophilic, statins.[15]

These results contrast with findings from randomized clinical trials of statin therapy which have largely failed to find any protective effect of statins on cancer survival.[16] It should be noted, however, that the trials were designed with cardiovascular outcomes as the primary outcomes and thus may not be properly powered to detect differences in cancer outcomes. The discrepancy in findings has also been attributed in part to sources of biases commonly seen in observational studies including prevalent user bias (prevalent users being exposed before the start of follow-up) and immortal-time bias (not crediting survival time before statin initiation to the nonuse group) that threaten the validity of the findings.[17-19]

In this study, we sought to assess whether statin use is associated with reduced risks of cancer recurrence and cancer-specific mortality in breast cancer patients and whether the association

varies by statin lipophilicity/hydrophilicity. In particular, this study employed several strategies to minimize potential biases in a comprehensive assessment of different aspects of statin use in a large, nationally representative population.

Methods

Study Population

In this retrospective cohort study, we used the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database for our analyses. The SEER-Medicare database links data on cancer cases from the SEER program with the medical claims data on healthcare utilization from the Medicare program. Cancer cases from the SEER program are collected by 18 cancer registries that cover 28% of the U.S. population.[20] The Medicare data include claims files from inpatient and outpatient care, physician service, and prescription medications for Medicare beneficiaries over age 65.[21] The linked database creates a nationally representative elderly population with cancer.

We used the SEER records to retrieve information on patient demographics and tumor characteristics and the Master Beneficiary Summary File (MBSF) to ascertain Medicare enrollment. Data on cancer treatments and comorbidities were retrieved from Medicare Provider Analysis and Review (MedPAR), Outpatient, and Carrier Claims (NCH) files. Pharmacy claims data on statin use including date of prescription fill, length of prescription, and statin type were obtained from Part D Drug Event (PDE) files.

The study cohort consisted of women diagnosed with breast cancer at age 66 years or older in the SEER-Medicare database during 2008–2017 (n = 370,876). Women with cancer diagnoses from autopsy or death certificates alone (n = 2,654), those with a prior cancer (n = 85,756), and those with distant stage cancer (n = 65,561) were excluded. We further excluded individuals

who were not continuously enrolled in Medicare Parts A, B and D for at least 12 months before and after cancer diagnosis and those who were concurrently enrolled in Medicare Parts A and B and a health maintenance organization (HMO). This resulted in a cohort of 72,380 women eligible for the breast cancer mortality analyses. The algorithm used to identify patients who experienced a recurrence relied on information on receipt of cancer-directed surgery for the incident cancer. Thus, for our analyses on breast cancer recurrence we excluded patients with breast cancer who did not receive a mastectomy or lumpectomy (n = 8,004). Additionally, those who died within 365 days of the incident cancer diagnosis (n = 1,778) and those with a record of second primary cancer in SEER (n = 3,517) were excluded, yielding a cancer recurrence cohort of 59,081 eligible women. The study was approved by the Institutional Review Board at the Fred Hutchinson Cancer Center.

Exposure assessment

Ever use of statins post-cancer diagnosis was our primary exposure. Patients were considered statin users if they had at least two statin prescription fills after their incident cancer diagnosis and remained users from the time of their second prescription fill. We also examined duration of statin use, statin intensity, and statin solubility. We defined duration of use as the cumulative number of days on a statin prescription during follow-up. We allowed a gap of 60 days between the runout date of one prescription and the start date of the following prescription and considered a patient exposed both during this period and for 60 days after the end of the last prescription. We categorized duration of use as <1 year, 1–<2 years, 2–<3 years and ≥ 3 years of statin use. We classified statin intensity (high, moderate and low) according to guidelines from the American College of Cardiology/American Heart Association.[22] We categorized statins as lipophilic (simvastatin, atorvastatin, fluvastatin, lovastatin and pitavastatin) or hydrophilic (rosuvastatin and pravastatin) based on statin solubility.

Outcome assessment

Our outcomes were breast cancer death and breast cancer recurrence. Cancer death was ascertained based on SEER data on death certificates that list breast cancer death as the primary cause of death. Cancer recurrences are not captured by cancer registries, so breast cancer recurrence was assessed using a validated algorithm based on administrative data codes for procedures and diagnoses that are suggestive of recurrence such as a diagnostic code for secondary neoplasm without any accompanying SEER records of subsequent breast and/or non-breast new primary cancers after the first primary breast cancer (a detailed list of codes has been described previously[23, 24]). A decision tree was then built using classification and regression tree analysis to classify patients as having or not having experienced a breast cancer recurrence. The algorithm has been validated against data abstracted from medical records and yielded 69% sensitivity, 99% specificity, and a positive predictive value of 86%.[23]

Statistical Analysis

We conducted our primary analyses in patients without pre-diagnosis statin use (i.e., who had fewer than two prescriptions filled in the year prior to diagnosis) in order to address potential prevalent user bias. Therefore, after excluding women with pre-diagnosis use, 38,858 and 28,522 eligible women remained for analyses of breast cancer mortality and breast cancer recurrence, respectively. We conducted a sensitivity analysis in which patients without pre-diagnosis use were defined as those who had no prescription fills in the year prior to diagnosis. We also included a full cohort analysis that included individuals with pre-diagnosis statin use for reference.

We stratified cohort characteristics by post-diagnosis statin use. Cause-specific multivariable Cox proportional hazards models were fitted to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the risk of breast cancer recurrence and the risk of breast cancer-

specific mortality associated with post-diagnosis statin use compared with nonuse. Competing events for analyses of breast cancer recurrence (deaths without recurrence) and for analyses of breast cancer mortality (deaths other than breast cancer deaths) were treated as censoring. All models were adjusted for age at diagnosis, race, year of diagnosis, tumor stage and grade, receipt of cancer-directed surgery, chemotherapy, radiotherapy and hormone therapy, depression, cardiovascular disease (myocardial infarction, heart failure, stroke, or peripheral vascular disease), hyperlipidemia, hypertension, and diabetes. Receipt of cancer treatment (cancer-directed surgery, chemotherapy, radiotherapy and hormone therapy) was defined as any treatment-related claims within 180 days after cancer diagnosis. Hormone therapy was defined as any prescription of tamoxifen, anastrozole, exemestane, or letrozole. Baseline comorbidities were defined as any claims containing the diagnostic codes for the comorbidities within the year prior to cancer diagnosis. A list of codes used to define the variables is shown in **Supplemental Table 1**. Covariates with missing data were handled by multiple imputation by chained equations to impute the missing value based on all the covariates including the outcomes and generate ten imputed datasets.[25] Models were then fit for each imputed dataset, and estimates were combined across the datasets using Rubin's rules.

We treated post-diagnosis statin exposures as time-varying such that patients contributed unexposed person-time to the nonuser group before they became a statin user. In stratified analysis, we examined statin use vs. nonuse by molecular cancer subtype defined by joint hormone receptor and HER2 status (subtype information available only for patients diagnosed from 2010 through 2017). In addition, statin use by intensity (high, moderate, low intensity vs. nonuse), solubility (hydrophilic, lipophilic vs. nonuse) and by overall duration of use were assessed. Duration analyses were modeled as time-varying such that statin users contributed person-time to the lowest duration category before moving into the higher duration category. Potential effect modification by age, cancer stage, and cancer treatments (surgery, radiation,

chemotherapy, hormone therapy) was assessed, but none of the interaction terms were statistically significant ($p>0.05$).

To address concerns of reverse causation and confounding by disease progression,[26] we lagged the statin exposures by 6 months so that individuals were only classified as users after 6 months had passed after the onset of statin use. We varied the lag time from 0, 1, 6, to 12 months in sensitivity analyses. For all analyses, patients were followed until the earliest of 1) recurrence (for analyses of breast cancer recurrence only); 2) death; 3) disenrollment from Medicare Part A, B, or D; or 4) the end of the follow-up period (December 31, 2018). Additionally, for analyses of breast cancer recurrence, recurrence was assessed starting 12 months post the incident cancer diagnosis to reduce the likelihood of false positives. We therefore modeled time from cancer diagnosis to recurrence with a delayed entry of 12 months post diagnosis.

The proportional hazards assumption was checked using the Schoenfeld residuals and held for all models. R version 4.2.2,[27] the *survival* [28] and the *mice* packages[25] were used for data analysis.

Results

The median (interquartile range) follow-up was 2.9 (1.2–5.3) years for breast cancer recurrence and 3.7 (2.1–6.1) years for breast cancer-specific mortality. There were 1,446 recurrences in the recurrence cohort and 2,215 breast cancer deaths in the mortality cohort. Among post-diagnosis statin users, the mean (interquartile range) duration of post-diagnosis statin use was 2.2 (0.6–3.2) years for the recurrence cohort and 2.2 (0.6–3.3) years for the mortality cohort.

Post-diagnosis statin users (23% in both cohorts) were more likely to be younger, have earlier year of diagnosis, receive radiation therapy, and have baseline comorbidities (including cardiovascular disease, diabetes, hypertension, and hyperlipidemia) compared with post-diagnosis nonusers in both cohorts (**Table 1**). Statin users in the mortality cohort were also more likely to have cancer-directed surgery and hormone therapy compared with nonusers.

Ever use of statins post-diagnosis was not associated with risk of breast cancer recurrence (hazard ratio [HR]= 1.05, 95% confidence interval [CI]: 0.91–1.21), but was associated with a reduced risk of breast cancer-specific mortality (HR=0.85, 95% CI: 0.75–0.96) (**Table 2**). Similarly, in the full cohort analysis in which individuals with and without pre-diagnosis use were analyzed together, the HR for recurrence was 0.94 (95% CI: 0.85, 1.03), and the HR for breast cancer-specific mortality was 0.87 (95% CI: 0.81, 0.94) (**Table 2**).

In subtype analysis, no significant association with recurrence was found in any of the breast cancer subtypes. The association with cancer-specific mortality was likewise non-significant except in hormone receptor-positive (HR+)/human epidermal growth factor receptor 2-negative (HER2-) breast cancer, where a significant inverse association between statin use post-diagnosis and cancer-specific mortality was observed (HR=0.71, 95% CI: 0.57–0.88) (**Table 3**).

In the duration analyses, as the duration of statin use increased, the risk of cancer-specific mortality generally decreased ($p_{trend} < 0.001$) (**Table 4**). No dose-response relationship was observed for cancer recurrence ($p_{trend} > 0.05$). We found no significant evidence of a trend in the association with recurrence and with cancer-specific mortality by varying levels of statin intensity ($p_{trend} > 0.05$) (**Table 4**). The association between statin use post-diagnosis and recurrence did not vary by statin solubility (**Table 4**). Similarly, no difference in the risk of cancer-specific mortality by statin solubility was observed (**Table 4**).

Sensitivity analyses involving patients without pre-diagnosis statin use defined as those with either fewer than two prescription fills or no prescription fills in the year prior to diagnosis yielded nearly identical results (**Supplemental Table 3**). Estimates of the HR for recurrence and for cancer-specific mortality did not change substantially with differing lag time of statin exposure (0, 1, 6, and 12 months) (data not shown).

Discussion

This large, population-based study sought to address whether statin use after cancer diagnosis improves cancer outcomes in women with breast cancer. A null association with recurrence and a significant 15% risk reduction in cancer-specific mortality would suggest that statins may have a protective effect against breast cancer mortality but not against breast cancer recurrence.

The protective association with cancer-specific survival is further supported by a dose-response relationship by duration as the association with cancer-specific mortality generally but inconsistently became stronger with increasing duration of statin use. The less-than-smooth relationship could be due to the measure of duration being an inexact reflection of actual use, and variations in adherence could have contributed to the slight fluctuations in the risk estimates. No dose-response relationship by statin intensity was observed either with cancer-specific mortality or recurrence. Statin intensity, which was defined based on the level of LDL-cholesterol reduction, may not represent the optimal dosing classification for cancer treatment. The effect of statins may be non-linear, as statins have previously been shown to have biphasic effects on endothelial cells involved in angiogenesis *in vitro*.[29] The associations with recurrence and cancer-specific mortality also did not vary by statin solubility. Despite some earlier cohort studies suggesting differential responses by statin solubility,[13-15] the most recent meta-analysis of cohort studies in breast cancer found no statistically different associations with recurrence

and breast cancer death between hydrophilic and lipophilic statin use. A meta-analysis of 22 clinical trials of statin therapy also found no difference in the rate ratios of cancer death by statin solubility.[16] As these findings suggest, it is likely that there is no differential response in breast cancer outcomes based on statin solubility.

Our findings of an inverse association between statin use and risk of breast cancer-specific mortality are consistent with several large observational studies from Finland,[30] Sweden,[31] Norway,[32] South Korea,[33] and New Zealand[34] that reported improved breast cancer survival in statin users. Our estimates (HR=0.85, 95% CI: 0.75–0.96) are also similar to those of a previous study of women in the SEER-Medicare and Texas Cancer Registry-Medicare databases diagnosed between 2008 and 2015 (HR=0.83, 95% CI: 0.66–1.04).[35] On the other hand, studies from England,[13] Scotland,[14] and Ireland[36] failed to find such an association between statin use and breast cancer survival. The most recent meta-analysis of seventeen cohort studies suggests improved survival with statin use (pooled HR=0.72, 95% CI: 0.60–0.86 for breast cancer recurrence; pooled HR=0.80, 95% CI: 0.72–0.90 for breast cancer mortality), although with significant between-study heterogeneity.[12]

The null association between statin use and risk of breast cancer recurrence observed in our study could be due to our relatively short follow-up (median of 2.9 years). A New Zealand study with a median follow-up of 4.5 years examined both risks of breast cancer death and recurrence and found a significant risk reduction in breast cancer death but no association with recurrence[34], similar to our results. However, in studies with longer follow-up (median > 5 years), statin use appears associated with a reduced risk of recurrence. While a few studies (median follow-up ranging from 5 to 6.3 years) found a non-significant reduction in breast cancer recurrence risk with statin use,[37-39] a Danish nationwide study with a median follow-up of 6.8 years found a 5-year adjusted HR of 0.80 (95%CI: 0.64–1.00) and 10-year adjusted HR of 0.83

(95% CI: 0.70–0.98) with breast cancer recurrence.[15] A Singaporean study with an even longer median follow-up of 8.7 years reported a null association with breast cancer recurrence in the first 5 years of follow up (HR=0.98, 95% CI: 0.77–1.26) but a dramatic reduction in recurrence risk in years 6 to 10 (HR=0.49, 95% CI: 0.30–0.80).[40] In addition, all of the aforementioned studies on recurrence included younger, pre-menopausal women, while our cohort only included women aged 66 and older. It is possible that an association with breast cancer recurrence may be observed in a younger cohort that is followed up over a long period of time.

In our stratified analyses by tumor subtype, we found a significant association with cancer-specific mortality only in HR+/HER2- breast cancer (HR=0.71, 95% CI: 0.57–0.88), which was also the predominant subtype in the study. Our results differ from the earlier SEER-Medicare study that reported a significant association only in triple negative breast cancer (TNBC) (HR=0.42, 95% CI: 0.20–0.88),[35] despite very similar estimates for the full-cohort analysis. It is unclear why their number of events (breast cancer deaths) for TNBC (<25) and non-TNBC (<100) was very low compared to the overall number for the full cohort (>1,000), which could have contributed to the differences in the estimates. Our findings are similar to other studies that conducted a tumor subtype analysis. In a Singaporean study, statin use was associated with a reduced risk of cancer-specific mortality in estrogen receptor-positive (ER+)/HER2- breast cancer only (HR=0.69, 95% CI: 0.49–0.97), but not in ER+/HER2+, ER-/HER2+, or TNBC,[40] while in a New Zealand study, a protective association with breast cancer death was again found in ER+ breast cancer only (HR=0.77, 95% CI: 0.63–0.94) but not in ER- breast cancer or TNBC[34]. It has been hypothesized that statins may exert greater effect in ER+ tumors by lowering levels of serum 27-hydroxy cholesterol (27HC), a cholesterol derivative which acts as an ER ligand and potentiates ER-dependent tumor growth.[41] However, evidence from a phase II clinical trial suggests that the anti-proliferative effect brought on by statins does not correlate

with changes in 27HC and may not depend on 27HC reduction.[42] The underlying mechanism by which statins may elicit a favorable response in ER+ tumors remains to be explored.

A strength of our study is the large sample size and highly generalizable findings to the elderly US population. Our comprehensive assessment of statin use by duration, intensity, and solubility provides a useful complement to our primary analysis of ever use. In addition, this is, to our knowledge, the first study to assess the relationship between statin use and breast cancer recurrence in an elderly population. In our study, we sought to minimize potential biases present in previous studies.[17] Our analysis focused on individuals without pre-diagnosis use to reduce any risk of potential prevalent user bias. Attributing the unexposed person-time before a patient became a user to the nonuser group helped minimize immortal time bias. Confounding due to disease progression and reverse causation are biases commonly seen in observational studies of post-cancer diagnosis exposures on survival,[26] so we addressed the biases by lagging the statin exposures. As such, our study provides a more unbiased assessment of the association between statin use and breast cancer survival compared to previous studies.

Our study is subject to several limitations. We only included women age 66 and older in our analysis, so the findings may have limited generalizability to younger breast cancer patients. Our follow-up time was relatively short, limiting our ability to examine the long-term effect of statin use. Our statin exposure may be potentially misclassified as it was defined based on prescriptions fills, which may not be the equivalent of actual statin use. Misclassification of recurrence outcomes is also possible given the relatively low sensitivity (69%) of the claims data-based algorithm we used to identify recurrences, although the specificity (99%) and positive predictive value (86%) were both high. The comorbidity variables were assessed based on diagnostic codes, so misclassification and residual confounding is likely. Information on behavioral factors such as physical activity and diet, which is not available in the SEER-

Medicare database, could also lead to unmeasured confounding. Lastly, healthy user bias may be present in this study, but statin users were less likely to be healthy due to a higher burden of baseline comorbidities compared to nonusers.

In conclusion, we found that statin use post-diagnosis was associated with a reduction in the risk of breast cancer death, but was not associated with risk of breast cancer recurrence in elderly women with localized and regional stage breast cancer. Future observational studies, preferably with longer follow-up, are needed to clarify and confirm the relationship between statin use and risk of breast cancer recurrence in the elderly patient population. The association we observed between statin use and risk of breast cancer-specific mortality suggests that statin initiation may confer a benefit on cancer survival in those who were not using before cancer diagnosis and should be confirmed in randomized trials of statin therapy in patients with breast cancer. As these cholesterol-lowering medications are widely used and generally safe, statins may offer an opportunity to improve cancer outcomes in breast cancer survivors.

Table 1. Baseline characteristics of women diagnosed with breast cancer in the SEER-Medicare database from 2008-2017 by post-diagnosis statin use[1]

	Breast cancer recurrence cohort		*Breast cancer mortality cohort*	
Duration of follow-up (years), median (interquartile range)	2.9 (1.2–5.3)		3.7 (2.1–6.1)	
Outcomes, N	1,446 recurrences		2,215 breast cancer deaths	
	No use (N = 22,047) N (%)	Statin use (N = 6,475) N (%)	No use (N = 30,022) N (%)	Statin use (N = 8,836) N (%)
Demographics				
Age at diagnosis				
65-69	5,661 (25.7)	1,826 (28.2)	7,470 (24.9)	2,381 (26.9)
70-74	5,991 (27.2)	1,981 (30.6)	7,797 (26.0)	2,650 (30.0)
75-79	4,552 (20.6)	1,363 (21.1)	5,852 (19.5)	1,856 (21.0)
80-84	3,257 (14.8)	865 (13.4)	4,359 (14.5)	1,173 (13.3)
85+	2,586 (11.7)	440 (6.8)	4,544 (15.1)	776 (8.8)
Race				
White	19,859 (90.1)	5,709 (88.2)	26,775 (89.2)	7,693 (87.1)
Black	1,262 (5.7)	455 (7.0)	1,982 (6.6)	694 (7.9)
Other	867 (3.9)	296 (4.6)	1,184 (3.9)	422 (4.8)
Unknown	59 (0.3)	15 (0.2)	81 (0.3)	27 (0.3)
Cancer characteristics				
Year of diagnosis				
2008 – 2010	5,428 (24.5)	2,482 (38.4)	7,019 (23.5)	3,066 (34.7)
2011 – 2013	6,097 (27.7)	2,177 (33.6)	7,706 (25.7)	2,786 (31.6)
2014 – 2017	10,522 (47.7)	1,816 (28.0)	15,297 (51.0)	2,984 (33.8)
Summary stage at diagnosis				
Localized	17,264 (78.3)	5,110 (78.9)	22,128 (73.7)	6,692 (75.7)
Regional	4,783 (21.7)	1,365 (21.1)	7,894 (26.4)	2,144 (24.3)
Grade				
I	5,913 (26.8)	1,724 (26.6)	7,392 (24.6)	2,263 (25.6)
II	10,316 (46.8)	3,037 (46.9)	13,706 (45.7)	4,091 (46.3)
III - IV	4,922 (22.3)	1,414 (21.8)	7,261 (24.1)	2,017 (22.8)
Unknown	896 (4.1)	300 (4.6)	1,663 (5.5)	465 (5.3)
Breast cancer subtype (only available for 2010+) *				
HR+/Her2+	1,251 (5.7)	316 (4.9)	1,878 (6.3)	467 (5.3)
HR-/Her2+	457 (2.1)	109 (1.7)	749 (2.5)	190 (2.2)
HR+/Her2-	14,349 (65.1)	3,693 (57.0)	19,020 (63.4)	5,118 (57.9)
Triple Negative	1,373 (6.2)	324 (5.0)	2,092 (7.0)	486 (5.5)
Unknown	4,617 (20.9)	2,033 (31.4)	6,283 (20.9)	2,575 (29.1)
Cancer treatments				
Surgery				
Yes	22,047 (100.0)	6,475 (100.0)	26,577 (88.5)	8,186 (92.6)

No	0 (0)	0 (0)	3,445 (11.5)	650 (7.4)
Radiation therapy				
Yes	11,246 (51.0)	3,503 (54.1)	13,442 (44.8)	4,375 (49.5)
No	10,801 (49.0)	2,972 (45.9)	16,580 (55.2)	4,461 (50.5)
Chemotherapy				
Yes	4,581 (20.8)	1,421 (21.9)	6,900 (23.0)	2,071 (23.4)
No	17,466 (79.2)	5,054 (78.1)	23,122 (77.0)	6,765 (76.6)
Hormone therapy				
Yes	12,214 (55.4)	3,651 (56.4)	15,880 (52.9)	4,939 (55.9)
No	9,833 (44.6)	2,824 (43.6)	14,142 (47.1)	3,897 (44.1)
Baseline comorbidities				
Depression				
Yes	1,389 (6.3)	404 (6.2)	2,037 (6.8)	586 (6.6)
No	20,658 (93.7)	6,071 (93.8)	27,985 (93.2)	8,250 (93.4)
Cardiovascular disease				
Yes	1,955 (8.9)	733 (11.3)	3,181 (10.6)	1,099 (12.4)
No	20,658 (91.1)	5,742 (88.7)	26,841 (89.4)	7,737 (87.6)
Diabetes				
Yes	2,588 (11.7)	1,438 (22.2)	3,746 (12.5)	2,075 (23.5)
No	19,459 (88.3)	5,037 (77.8)	26,276 (87.5)	6,761 (76.5)
Hypertension				
Yes	9,298 (42.2)	3,419 (52.8)	12,922 (43.0)	4,731 (53.5)
No	12,749 (57.8)	3,056 (47.2)	17,100 (57.0)	4,105 (46.5)
Hyperlipidemia				
Yes	4,490 (20.4)	2,469 (38.1)	5,915 (19.7)	3,414 (38.6)
No	17,557 (79.6)	4,006 (61.9)	24,107 (80.3)	5,422 (61.4)

[1] Only patients without pre-diagnosis statin use were included. Patients identified as post-diagnosis statin users/non-users after lagging exposure by 6 months.

* HR+ = hormone receptor-positive, HR- = hormone receptor-negative, HER2 = human epidermal growth factor receptor 2

Table 2. Association of post-diagnosis statin use with cancer outcomes [1] [2] [3]

	Breast cancer recurrence			Breast cancer death		
	Follow-up time (person-years)	**Number of recurrences**	**HR (95% CI)**	**Follow-up time (person-years)**	**Number of cancer deaths**	**HR (95% CI)**
Primary analysis: excluding individuals with pre-diagnosis use						
No use	91,683	1,194	ref	142,148	1,908	ref
Ever use	18,968	252	1.05 (0.91, 1.21)	27,995	307	**0.85 (0.75, 0.96)**
Analysis including individuals with pre-diagnosis use						
No use	123,195	1,577	ref	167,030	2,071	ref
Ever use	79,030	981	0.94 (0.85, 1.03)	142,325	1,661	**0.87 (0.81, 0.94)**

Abbreviations: HR=hazard ratio, CI=confidence interval.

[1] Pre-diagnosis use was defined as two or more statin prescriptions filled in the year prior to diagnosis.

[2] Ever use = ever use of statins post-diagnosis. Exposure lagged by 6 months.

[3] All models were adjusted for age at diagnosis, race, year of diagnosis, tumor stage and grade, receipt of surgery, chemotherapy, radiotherapy and hormone therapy, depression, cardiovascular disease (myocardial infarction, heart failure, stroke, or peripheral vascular disease), hyperlipidemia, hypertension, and diabetes.

Table 3. Association of post-diagnosis statin use with cancer outcomes by molecular subtype[1 2 3]

Cancer subtype	Breast cancer recurrence		Breast cancer death	
	Number of recurrence (%)	HR (95% CI)	Number of cancer deaths (%)	HR (95% CI)
HR+/HER2-	696 (72)	1.03 (0.83, 1.28)	870 (63)	**0.71 (0.57, 0.88)**
Triple Negative	144 (15)	1.22 (0.72, 2.09)	290 (21)	1.01 (0.69, 1.47)
HR+/HER2+	93 (10)	1.03 (0.57, 1.86)	139 (10)	1.02 (0.57, 1.84)
HR-/HER2+	35 (4)	2.07 (0.69, 6.19)	84 (6)	1.04 (0.51, 2.11)

Abbreviations: HR=hazard ratio, CI=confidence interval, HR+ = hormone receptor-positive, HR- = hormone receptor-negative, HER2 = human epidermal growth factor receptor 2.

[1] Only patients without pre-diagnosis use were included in the analyses.

[2] Exposure lagged by 6 months.

[3] All models were adjusted for age at diagnosis, race, marital status, year of diagnosis, tumor stage and grade, receipt of surgery, chemotherapy, radiotherapy and hormone therapy, depression, cardiovascular disease (myocardial infarction, heart failure, stroke, or peripheral vascular disease), hyperlipidemia, hypertension, and diabetes.

Table 4. Association of post-diagnosis statin use with cancer outcomes by overall duration of use, statin intensity and solubility [1 2 3 4]

	Breast cancer recurrence			Breast cancer death		
	Follow-up time (person-years)	**Number of recurrences**	**HR (95% CI)**	**Follow-up time (person-years)**	**Number of cancer deaths**	**HR (95% CI)**
Duration of use						
No use	91,683	1,194	ref	142,148	1,908	ref
<1 year	7,131	122	1.17 (0.97, 1.41)	10,331	155	0.89 (0.74, 1.07)
1 to < 2 years	3,689	45	0.91 (0.67, 1.24)	5,278	53	**0.72 (0.55, 0.95)**
2 to < 3 years	2,598	37	1.06 (0.76, 1.49)	3,763	47	0.83 (0.59, 1.14)
≥ 3 years	5,550	48	0.82 (0.61, 1.12)	8,623	52	**0.57 (0.42, 0.75)**
			p_{trend} = 0.10			p_{trend} < 0.001
Statin Intensity						
No use	91,683	1,194	ref	142,148	1,908	ref
Low	3,675	51	1.07 (0.81, 1.43)	5,253	71	1.04 (0.82, 1.32)
Moderate	12,877	162	1.00 (0.85, 1.19)	19,036	187	**0.76 (0.65, 0.89)**
High	2,416	39	1.25 (0.90, 1.73)	3,706	49	1.00 (0.75, 1.34)
			p_{trend} = 0.41			p_{trend} = 0.88
Statin solubility (nonuse as the reference group)						
No use	91,683	1,194	ref	142,148	1,908	ref
Hydrophilic	5,375	66	1.00 (0.78, 1.29)	7,660	77	0.83 (0.66, 1.05)
Lipophilic	13,594	186	1.07 (0.91, 1.26)	20,335	230	**0.85 (0.74, 0.98)**
Statin solubility (lipophilic use as the reference group)						
Lipophilic	13,594	186	ref	20,335	230	ref
Hydrophilic	5,375	66	0.94 (0.71, 1.25)	7,660	77	0.96 (0.74, 1.24)

Abbreviations: HR=hazard ratio, CI=confidence interval

[1] Only patients without pre-diagnosis use were included in the analyses.

[2] Exposure lagged by 6 months.

[3] All models were adjusted for age at diagnosis, race, year of diagnosis, tumor stage and grade, receipt of surgery, chemotherapy, radiotherapy and hormone therapy, depression, cardiovascular disease (myocardial infarction, heart failure, stroke, or peripheral vascular disease), hyperlipidemia, hypertension, and diabetes.

[4] Only statin users included in the trend analysis

Supplemental Table 1. Codes used to define cancer subtypes, cancer treatments, and comorbidities

Variable	Codes
Cancer subtype	SEER Breast Subtype (2010+) variable: HR+/HER2- (Luminal A); HR-/HER2- (Triple Negative); HR+/HER2+ (Luminal B); HR-/HER2+ (HER2-enriched)
Cancer Treatments	
Mastectomy	ICD-9: 85.4, 85.41, 85.42, 85.43, 85.44, 85.45, 85.46, 85.47, 85.48
	ICD-10: 0HTT0ZZ, 0HTU0ZZ, 07T50ZZ, 07T60ZZ, 07T70ZZ, 07T80ZZ, 07T90ZZ, 0KTH0ZZ, 0KTJ0ZZ, 0HTV0ZZ
	HCPCS: 19180, 19182, 19200, 19220, 19240, 19303, 19304, 19305, 19306, 19307
Lumpectomy	ICD-9: 85.2, 85.20, 85.21, 85.22, 85.23, 85.25
	ICD-10: 0H5T0ZZ, 0H5T3ZZ, 0H5T7ZZ, 0H5T8ZZ, 0H5TXZZ, 0H5U0ZZ, 0H5U3ZZ, 0H5U7ZZ, 0H5U8ZZ, 0H5UXZZ, 0H5V0ZZ, 0H5V3ZZ, 0H5V7ZZ, 0H5V8ZZ, 0H5VXZZ, 0HBT0ZZ, 0HBT3ZZ, 0HBT7ZZ, 0HBT8ZZ, 0HBTXZZ, 0HBU0ZZ, 0HBU3ZZ, 0HBU7ZZ, 0HBU8ZZ, 0HBUXZZ, 0HBV0ZZ, 0HBV3ZZ, 0HBV7ZZ, 0HBV8ZZ, 0HBVXZZ, 0H5W0ZZ, 0H5W3ZZ, 0H5W7ZZ, 0H5W8ZZ, 0H5WXZZ, 0H5X0ZZ, 0HBW0ZZ, 0HBW3ZZ, 0HBW7ZZ, 0HBW8ZZ, 0HBWXZZ, 0HBX0ZZ, 0HBX3ZZ, 0HBX7ZZ, 0HBX8ZZ, 0HBXXZZ, 0HTWXZZ, 0HTXXZZ
	HCPCS: 19110, 19120, 19125, 19126, 19160, 19162, 19301, 19302
Chemotherapy	ICD-9 Procedure: 99.25 ICD-9 Diagnosis: V58.1, V66.2, V67.2
	ICD-10 Procedure: 3E03305, 3E04305, XW03351, XW033B3, XW033C3, XW04351, XW043B3, XW043C3 ICD-10 Diagnosis: Z51.11
	HCPCS: J9000-J9999 (exclude J9003, J9165, J9175, J9202, J9209, J9212-J9226, J9240, J9295, J9395), Q0083-Q0085, J8520, J8521, J8530, J8540, J8560, J8597, J8610, J8999, 96401-96549
	Revenue center code: 0331, 0332, 0335
Radiation therapy	ICD-9 Procedure: 92.2, 92.20 – 92.29, 92.3, 92.30 – 92.39, 92.41 ICD-9 Diagnosis: V58.0, V66.1, V67.1
	ICD-10 Procedure: 3E0P304, 3E0P704, 3E0P804, DMY0***, DMY1***, DM00***, DM01***, DM10***, DM11*** ICD-10 Diagnosis: Z51.0, Z51.89, Z08
	HCPCS: 77371-77373, 77401-77525, 77761-77799, G0173, G0251, G0339, G0340
	Revenue center code: 0330, 0333
Hormone therapy	GNN variable in the PDE file: combination or single therapies including any of the following: “TAMOXIFEN”, “ANASTROZOLE”, “EXEMESTANE”, “LETROZOLE”
Comorbidities*	
Depression	ICD-9: 296.20, 296.21, 296.22, 296.23, 296.24, 296.25, 296.26, 296.30, 296.31, 296.32, 296.33, 296.34, 296.35, 296.36, 300.4, 311
	ICD-10: F32.0, F32.1, F32.2, F32.3, F32.4, F32.5, F32.89, F32.9, F33.0, F33.1, F33.2, F33.3, F33.40, F33.41, F33.42, F33.8, F33.9, F34.1
Hyperlipidemia	ICD-9: 272.0, 272.1, 272.2, 272.3, 272.4
	ICD-10: E78.0, E78.00, E78.01, E78.1, E78.2, E78.3, E78.4, E78.41, E78.49, E78.5
Hypertension	ICD-9: 362.11, 401.0, 401.1, 401.9, 402.00, 402.01, 402.10, 402.11, 402.90, 402.91, 403.00, 403.01, 403.10, 403.11, 403.90, 403.91, 404.00, 404.01, 404.02, 404.03, 404.10, 404.11, 404.12, 404.13, 404.90, 404.91, 404.92, 404.93, 405.01, 405.09, 405.11, 405.19, 405.91, 405.99, 437.2

	ICD-10: H35.031, H35.032, H35.033, H35.039, I10, I11.0, I11.9, I12.0, I12.9, I13.0, I13.10, I13.11, I13.2, I15.0, I15.1, I15.2, I15.8, I15.9, I67.4, N26.2
Diabetes	ICD-9: 249.00-249.91, 250.00-250.93, 357.2, 362.01, 362.02, 362.03, 362.04, 362.05, 362.06, 366.41
	ICD-10: E08.00-E08.9, E09.00-E09.9, E10.10-E10.9, E11.00-E11.9, E13.00-E13.9
Myocardial infarction	ICD-9: 410.01, 410.11, 410.21, 410.31, 410.41, 410.51, 410.61, 410.71, 410.81, 410.91 (ONLY first or second DX on the claim)
	ICD-10: I21.01, I21.02, I21.09, I21.11, I21.19, I21.21, I21.29, I21.3, I21.4, I21.9, I21.A1, I21.A9, I22.0, I22.1, I22.2, I22.8, I22.9 (ONLY first or second DX on the claim)
Heart failure	ICD-9: 398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 428.0, 428.1, 428.20, 428.21, 428.22, 428.23, 428.30, 428.31, 428.32, 428.33, 428.40, 428.41, 428.42, 428.43, 428.9
	ICD-10: I09.81, I11.0, I13.0, I13.2, I50.1, I50.20, I50.21, I50.22, I50.23, I50.30, I50.31, I50.32, I50.33, I50.40, I50.41, I50.42, I50.43, I50.810, I50.811, I50.812, I50.813, I50.814, I50.82, I50.83, I50.84, I50.89, I50.9
Stroke	ICD-9: 430, 431, 433.00-433.91, 434.00-434.91, 435.0-435.9, 436, 997.02
	ICD-10: G45.0-G45.9, G46.0-G46.8, G97.31, G97.32, I60.00-I60.9, I61.0-I61.9, I62.00-I62.9, I63.00-I63.9, I66.01-I66.9, I67.841, I67.848, I67.89, I97.810, I97.811, I97.820, I97.821
Peripheral vascular disease	ICD-9: 440.0, 440.1, 440.2, 440.20, 440.21, 440.22, 440.23, 440.29, 440.4, 443.8, 443.81, 443.82, 443.89, 443.9
	ICD-10: E08.51, E08.52, E09.51, E09.52, E10.51, E10.52, E11.51, E11.52, E13.51, E13.52, I70.0, I70.1, I70.201, I70.202, I70.203, I70.208, I70.209, I70.211, I70.212, I70.213, I70.218, I70.219, I70.221, I70.222, I70.223, I70.228, I70.229, I70.231, I70.232, I70.233, I70.234, I70.235, I70.238, I70.239, I70.241, I70.242, I70.243, I70.244, I70.245, I70.248, I70.249, I70.25, I70.291, I70.292, I70.293, I70.298, I70.299, I70.92, I73.81, I73.89, I73.9, I79.1, I79.8

* Comorbidity codes are based on codes provided by Chronic Conditions Data Warehouse: https://www2.ccwdata.org/web/guest/condition-categories.

Supplemental Table 2. Cohort selection

Inclusion criteria	**Cases Remaining**
All breast cancer cases in SEER Medicare diagnosed ≥ 66 years of age in the years 2008-2017 among females	370,876
Diagnosed in some way other than autopsy or death certificate alone	368,222
Without a history of prior cancer (first primary cancer only)	282,466
Summary stage: localized – regional diseases	216,905
With continuous Medicare enrollment at least 12 months before and after cancer diagnosis (unless died)	
Part A/B enrollment	199,122
No concurrent health maintenance organization (HMO) enrollment	123,302
Part D enrollment	72,380
Additionally for analyses of breast cancer recurrence:	
Received cancer-directed surgery	64,376
Survived at least 365 days after the incident cancer diagnosis	62,598
No SEER record of second primary cancer	59,081

Supplemental Table 3. Sensitivity analyses[1 2 3]

Patients without pre-diagnosis use defined as either those with fewer than 2 prescription fills or those with no prescription fills in the year prior to diagnosis*

		Among those without pre-diagnosis use (<2 prescription fills)			*Among those without pre-diagnosis use (0 prescription fills)*		
		Follow-up time (person-years)	**Number of outcomes**	**HR (95% CI)**	**Follow-up time (person-years)**	**Number of outcomes**	**HR (95% CI)**
Breast cancer (recurrence)	No use	91,683	1,194	ref	86,814	1,138	ref
	Ever use	18,968	252	1.05 (0.91, 1.21)	14,039	196	1.06 (0.91, 1.26)
Breast cancer (death)	No use	142,148	1,908	ref	136,031	1,851	ref
	Ever use	27,995	307	**0.85 (0.75, 0.96)**	19,377	222	**0.85 (0.73, 0.98)**

Abbreviations: HR=hazard ratio, CI=confidence interval

[1] Only patients without pre-diagnosis use were included in the analyses.

[2] Ever use = ever use of statins post-diagnosis.

[3] All models were adjusted for age at diagnosis, race, year of diagnosis, tumor stage and grade, receipt of surgery, chemotherapy, radiotherapy and hormone therapy, depression, cardiovascular disease (myocardial infarction, heart failure, stroke, or peripheral vascular disease), hyperlipidemia, hypertension, and diabetes.

* Exposure lagged by 6 months.

Chapter 2. Association of statin use with survival in patients with common cancers

Abstract

Background: Preclinical *in vitro* evidence and earlier observational studies suggest improved survival associated with statin use in cancer patients but are contradicted by findings from clinical trials. This study aimed to assess the association between statin use after cancer diagnosis and cancer survival in six common cancers.

Methods: This study included individuals aged ≥66 years diagnosed with prostate cancer, colorectal cancer, lung cancer, bladder cancer, pancreatic cancer or non-Hodgkin lymphoma (NHL) from 2008 through 2017 in the SEER-Medicare database. Statin use was defined as two or more statin prescription fills after cancer diagnosis. Cox proportional hazard regression models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the association of post-diagnosis statin use with cancer-specific mortality for all six cancers.

Results: Statin use post-diagnosis was associated with a reduced risk of cancer-specific mortality in lung cancer (HR=0.81, 95% CI: 0.74–0.88) and pancreatic cancer (HR=0.72, 95% CI: 0.59–0.87). The association was not statistically significant for prostate cancer (HR=0.92, 95% CI: 0.79–1.08), colorectal cancer (HR=0.92, 95% CI: 0.81–1.03), bladder cancer (HR=0.87, 95% CI: 0.71–1.07), or NHL (HR=1.29, 95% CI: 0.96–1.72). However, statin use was associated with a reduced risk of cancer-specific mortality in bladder cancer patients with localized disease (HR=0.77, 95% CI: 0.60–0.98) in stratified analysis. A dose-response relationship by duration of statin use was observed in lung cancer and pancreatic cancer, and no pattern of association by statin intensity or statin solubility was observed across the six cancers.

Conclusions: Consistent with prior work, statin use after cancer diagnosis appears associated with improved survival in lung cancer and pancreatic cancer. Clinical trials of statin therapy in lung and pancreatic cancer patients are warranted to confirm these findings.

Introduction

Statins are cholesterol-lowering medications and among the most commonly prescribed medications in the United States.[1] They have also been shown to exert inhibitory effects on cancer cells through inhibition of cell proliferation, reduction of invasiveness and metastasis, and promotion of apoptosis.[2-4] In addition, statins can act synergistically with chemotherapy drugs to target signaling pathways to induce cell cycle arrest and cell death.[5]

Consistent with the *in vitro* evidence, many observational studies suggest a reduction of cancer-specific mortality associated with statin use in a number of cancers including breast cancer,[43, 44] colorectal cancer,[8] lung cancer,[9] prostate cancer,[10] and pancreatic cancer.[11] In contrast, clinical trials of statin therapy have produced mostly negative results.[16] A meta-analysis of ten randomized-controlled trials of adjuvant statin therapy with a median follow-up of 23 months in patients with advanced (stage III or higher) cancer found no improvement in overall or progression-free survival across cancer types.[45] Specifically, in trials of patients with advanced stage cancers including small-cell lung cancer,[46] colorectal cancer,[47] and pancreatic cancer,[48] the addition of statins to standard chemotherapy offered no additional benefit compared with chemotherapy alone. However, statin therapy did prolong overall survival in a subgroup of advanced stage non-small cell lung cancer patients.[49]

It is possible that longer follow-up may reveal potential benefit in cancer patients with earlier stage disease. The contradictory findings from the clinical trials and observational studies may also be partly explained by methodological limitations in previous observational studies including selection bias due to the inclusion of prevalent users (individuals with pre-diagnosis statin exposure) and immortal-time bias due to inappropriately classifying unexposed survival time before statin initiation as exposed.[17-19]

The aim of this study was to assess whether statin use after cancer diagnosis is associated with improved cancer survival in six common cancers: prostate cancer, colorectal cancer, lung cancer, bladder cancer, pancreatic cancer and non-Hodgkin lymphoma (NHL). This study sought to minimize potential biases and evaluate multiple aspects of statin use using a large, nationally representative database.

Methods

The Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database was used for this retrospective cohort study.

Study Population

The SEER program of cancer registries collects data on cancer cases from 18 geographic areas in the United States, encompassing 28% of the U.S. population.[20] The Medicare claims files include information on inpatient care (Part A), physician service and outpatient care (Part B), and prescription drugs (Part D) for individuals over age 65 in the US.[21] The linked SEER-Medicare database forms a dataset with detailed information on healthcare utilization in an elderly population with cancer.

The SEER files were used to identify cancer cases from 2008 to 2017 (the latest year available at the time of data request). Information on patient demographics and tumor characteristics was retrieved from the SEER data. The Master Beneficiary Summary File (MBSF) was used to ascertain Medicare enrollment. Medicare Provider Analysis and Review (MedPAR), Outpatient, and Carrier Claims (NCH) files were used to retrieve data on cancer treatments and comorbidities. Part D Drug Event (PDE) files were used to extract pharmacy claims data on statin prescription fills.

The study cohort included all cases of localized and regional stage prostate, colorectal, lung, bladder, pancreatic cancer and NHL diagnosed in the years 2008–2017 in individuals aged 66 years or older in the SEER-Medicare database. All eligible individuals had continuous Medicare Part A/B/D enrollment with no concurrent health maintenance organization (HMO) enrollment for at least 12 months before and after cancer diagnosis (unless they died during the first 12 months after diagnosis). We excluded individuals with a prior cancer, those with cancer diagnoses from autopsy or death certificates alone, and those with distant stage disease to allow for a sufficient follow-up period. The study was approved by the Institutional Review Board at the Fred Hutchinson Cancer Center.

Exposure

Our primary exposure was ever use of any statin after the incident cancer diagnosis. Patients were categorized as statin users from the time they received their second statin prescription post-diagnosis. We further characterized statin use by overall duration of use, intensity, and statin solubility. The overall duration of use was calculated as the sum of days with a statin prescription. Consecutive prescriptions were considered continuous if there were 60 or fewer days between the end of one prescription fill and the start of the following prescription fill to account for gaps between prescriptions. With prospective filling of the gaps,[50] a patient was considered exposed for 60 days after the last supply elapsed. Duration of use was modelled as a categorical variable as <1 year, 1–<2 years, 2–<3 years, and ≥ 3 years of statin use. Intensity was categorized as high, moderate and low intensity statin therapy in accordance with classification guidelines from the American College of Cardiology/American Heart Association.[22] Statin solubility was characterized as either lipophilic (simvastatin, atorvastatin, fluvastatin, lovastatin and pitavastatin) or hydrophilic (rosuvastatin and pravastatin).

Outcome

Our primary outcome was death from each of the six cancer types. Cancer death was determined using SEER data on primary cause of death based on death certificates.

Covariates

Covariates included demographic factors (age at diagnosis, sex, race); cancer characteristics (year of diagnosis, tumor stage and grade at diagnosis, cancer subtype); cancer treatments (cancer-directed surgery, chemotherapy, radiotherapy, immunotherapy, hormone therapy); and baseline comorbidities (depression, cardiovascular disease [myocardial infarction, heart failure, stroke, or peripheral vascular disease], hyperlipidemia, hypertension, diabetes). Major histologic subtypes of lung cancer, bladder cancer, and NHL were identified based on histologic ICD-O-3 codes. Receipt of cancer treatment was defined as any cancer-directed surgery, chemotherapy, radiotherapy, immunotherapy or hormone therapy-related claims within 180 days after cancer diagnosis. Hormone therapy for prostate cancer was defined as androgen deprivation therapy (orchiectomy and use of luteinizing hormone-releasing hormone agonists). Baseline comorbidities were defined as claims of diagnoses within the year prior to cancer diagnosis. **Supplemental Table 1** contains the list of codes used to define the variables.

Statistical Analysis

To address prevalent user bias, our primary analyses were restricted to patients without pre-diagnosis statin use, defined as those with fewer than two prescriptions filled in the year prior to diagnosis. In a sensitivity analysis, patients without pre-diagnosis use were defined as those who had no statin prescription fills in the year prior to diagnosis. A full cohort analysis that included both individuals with and without pre-diagnosis statin use was also conducted for reference.

For each of the six cancer cohorts, characteristics were stratified by post-diagnosis statin use. We fitted cause-specific Cox regression models to assess the association between post-diagnosis statin use and cancer-specific mortality for each of the six cancer types while accounting for competing risks. Competing events were deaths from causes other than the cancer of interest and were treated as censoring. All models were adjusted for age at diagnosis, sex, race, year of diagnosis, tumor stage and grade, receipt of surgery, chemotherapy, radiotherapy, hormone therapy and immunotherapy, depression, cardiovascular disease (myocardial infarction, heart failure, stroke, or peripheral vascular disease), hyperlipidemia, hypertension, and diabetes. We used multiple imputation by chained equations to impute the missing value in covariates with missing data.[25] We generated ten imputed datasets, fitted models for each imputed dataset, and combined the estimates using Rubin's rules.

Statin exposures after cancer diagnosis were treated as time-varying by counting the unexposed person-time before one became a user towards the nonuser group. We further evaluated statin use vs. nonuse stratified by histologic subtype in lung cancer, bladder cancer, and NHL and by cancer site (colon/rectum) in colorectal cancer. In addition, we assessed statin use by intensity (high, moderate, low intensity vs. nonuse), solubility (hydrophilic, lipophilic vs. nonuse) and by overall duration of use. We treated duration exposures as time-varying such that the time one spent before reaching a higher duration category counted towards the lower duration category. Additionally, we tested for potential effect modification by age, cancer stage, and cancer treatments, but the interaction terms were not statistically significant ($p>0.05$), except for cancer stage in bladder cancer. We therefore stratified the results by cancer stage in bladder cancer.

Statin exposures were lagged (i.e. individuals were not considered users until a certain time had passed after statin initiation) to reduce the possibility of reverse causation and confounding by

disease progression.[26] Different cancer types progress at different rates,[51] so we lagged the exposure by 1 month for analyses of lung cancer and pancreatic cancer and 6 months for analyses of the four other cancer types. We conducted sensitivity analyses in which the statin exposure lag time varied from 0, 1, 6, to 12 months. For all analyses, patients were followed until the earliest of 1) death; 2) disenrollment from Medicare Part A, B, or D; or 3) the end of the follow-up period (December 31, 2018).

We used the Schoenfeld residuals to test the proportional hazards assumption, and the assumption held for all models. All analyses were conducted using R version 4.2.2,[27] the *survival* [28] and the *mice* packages.[25]

Results

Cohort characteristics

There were 34,618 eligible individuals in the prostate cancer cohort, 20,579 in the colorectal cancer cohort, 20,133 in the lung cancer cohort, 6,163 in the bladder cancer cohort, 4,538 in the pancreatic cancer cohort, and 3,270 in the NHL cohort (**Table 1)**. The median (interquartile range) follow-up and number of outcomes for each of the cancer cohorts are shown in **Table 2**. The mean duration of post-diagnosis statin use for each of the cancer cohorts ranged from 1.0 to 2.5 years (**Table 2)**. Post-diagnosis statin users in each of the cancer cohorts, ranging from 7% to 32% of patients, tended to be younger, have earlier year of diagnosis and localized stage disease, and were more likely to have baseline comorbidities (including cardiovascular disease, diabetes, hypertension, and hyperlipidemia) compared with post-diagnosis nonusers across all six cancer types (**Table 2**). Statin users were also more likely to have lower grade tumor and to receive cancer-directed surgery and less likely to receive radiation treatment compared to nonusers in colorectal cancer, lung cancer, bladder cancer and pancreatic cancer. Statin users

were less likely to receive chemotherapy in lung cancer but more likely to receive chemotherapy in bladder cancer and pancreatic cancer.

Association between statin use and cancer-specific mortality

From multivariable-adjusted Cox regression models (**Table 3**), we observed a statistically significant association between ever use of statins post-diagnosis and reduced risk of cancer-specific mortality in lung cancer (hazard ratio [HR]= 0.81, 95% confidence interval [CI]: 0.74–0.88) and pancreatic cancer (HR=0.72, 95% CI: 0.59–0.87). No significant association between statin use and cancer-specific mortality was found in prostate cancer, colorectal cancer, bladder cancer or NHL. In the full cohort analyses which included individuals with pre-diagnosis statin use, a statistically significant reduction of cancer-specific mortality risk was observed for all cancer types except NHL (**Table 3**).

In stratified analyses (**Table 4**), no significant association between statin use post-diagnosis and cancer-specific mortality was found for either colon cancer or rectal cancer. For lung cancer subtypes, statin use post-diagnosis was associated with a significant reduced risk of cancer-specific mortality in squamous cell carcinoma, adenocarcinoma and large cell carcinoma, three non-small cell lung cancer (NSCLC) subtypes, but not in small cell lung cancer. No significant association was observed in either of the bladder cancer subtypes. However, statin use was associated with a reduced risk of cancer-specific mortality in localized (HR=0.77, 95% CI: 0.60–0.98) but not regional stage bladder cancer.

Duration of use, statin intensity, and statin solubility

Risk of cancer-specific mortality generally decreased with longer duration of statin use for both lung cancer (p_{trend} =0.009) and pancreatic cancer (p_{trend} = 0.04) (**Table 5**). A linear trend by duration was also found in prostate cancer (p_{trend} <0.001), with a significant risk reduction

observed in the highest duration category (≥3 years of use) but not in any of the lower duration categories (**Table 5**). No dose-response relationship by duration was observed in colorectal cancer, bladder cancer, or NHL (**Table 5**).

No patterns of association by statin intensity were observed ($p_{trend} > 0.05$) (**Supplemental Table 2**). Estimates of the HR for cancer-specific mortality were similar between hydrophilic and lipophilic statin use in each of the six cancer types (**Supplemental Table 3**).

Sensitivity analyses

Our results remained nearly identical whether patients without pre-diagnosis use were defined as those with fewer than two prescription fills or no prescription fills in the year prior to diagnosis (**Supplemental Table 4**). The results also did not change substantially as the statin exposure lag time varied from 0, 1, 6, to 12 months (data not shown).

Discussion

In this large, population-based study of six common cancers, we found evidence that suggests that statin use post-diagnosis improves lung cancer and pancreatic cancer survival. A 19% reduction in the risk of cancer-specific mortality was observed in lung cancer, while in pancreatic cancer, the reduction was 28%. In prostate cancer, colorectal cancer, bladder cancer, and NHL, the association between statin use and cancer-specific mortality was not statistically significant.

The risk reduction found in lung cancer and pancreatic cancer is also supported by a dose-response relationship by duration of use as increasing duration was generally associated with decreasing risk of cancer-specific mortality. On the other hand, while a significant linear trend by duration was found in prostate cancer, a significant risk reduction was observed only for ≥3 years of use but not for any of the lower duration categories. This suggests that any potential

protective effect of statins may be exhibited only with long-term use in prostate cancer, but the influence of healthy adherer bias cannot be ruled out.[52] Long-term adherers of statin therapy may have better cancer prognosis and healthier lifestyle than non-users, which would lead to a biased protective effect of statin use in these users.

We observed no dose-response relationship by statin intensity in any of the six cancer types. It should be noted that statin treatment intensity was classified based on the level of LDL-cholesterol reduction and thus may not represent the optimal measure for the effect of statins on cancer outcomes. Statins have been shown to be pro-angiogenic at low therapeutic concentrations but anti-angiogenic at high concentrations *in vitro*.[29] The effect of statins on cancer cells may likewise be non-linear. The risk of cancer-specific mortality did not vary by statin solubility in any of the six cancer types. A meta-analysis of clinical trials found no statistically significant difference in the rate ratios of cancer death between hydrophilic and lipophilic statin use.[16] Thus statin solubility does not appear to play a role in the association between statin use and cancer survival.

For lung cancer, our findings of an inverse association between statin use and risk of lung cancer death are similar to a previous SEER-Medicare study which included a subset of our study cohort[53] and another study of patients with stage IV disease (not included in our study).[54] A meta-analysis of three cohort studies found a pooled HR of 0.89 (95% CI: 0.84–0.94) between statin use and lung cancer-specific mortality, although with high between-study heterogeneity.[9] Our study is also in accordance with results from some clinical trials. We found a significant association in NSCLC subtypes but not in small cell lung cancer (SCLC), which are consistent with findings from a phase II trial of simvastatin that prolonged overall survival in gefitinib-resistant advanced stage NSCLC patients[49] and a phase III trial of pravastatin that found no

effect among SCLC patients.[46] Our results suggest subtype-specific effects of statin use which should be validated in future research.

For pancreatic cancer, our study is, to our knowledge, the first study to evaluate the association between post-diagnosis statin use and pancreatic cancer-specific survival. Nearly all of the previous studies on pancreatic cancer only evaluated overall survival.[55-60] Only one study focused on pancreatic cancer-specific survival (HR=0.89, 95% CI: 0.81–0.98),[61] however their exposure was pre-diagnosis use. The most recent meta-analysis of the aforementioned cohort studies found improved overall survival in statin users (pooled HR=0.75, 95% CI: 0.59–0.90), although with significant heterogeneity between the studies.[11] Our findings of improved pancreatic cancer-specific survival associated with post-diagnosis statin use therefore provides stronger evidence for causal inference. Our results also align with those from a pooled analysis of two phase III clinical trials that reported that statin users had better overall and progression-free survival than nonusers.[62]

For the four other cancer types, we failed to find an association between statin use and cancer-specific mortality. In contrast, the full cohort analyses that did not exclude individuals with pre-diagnosis use resulted in lower, statistically significant HR estimates except for NHL, indicating the degree of prevalent user bias in those analyses.

In prostate cancer, the 8% reduction in the risk of cancer-specific mortality was non-significant. Our findings are similar to a previous SEER-Medicare study that reported a null association,[63] as well as a Finnish nationwide study,[64] a Canadian study,[65] and a US study.[66] On the other hand, a significant association was observed in studies from Canada,[67] Denmark,[68] the UK,[69] and the US Veterans Affairs cohort.[70] The most recent meta-analysis of eighteen cohort studies found a 24% (95% CI: 16%–31%) reduction in the risk of prostate cancer-specific

mortality associated with statin use, but with significantly high heterogeneity between the studies.[71] Given that we obtained lower and significant HR estimates when we included prevalent users in our analysis, the potential influence of prevalent user bias in these previous studies cannot be ignored.

For colorectal cancer, we likewise observed a nonsignificant 8% reduction in the risk of cancer-specific mortality associated with post-diagnosis statin use that became lower and significant with the inclusion of prevalent users. Our findings are in line with previous cohort studies from Germany[72] and Denmark[73] and a prospective observational study of clinical trial enrollees[74] that found null associations. The most recent meta-analysis of eight cohort studies found statin use post-diagnosis associated with a 21% (95%CI: 11%–30%) reduction in the risk of colorectal cancer death, again with significant heterogeneity between the studies.[8] In addition to the threat of prevalent user bias, it has been suggested that incomplete adjustment of confounders such as stage at diagnosis could have led to spuriously significant associations in some studies.[72]

Similarly for bladder cancer, the 13% reduction in the risk of cancer-specific mortality was nonsignificant. Only a few studies have assessed statin use in bladder cancer. Our results are consistent with a large study of 13,811 bladder cancer patients that found a null association between statin use and cancer-specific survival (HR=1.04, 95% CI: 0.99–1.09),[75] as well as several other smaller studies.[76-78] However, none of the previous studies conducted stratified analysis by stage, while we found that statin use was associated with a reduced risk of cancer-specific mortality in those with localized stage disease, which warrants further investigation in larger cohorts.

For NHL, given the wide confidence interval for the nonsignificant 29% increase in cancer-specific mortality risk (95% CI: 0.96–1.72), there is inconclusive evidence for an association

between statin use and NHL survival. Interestingly, the full cohort analyses that included prevalent users produced a null association only in NHL (HR=1.01, 95% CI: 0.86–1.19) out of the six cancers. Our results are similar to a large study of 16,098 patients that found statin use post-diagnosis was not associated with NHL-specific mortality (HR=0.93, 95% CI: 0.77–1.12).[79] Other studies have shown either a null association[80, 81] or improved survival[80, 82] in different NHL subtypes. We could only assess DLBCL due to a limited sample size and found a null association. Given the substantial variation in etiology and response to treatment in NHL subtypes, future subtype-specific analysis may shed more light on the association between statin use and NHL survival.

By using the same analytic approach, our results allow for straightforward comparisons across multiple cancer sites. Given the potential biases present in previous studies,[17] we addressed prevalent user bias by analyzing post-diagnosis use in those without pre-diagnosis use only in each cancer type. We avoided immortal time bias by counting the time before someone became a user as unexposed person-time. Lagging of the exposure also mitigated confounding due to disease progression and reverse causation.[26] Our more robust methodology provides stronger evidence either for or against the effect of statin use on cancer survival in the six cancers. Other strengths of our study include a large sample size, high generalizability to the elderly US population, and detailed assessment of different aspects of statin use by duration, intensity, and solubility.

Limitations

Our study relied on pharmacy claims data for exposure ascertainment, which may not reflect true statin use. Our assessment of comorbidities was based on diagnostic codes which may lead to misclassification and residual confounding. Unmeasured confounding due to lifestyle factors such as diet and physical activity is also likely. Lastly, our findings could be affected by

healthy user bias, although statin users were more likely to have baseline comorbidities than nonusers and were thus less likely to be healthier.

In summary, by employing design and analytic strategies that sought to minimize various forms of biases, we examined post-diagnosis statin use in six common cancers in elderly patients with localized and regional disease. Our findings suggest that statin use after diagnosis improves cancer-specific survival in lung cancer and pancreatic cancer and should be confirmed in large clinical trials of statins as an adjuvant therapy in cancer treatment. Given the wide-spread use and safety of these cholesterol-lowering medications, statins hold great promise as anti-cancer agents in improving cancer outcomes. We do not have evidence that statin use confers the same protective benefit to incident statin users with prostate cancer, colorectal cancer, bladder cancer, or non-Hodgkin lymphoma, although there was heterogeneity in the association between statin use and bladder cancer survival by stage. For these four cancers, given our relatively short follow-up, future observational studies with longer follow-up should be conducted to clarify the uncertain association between statin use and cancer survival, with particular focus on early-stage bladder cancer patients. Larger sample sizes may enhance the detection of the potentially small effects of statin use in these cancers.

Table 1. Cohort selection

Inclusion criteria	Cases Remaining					
	Prostate	**Colorectal**	**Lung**	**Bladder**	**Pancreas**	**Non-Hodgkin lymphoma**
All cancer cases in SEER-Medicare diagnosed at age 66 years or older from 2008 to 2017	371,162	260,151	438,919	167,910	99,313	122,085
Diagnosed in some way other than autopsy or death certificate alone	366,758	256,452	426,443	166,590	95,059	120,854
Without a history of prior cancer (first primary cancer only)	320,103	195,324	307,298	116,284	71,403	87,045
Summary stage: localized – regional diseases	269,767	138,828	128,290	49,566	28,226	22,535
With continuous Medicare enrollment at least 12 months before and after cancer diagnosis (unless died)						
Part A/B enrollment	232,238	126,989	118,517	45,471	25,795	20,549
No concurrent health maintenance organization (HMO) enrollment	144,801	80,041	76,721	28,742	16,496	13,280
Part D enrollment	69,806	43,808	43,441	14,865	9,471	7,339
No statin use in the 12 months before cancer diagnosis	34,618	20,579	20,133	6,163	4,538	3,270

Table 2. Characteristics of individuals diagnosed with cancer in the SEER-Medicare database from 2008-2017 by post-diagnosis statin use[1,2]

	Prostate Cancer		**Colorectal Cancer**		**Lung Cancer**		**Bladder Cancer**		**Pancreatic Cancer**		**Non-Hodgkin Lymphoma**	
Duration of follow-up (years), median (interquartile range)	4.0 (2.2–6.8)		2.9 (1.3–5.3)		1.7 (0.7–3.5)		2.1 (0.9–4.2)		0.8 (0.3–1.7)		2.9 (1.2–5.4)	
Cancer deaths, N	1,013		2,493		6,861		1,126		2,474		368	
Duration of statin use (years), mean (interquartile range)	2.5 (0.7-3.8)		2.1 (0.5-3.1)		1.7 (0.4-2.4)		1.9 (0.4-2.8)		1.0 (0.2-1.2)		2.2 (0.5-3.3)	
	No use N = 23,601 (68%) N (%)	*Statin use* N = 11,017 (32%) N (%)	*No use* N = 15,933 (77%) N (%)	*Statin use* N = 4,646 (23%) N (%)	*No use* N = 16,219 (81%) N (%)	*Statin use* N = 3,914 (19%) N (%)	*No use* N = 4,843 (79%) N (%)	*Statin use* N = 1,320 (21%) N (%)	*No use* N = 4,205 (93%) N (%)	*Statin use* N = 333 (7%) N (%)	*No use* N = 2,465 (75%) N (%)	*Statin use* N = 805 (25%) N (%)
Demographics												
Age at diagnosis												
65-69	7,685 (32.6)	3,597 (32.6)	2,779 (17.4)	969 (20.9)	3,426 (21.1)	1,002 (25.6)	721 (14.9)	257 (19.5)	725 (17.2)	86 (25.8)	502 (20.4)	195 (24.2)
70-74	7,935 (33.6)	4,015 (36.4)	3,431 (21.5)	1,221 (26.3)	4,288 (26.4)	1,216 (31.1)	1,062 (21.9)	382 (28.9)	924 (22.0)	85 (25.5)	583 (23.7)	229 (28.4)
75-79	4,585 (19.4)	2,229 (20.2)	3,283 (20.6)	1,047 (22.5)	3,726 (23.0)	926 (23.7)	947 (19.6)	292 (22.1)	916 (21.8)	79 (23.7)	532 (21.6)	169 (21.0)
80-84	2,197 (9.3)	895 (8.1)	3,012 (18.9)	822 (17.7)	2,726 (16.8)	509 (13.0)	919 (19.0)	240 (18.2)	797 (19.0)	45 (13.5)	405 (16.4)	125 (15.5)
85+	1,199 (5.1)	281 (2.6)	3,428 (21.5)	587 (12.6)	2,053 (12.7)	261 (6.7)	1,194 (24.7)	149 (11.3)	843 (20.0)	38 (11.4)	443 (18.0)	87 (10.8)
Sex												
Male	23,601 (100)	11,017 (100)	6,298 (39.5)	2,100 (45.2)	6,668 (41.1)	1,594 (40.7)	3,219 (66.5)	973 (73.7)	1,559 (37.1)	152 (45.6)	1,002 (40.6)	356 (44.2)
Female	0 (0.0)	0 (0.0)	9,635 (60.5)	2,546 (54.8)	9,551 (58.9)	2,320 (59.3)	1,624 (33.5)	347 (26.3)	2,646 (62.9)	181 (54.4)	1,463 (59.4)	449 (55.8)
Race												
White	19,457 (82.4)	9,156 (83.1)	13,560 (85.1)	3,854 (83.0)	14,164 (87.3)	3,452 (88.2)	4,390 (90.6)	1,204 (91.2)	3,582 (85.2)	283 (85.0)	2,210 (89.7)	722 (89.7)

Black	2,526 (10.7)	1,036 (9.4)	1,282 (8.0)	420 (9.0)	1,327 (8.2)	260 (6.6)	221 (4.6)	47 (3.6)	336 (8.0)	22 (6.6)	104 (4.2)	31 (3.9)
Other	1,100 (4.7)	612 (5.6)	1,036 (6.5)	360 (7.7)	–*	–*	213 (4.4)	–*	–*	28 (8.4)	129 (5.2)	39 (4.8)
Unknown	518 (2.2)	213 (1.9)	55 (0.3)	12 (0.3)	–*	–*	19 (0.4)	–*	–*	0 (0.0)	22 (0.9)	13 (1.6)
Cancer characteristics												
Year of diagnosis												
2008 – 2010	6,262 (26.6)	4,448 (40.4)	4,853 (30.5)	1,819 (39.2)	4,601 (28.4)	1,219 (31.1)	1,285 (26.6)	413 (31.3)	1,076 (25.6)	79 (23.7)	591 (23.9)	267 (33.2)
2011 – 2013	5,780 (24.4)	3,347 (30.4)	4,266 (26.8)	1,440 (31.1)	4,389 (27.1)	1,130 (28.9)	1,275 (26.4)	426 (32.2)	1,117 (26.6)	93 (27.9)	650 (26.3)	278 (34.6)
2014 – 2017	11,559 (49.0)	3,222 (29.3)	6,814 (42.8)	1,387 (29.8)	7,229 (44.6)	1,565 (40.1)	2,283 (47.2)	481 (36.5)	2,012 (47.9)	161 (48.3)	1,224 (49.6)	260 (32.3)
Summary stage at diagnosis												
Localized	20,565 (87.1)	9,744 (88.4)	7,811 (49.0)	2,583 (55.6)	7,335 (45.2)	2,275 (58.1)	4,045 (83.5)	1,161 (88.0)	1,144 (27.2)	135 (40.5)	– *	–*
Regional	3,036 (12.9)	1,273 (11.5)	8,122 (51.0)	2,063 (44.4)	8,884 (54.8)	1,639 (41.9)	798 (16.5)	159 (12.1)	3,061 (72.8)	198 (59.4)	– *	–*
Grade												
I	3,145 (13.3)	979 (8.9)	1,468 (9.2)	478 (10.3)	1,266 (7.8)	514 (13.1)	101 (2.1)	44 (3.3)	312 (7.4)	68 (20.4)	N/A	N/A
II	9,437 (40.0)	4,490 (40.8)	10,290 (64.6)	3,065 (66.0)	3,621 (22.3)	1,248 (31.9)	399 (8.2)	149 (11.3)	785 (18.7)	86 (25.8)	N/A	N/A
III - IV	10,218 (43.3)	5,275 (47.9)	2,899 (18.2)	749 (16.1)	4,478 (27.7)	987 (25.2)	3,821 (78.9)	1,013 (76.8)	664 (15.8)	56 (16.8)	N/A	N/A
Unknown	801 (3.4)	273 (2.5)	1276 (8.0)	354 (7.6)	6,854 (42.3)	1,165 (29.8)	522 (10.8)	114 (8.6)	2,444 (58.1)	123 (36.9)	0 (0.0)	0 (0.0)
Cancer treatments												
Surgery												
Yes	4,739 (20.1)	2,352 (21.3)	13,403 (84.1)	4,061 (87.4)	5,239 (32.3)	2,194 (56.1)	4,570 (94.4)	1,275 (96.6)	1,275 (30.3)	186 (55.9)	N/A	N/A
No	18,862 (79.9)	8,665 (78.7)	2,530 (15.9)	585 (12.6)	10,980 (67.7)	1,720 (43.9)	273 (5.6)	45 (3.4)	2,930 (69.7)	147 (44.1)	N/A	N/A
Radiation therapy												
Yes	9,025 (38.2)	4,604 (41.8)	2,526 (15.9)	624 (13.4)	6,557 (40.4)	1,333 (34.1)	781 (16.1)	127 (9.6)	981 (23.3)	73 (21.9)	866 (35.1)	254 (31.6)

No	14,576 (61.8)	6,413 (58.2)	13,407 (84.1)	4,022 (86.6)	9,662 (59.6)	2,581 (65.9)	4,062 (83.9)	1,193 (90.4)	3,224 (76.7)	260 (78.1)	1,599 (64.9)	551 (68.4)
Chemotherapy												
Yes	6,921 (29.3)	3,207 (29.1)	3,621 (22.7)	1,087 (23.4)	4,891 (30.2)	1,063 (27.2)	2,740 (56.6)	830 (62.9)	2,063 (49.1)	186 (55.9)	1125 (45.6)	384 (47.7)
No	16,680 (70.7)	7,810 (70.9)	12,312 (77.3)	3,559 (76.6)	11,328 (69.8)	2,851 (72.8)	2,103 (43.4)	490 (37.1)	2,142 (50.9)	147 (44.1)	1,340 (54.4)	421 (52.3)
Hormone therapy												
Yes	7,139 (30.2)	3,339 (30.3)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
No	16,462 (69.8)	7,678 (69.7)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Immunotherapy												
Yes	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	258 (10.5)	84 (10.4)
No	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	2,207 (89.5)	721 (89.6)
Baseline comorbidities												
Depression												
Yes	729 (3.1)	337 (3.1)	1,038 (6.5)	253 (5.4)	1,513 (9.3)	325 (8.3)	276 (5.7)	46 (3.5)	324 (7.7)	24 (7.2)	161 (6.5)	42 (5.2)
No	22,872 (96.9)	10,680 (96.9)	14,895 (93.5)	4,393 (94.6)	14,706 (90.7)	3,589 (91.7)	4,567 (94.3)	1,274 (96.5)	3,881 (92.3)	309 (92.8)	2,304 (93.5)	763 (94.8)
Cardiovascular disease												
Yes	1,710 (7.2)	1,036 (9.4)	2,593 (16.3)	862 (18.6)	3,283 (20.2)	885 (22.6)	820 (16.9)	239 (18.1)	698 (16.6)	55 (16.5)	328 (13.3)	104 (12.9)
No	21,891 (92.8)	9,981 (90.6)	13,340 (83.7)	3,784 (81.4)	12,936 (79.8)	3,029 (77.4)	4,023 (83.1)	1,081 (81.9)	3,507 (83.4)	278 (83.5)	2,137 (86.7)	701 (87.1)
Diabetes												
Yes	2,899 (12.3)	2,329 (21.1)	2,768 (17.4)	1,328 (28.6)	2,723 (16.8)	951 (24.3)	763 (15.8)	352 (26.7)	1,198 (28.5)	139 (41.7)	375 (15.2)	179 (22.2)
No	20,702 (87.7)	8,688 (78.9)	13,165 (82.6)	3,318 (71.4)	13,496 (83.2)	2,963 (75.7)	4,080 (84.2)	968 (73.3)	3,007 (71.5)	194 (58.3)	2,090 (84.8)	626 (77.8)
Hypertension												
Yes	9,245 (39.2)	5,382 (48.9)	7,905 (49.6)	2,711 (58.4)	8,461 (52.2)	2,380 (60.8)	2,305 (47.6)	775 (58.7)	2,373 (56.4)	211 (63.4)	1,115 (45.2)	437 (54.3)
No	14,356 (60.8)	5,635 (51.1)	8,028 (50.4)	1,935 (41.6)	7,758 (47.8)	1,534 (39.2)	2,538 (52.4)	545 (41.3)	1,832 (43.6)	122 (36.6)	1,350 (54.8)	368 (45.7)

Hyperlipidemia												
Yes	4,588 (19.4)	4,071 (37.0)	3,407 (21.4)	1,857 (40.0)	3,963 (24.4)	1,705 (43.6)	1,087 (22.4)	573 (43.4)	1,299 (30.9)	176 (52.9)	588 (23.9)	345 (42.9)
No	19,013 (80.6)	6,946 (63.0)	12,526 (78.6)	2,789 (60.0)	12,256 (75.6)	2,209 (56.4)	3,756 (77.6)	747 (56.6)	2,906 (69.1)	157 (47.1)	1,877 (76.1)	460 (57.1)

[1] Only patients without pre-diagnosis use were included in the analyses.

[2] Patients identified as statin users/non-users after lagging exposure by 6 months (for prostate cancer, colorectal cancer, bladder cancer, and non-Hodgkin lymphoma) or 1 month (for lung cancer and pancreatic cancer).

*Number suppressed due to SEER-Medicare data use restrictions.

Table 3. Association of post-diagnosis statin use with cancer-specific mortality[1 2 3]

		Primary analysis: excluding individuals with pre-diagnosis use			*Analysis including individuals with pre-diagnosis use*		
		Follow-up time (person-years)	**Number of cancer deaths**	**HR (95% CI)**	**Follow-up time (person-years)**	**Number of cancer deaths**	**HR (95% CI)**
Prostate cancer	No use	124,096	779	ref	149,979	836	ref
	Ever use	37,628	234	0.92 (0.79, 1.08)	169,052	966	**0.87 (0.78, 0.96)**
Colorectal cancer	No use	68,590	2,163	ref	83,986	2,488	ref
	Ever use	14,119	330	0.92 (0.81, 1.03)	72,310	1,879	**0.85 (0.80, 0.91)**
Lung cancer	No use	40,731	6,146	ref	51,909	8,325	ref
	Ever use	9,880	715	**0.81 (0.74, 0.88)**	55,128	5,288	**0.77 (0.73, 0.81)**
Bladder cancer	No use	16,922	1,006	ref	21,855	1,207	ref
	Ever use	3,572	120	0.87 (0.71, 1.07)	21,053	912	**0.82 (0.74, 0.90)**
Pancreatic cancer	No use	5,708	2,363	ref	7,897	3,420	ref
	Ever use	627	111	**0.72 (0.59, 0.87)**	4,845	1,401	**0.80 (0.73, 0.86)**
Non-Hodgkin lymphoma	No use	11,050	302	ref	13,478	371	ref
	Ever use	2,416	66	1.29 (0.96, 1.72)	12,075	343	1.01 (0.86, 1.19)

Abbreviations: HR=hazard ratio, CI=confidence interval

[1] Pre-diagnosis use was defined as two or more statin prescriptions filled in the year prior to diagnosis.

[2] Ever use = ever use of statins post-diagnosis. Exposure lagged by 6 months for prostate cancer, colorectal cancer, bladder cancer, and non-Hodgkin lymphoma; lagged by 1 month for lung cancer and pancreatic cancer.

[3] All models were adjusted for age at diagnosis, sex, race, year of diagnosis, tumor stage and grade, receipt of surgery, chemotherapy, radiotherapy, hormone therapy and immunotherapy, depression, cardiovascular disease (myocardial infarction, heart failure, stroke, or peripheral vascular disease), hyperlipidemia, hypertension, and diabetes.

Table 4. Association of post-diagnosis statin use with cancer-specific mortality stratified by cancer site, subtype or stage at diagnosis[1 2 3]

	N of cancer deaths (%)	HR (95% CI)
Colorectal cancer		
Cancer site		
Colon cancer	1,780 (71)	0.96 (0.83, 1.11)
Rectal cancer	713 (29)	0.85 (0.69, 1.06)
Lung cancer		
Cancer subtype		
Squamous cell carcinoma	2,307 (34)	**0.81 (0.70, 0.93)**
Adenocarcinoma	2,154 (31)	**0.79 (0.69, 0.90)**
Large cell carcinoma	96 (1)	**0.38 (0.16, 0.89)**
Small cell carcinoma	722 (11)	0.95 (0.73, 1.23)
Other	1,582 (23)	0.84 (0.69, 1.01)
Bladder cancer		
Cancer subtype		
PTCC	467 (41)	0.92 (0.69, 1.24)
NPTCC	572 (51)	0.84 (0.63, 1.13)
Other	87 (8)	0.79 (0.31, 2.03)
Stage at diagnosis		
Localized	814 (72)	**0.77 (0.60, 0.98)**
Regional	312 (28)	1.22 (0.85, 1.74)
Non-Hodgkin lymphoma		
Cancer subtype		
DLBCL	164 (45)	1.33 (0.82, 2.16)
Other	204 (55)	1.21 (0.84, 1.75)

Abbreviations: HR=hazard ratio, CI=confidence interval, PTCC = papillary transitional cell carcinoma, NPTCC = non-papillary transitional cell carcinoma, DLBCL= diffuse large B-Cell lymphoma

[1] Only patients without pre-diagnosis use were included in the analyses.

[2] Exposure lagged by 6 months for prostate cancer, colorectal cancer, bladder cancer, and non-Hodgkin lymphoma; lagged by 1 month for lung cancer and pancreatic cancer.

[3] All models were adjusted for age at diagnosis, sex, race, year of diagnosis, tumor stage and grade, receipt of surgery, chemotherapy, radiotherapy, hormone therapy and immunotherapy, depression, cardiovascular disease (myocardial infarction, heart failure, stroke, or peripheral vascular disease), hyperlipidemia, hypertension, and diabetes.

Table 5. Association of post-diagnosis statin use with cancer-specific mortality by overall duration of use [1 2 3 4]

	Duration	Follow-up time (person-years)	Number of cancer deaths	HR (95% CI)
Prostate cancer	No use	124,096	779	ref
	<1 year	12,391	109	1.17 (0.94, 1.46)
	1 to < 2 years	6,939	41	0.85 (0.62, 1.17)
	2 to < 3 years	5,120	33	0.91 (0.64, 1.29)
	≥ 3 years	13,178	51	**0.51 (0.38, 0.69)**
				$p_{trend} < 0.001$
Colorectal cancer	No use	68,590	2,163	ref
	<1 year	5,460	156	0.85 (0.72, 1.02)
	1 to < 2 years	2,700	80	1.04 (0.83, 1.31)
	2 to < 3 years	1,747	44	1.13 (0.83, 1.54)
	≥ 3 years	4,212	50	0.75 (0.56, 1.01)
				$p_{trend} = 0.42$
Lung cancer	No use	40,731	6,146	ref
	<1 year	4,144	416	**0.85 (0.77, 0.94)**
	1 to < 2 years	1,903	121	**0.72 (0.60, 0.87)**
	2 to < 3 years	1,227	85	0.91 (0.73, 1.14)
	≥ 3 years	2,606	93	**0.62 (0.50, 0.77)**
				$p_{trend} = 0.009$
Bladder cancer	No use	16,922	1,006	ref
	<1 year	1,355	70	0.89 (0.70, 1.14)
	1 to < 2 years	698	25	0.91 (0.60, 1.36)
	2 to < 3 years	486	8	0.55 (0.27, 1.11)
	≥ 3 years	1,033	17	0.88 (0.53, 1.49)
				$p_{trend} = 0.55$
Pancreatic cancer	No use	5,708	2,363	ref
	<1 year	323	85	**0.77 (0.62, 0.96)**
	1 to < 2 years	118	14	**0.53 (0.34, 0.83)**
	2 to < 3 years	79	6	**0.27 (0.10, 0.73)**
	≥ 3 years	108	6	0.52 (0.25, 1.08)
				$p_{trend} = 0.04$
Non-Hodgkin lymphoma	No use	11,050	302	ref
	<1 year	866	38	1.43 (0.95, 2.15)
	1 to < 2 years	462	8	0.82 (0.40, 1.68)
	2 to < 3 years	337	7	1.17 (0.54, 2.53)
	≥ 3 years	750	13	0.86 (0.47, 1.57)
				$p_{trend} = 0.54$

Abbreviations: HR=hazard ratio, CI=confidence interval

[1] Only patients without pre-diagnosis use were included in the analyses.

[2] Exposure lagged by 6 months for prostate cancer, colorectal cancer, bladder cancer, and non-Hodgkin lymphoma; lagged by 1 month for lung cancer and pancreatic cancer.

[3] All models were adjusted for age at diagnosis, sex, race, year of diagnosis, tumor stage and grade, receipt of surgery, chemotherapy, radiotherapy, hormone therapy and immunotherapy, depression, cardiovascular disease (myocardial infarction, heart failure, stroke, or peripheral vascular disease), hyperlipidemia, hypertension, and diabetes.

[4] Only statin users included in the trend analysis

Supplemental Table 1. Codes used to define cancer subtypes, cancer treatments, and comorbidities

Variable	Codes
Cancer subtype	
Lung cancer	Histologic ICD-O-3 code: Adenocarcinoma (8140, 8141, 8143, 8147, 8250-5, 8260, 8310, 8323, 8333, 8480, 8481, 8570-2, 8573, 8574, 8576), squamous cell carcinoma (8070-6, 8078), large cell carcinoma (8012-4), and small cell carcinoma (8002, 8041-5)
Bladder cancer	Histologic ICD-O-3 code: Papillary transitional cell carcinoma (PTCC):8130–8131; non-papillary transitional cell carcinoma (NPTCC): 8120–8124
Non-Hodgkin lymphoma	Histologic ICD-O-3 code: Diffuse large B-cell lymphoma (DLBCL): 9680, 9688, 9737, 9738, 9684, 9735, 9712, 9678, 9679; chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL): 9670, 9823; follicular lymphoma (FL): 9675, 9690-9691, 9695, 9698; peripheral T-cell lymphoma (PTCL): 9702, 9705, 9708, 9714, 9716, 9717, 9709, 9726, 9718
Cancer Treatments	
Prostate cancer surgery	ICD-9: 60.5
	ICD-10: 0VT00ZZ, 0VT04ZZ, 0VT07ZZ, 0VT08ZZ
	HCPCS: 55866, 55810, 55812, 55815, 55840, 55842, 55845
Lung cancer surgery	ICD-9: 32.3, 32.30, 32.39, 32.4, 32.41, 32.49, 32.5, 32.50, 32.59, 32.6
	ICD-10: 0BTC0ZZ, 0BTC4ZZ, 0BTD0ZZ, 0BTD4ZZ, 0BTF0ZZ, 0BTF4ZZ, 0BTG0ZZ, 0BTG4ZZ, 0BTH0ZZ, 0BTH4ZZ, 0BTJ0ZZ, 0BTJ4ZZ, 0BBC0ZZ, 0BBC4ZZ, 0BBD0ZZ, 0BBD4ZZ, 0BBF0ZZ, 0BBF4ZZ, 0BBG0ZZ, 0BBG4ZZ, 0BBH0ZZ, 0BBH4ZZ, 0BBJ0ZZ, 0BBJ4ZZ, 0BBK0ZZ, 0BBK3ZZ, 0BBK4ZZ, 0BBK7ZZ, 0BBL0ZZ, 0BBL4ZZ, 0BBM0ZZ, 0BBM3ZZ, 0BBM4ZZ, 0BBM7ZZ, 0BTK0ZZ, 0BTL0ZZ, 0BBL3ZZ, 0BBL7ZZ, 0BTM0ZZ, 0BTK4ZZ, 0BTL4ZZ, 0BTM4ZZ, 0BDN4ZZ, 0BDP4ZZ, 01B30ZZ, 01BL0ZZ, 0PB10ZZ, 0PB20ZZ
	HCPCS: 32663, 32666, 32667, 32668, 32669, 32670, 32671, 32505, 32506, 32507, 32608, 32440, 32442, 32445, 32480, 32482, 32484, 32486, 32488
Colorectal cancer surgery	
Colon surgery	ICD-9: 45.71, 45.72, 45.73, 45.74, 45.75, 45.76, 45.79, 45.81, 45.82, 45.83, 17.31, 17.32, 17.33, 17.34, 17.35, 17.36, 17.39
	ICD-10: 0DBE0ZZ, 0DBE3ZZ, 0DBE7ZZ, 0DBE8ZZ, 0DTH0ZZ, 0DTH7ZZ, 0DTH8ZZ, 0DTF0ZZ, 0DTF7ZZ, 0DTF8ZZ, 0DTK0ZZ, 0DTL0ZZ, 0DTL7ZZ, 0DTL8ZZ, 0DTLFZZ, 0DTG0ZZ, 0DTG7ZZ, 0DTG8ZZ, 0DTGFZZ, 0DTN0ZZ, 0DTN7ZZ, 0DTN8ZZ, 0DTNFZZ, 0DBGFZZ, 0DBLFZZ, 0DBMFZZ, 0DBNFZZ, 0DTMFZZ, 0DTE4ZZ, 0DTE0ZZ, 0DTE7ZZ, 0DTE8ZZ, 0DBE4ZZ, 0DTH4ZZ, 0DTF4ZZ, 0DTL4ZZ, 0DTG4ZZ, 0DTN4ZZ
	HCPCS: 44140, 44141, 44143, 44144, 44145, 44146, 44147, 44150, 44151, 44152, 44153, 44155, 44156, 44157, 44158, 44160, 44204, 44205, 44206, 44207, 44208, 44210, 44211, 44212
Rectal surgery	ICD-9: 48.50, 48.51, 48.52, 48.59, 48.61, 48.62, 48.63, 48.64, 48.69
	ICD-10: 0D1N0Z4, 0DTP0ZZ, 0DTP4ZZ, 0DTP7ZZ, 0DTP8ZZ, 0DTN0ZZ, 0DTN4ZZ, 0D1N4Z4, 0DBP0ZZ, 0DBP4ZZ
	HCPCS:45110, 45395, 45111, 45112, 45113, 45114, 45116, 45119, 45120, 45121, 45123 , 45126, 45160, 45170, 45397
Bladder cancer surgery	ICD-9: 57.6, 57.71, 57.79
	ICD-10: 0TBB0ZZ, 0TBB3ZZ, 0TBB4ZZ, 0TTB7ZZ, 0TTB8ZZ
	HCPCS: 51550, 51565, 51570, 51575, 51580, 51585, 51590, 51595, 51596, 51720, 52224, 52234, 52235, 52240

Pancreatic cancer surgery	ICD-9: 52.21, 52.22, 52.51, 52.52, 52.53, 52.59, 52.6, 52.7
	ICD-10: 0F5D8ZZ, 0FBD8ZZ, 0F5D0ZZ, 0F5D3ZZ, 0F5D7ZZ, 0F5G0ZZ, 0F5G3ZZ, 0FBD0ZZ, 0FBD3ZZ, 0FBD7ZZ, 0FBG0ZZ, 0FBG3ZZ, 0FTD0ZZ, 0FTD7ZZ, 0FBG0ZZ, 0FBG3ZZ, 0FBG4ZZ, 0FBG8ZZ, 0FTG0ZZ, 0FTG4ZZ
	HCPCS: 48150, 48152, 48153, 48154, 48155, 48145, 48146
Chemotherapy	ICD-9 Procedure: 99.25 ICD-9 Diagnosis: V58.1, V66.2, V67.2
	ICD-10 Procedure: 3E03305, 3E04305, XW03351, XW033B3, XW033C3, XW04351, XW043B3, XW043C3 ICD-10 Diagnosis: Z51.11
	HCPCS: J9000-J9999 (exclude J9003, J9165, J9175, J9202, J9209, J9212-J9226, J9240, J9295, J9395), Q0083-Q0085, J8520, J8521, J8530, J8540, J8560, J8597, J8610, J8999, 96401-96549
	Revenue center code: 0331, 0332, 0335
Radiation therapy	ICD-9 Procedure: 92.2, 92.20 – 92.29, 92.3, 92.30 – 92.39, 92.41 ICD-9 Diagnosis: V58.0, V66.1, V67.1
	ICD-10 Procedure: 3E0P304, 3E0P704, 3E0P804, DMY0***, DMY1***, DM00***, DM01***, DM10***, DM11*** ICD-10 Diagnosis: Z51.0, Z51.89, Z08
	HCPCS: 77371-77373, 77401-77525, 77761-77799, G0173, G0251, G0339, G0340
	Revenue center code: 0330, 0333
Immunotherapy (for non-Hodgkin lymphoma)	ICD-9: V58.12, 00.18, 99.28
	ICD-9: Z51.12, 3E00X0M, 3E0130M, 3E0230M, 3E0330M, 3E0430M, 3E0530M, 3E0630M
Hormone therapy	
Androgen deprivation therapy (for prostate cancer)	HCPCS: Orchiectomy: 54520, 54530, 54535, 54690; Use of luteinizing hormone-releasing hormone agonists: J0128, J1950, J3315, J9202, J9217, J9218, J9219, or J9225
Comorbidities*	
Depression	ICD-9: 296.20, 296.21, 296.22, 296.23, 296.24, 296.25, 296.26, 296.30, 296.31, 296.32, 296.33, 296.34, 296.35, 296.36, 300.4, 311
	ICD-10: F32.0, F32.1, F32.2, F32.3, F32.4, F32.5, F32.89, F32.9, F33.0, F33.1, F33.2, F33.3, F33.40, F33.41, F33.42, F33.8, F33.9, F34.1
Hyperlipidemia	ICD-9: 272.0, 272.1, 272.2, 272.3, 272.4
	ICD-10: E78.0, E78.00, E78.01, E78.1, E78.2, E78.3, E78.4, E78.41, E78.49, E78.5
Hypertension	ICD-9: 362.11, 401.0, 401.1, 401.9, 402.00, 402.01, 402.10, 402.11, 402.90, 402.91, 403.00, 403.01, 403.10, 403.11, 403.90, 403.91, 404.00, 404.01, 404.02, 404.03, 404.10, 404.11, 404.12, 404.13, 404.90, 404.91, 404.92, 404.93, 405.01, 405.09, 405.11, 405.19, 405.91, 405.99, 437.2
	ICD-10: H35.031, H35.032, H35.033, H35.039, I10, I11.0, I11.9, I12.0, I12.9, I13.0, I13.10, I13.11, I13.2, I15.0, I15.1, I15.2, I15.8, I15.9, I67.4, N26.2
Diabetes	ICD-9: 249.00-249.91, 250.00-250.93, 357.2, 362.01, 362.02, 362.03, 362.04, 362.05, 362.06, 366.41
	ICD-10: E08.00-E08.9, E09.00-E09.9, E10.10-E10.9, E11.00-E11.9, E13.00-E13.9
Myocardial infarction	ICD-9: 410.01, 410.11, 410.21, 410.31, 410.41, 410.51, 410.61, 410.71, 410.81, 410.91 (ONLY first or second DX on the claim)
	ICD-10: I21.01, I21.02, I21.09, I21.11, I21.19, I21.21, I21.29, I21.3, I21.4, I21.9, I21.A1, I21.A9, I22.0, I22.1, I22.2, I22.8, I22.9 (ONLY first or second DX on the claim)
Heart failure	ICD-9: 398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 428.0, 428.1, 428.20, 428.21, 428.22, 428.23, 428.30, 428.31, 428.32, 428.33, 428.40, 428.41, 428.42, 428.43, 428.9

	ICD-10: I09.81, I11.0, I13.0, I13.2, I50.1, I50.20, I50.21, I50.22, I50.23, I50.30, I50.31, I50.32, I50.33, I50.40, I50.41, I50.42, I50.43, I50.810, I50.811, I50.812, I50.813, I50.814, I50.82, I50.83, I50.84, I50.89, I50.9
Stroke	ICD-9: 430, 431, 433.00-433.91, 434.00-434.91, 435.0-435.9, 436, 997.02
	ICD-10: G45.0-G45.9, G46.0-G46.8, G97.31, G97.32, I60.00-I60.9, I61.0-I61.9, I62.00-I62.9, I63.00-I63.9, I66.01-I66.9, I67.841, I67.848, I67.89, I97.810, I97.811, I97.820, I97.821
Peripheral vascular disease	ICD-9: 440.0, 440.1, 440.2, 440.20, 440.21, 440.22, 440.23, 440.29, 440.4, 443.8, 443.81, 443.82, 443.89, 443.9
	ICD-10: E08.51, E08.52, E09.51, E09.52, E10.51, E10.52, E11.51, E11.52, E13.51, E13.52, I70.0, I70.1, I70.201, I70.202, I70.203, I70.208, I70.209, I70.211, I70.212, I70.213, I70.218, I70.219, I70.221, I70.222, I70.223, I70.228, I70.229, I70.231, I70.232, I70.233, I70.234, I70.235, I70.238, I70.239, I70.241, I70.242, I70.243, I70.244, I70.245, I70.248, I70.249, I70.25, I70.291, I70.292, I70.293, I70.298, I70.299, I70.92, I73.81, I73.89, I73.9, I79.1, I79.8

* Comorbidity codes are based on codes provided by Chronic Conditions Data Warehouse: https://www2.ccwdata.org/web/guest/condition-categories.

Supplemental Table 2. Association of post-diagnosis statin use with cancer-specific mortality by statin intensity [1 2 3 4]

	Intensity	Follow-up time (person-years)	Number of cancer deaths	HR (95% CI)
Prostate cancer	No use	124,096	779	ref
	Low	5,650	35	0.92 (0.65, 1.30)
	Moderate	25,666	155	0.89 (0.74, 1.06)
	High	6,312	44	1.08 (0.79, 1.47)
				p_{trend} = 0.39
Colorectal cancer	No use	68,590	2,163	ref
	Low	2,271	42	0.80 (0.59, 1.09)
	Moderate	9,586	239	0.97 (0.84, 1.12)
	High	2,263	49	0.82 (0.60, 1.06)
				p_{trend} = 0.83
Lung cancer	No use	40,731	6146	ref
	Low	1,589	110	**0.77 (0.63, 0.93)**
	Moderate	6,472	458	**0.81 (0.73, 0.89)**
	High	1,819	147	0.86 (0.72, 1.01)
				p_{trend} = 0.49
Bladder cancer	No use	16,922	1,006	ref
	Low	608	23	0.97 (0.64, 1.48)
	Moderate	2,249	69	0.86 (0.66, 1.10)
	High	715	28	0.84 (0.57, 1.23)
				p_{trend} = 0.71
Pancreatic cancer	No use	5,708	2,363	ref
	Low	102	19	0.66 (0.42, 1.04)
	Moderate	432	72	**0.70 (0.55, 0.89)**
	High	93	20	0.90 (0.58, 1.40)
				p_{trend} = 0.56
Non-Hodgkin lymphoma	No use	11,050	302	ref
	Low	384	9	1.01 (0.51, 2.00)
	Moderate	1,586	40	1.20 (0.85, 1.71)
	High	447	17	**1.88 (1.13, 3.14)**
				p_{trend} = 0.77

Abbreviations: HR=hazard ratio, CI=confidence interval

[1] Only patients without pre-diagnosis use were included in the analyses.

[2] Exposure lagged by 6 months for prostate cancer, colorectal cancer, bladder cancer, and non-Hodgkin lymphoma; lagged by 1 month for lung cancer and pancreatic cancer.

[3] All models were adjusted for age at diagnosis, sex, race, year of diagnosis, tumor stage and grade, receipt of surgery, chemotherapy, radiotherapy, hormone therapy and immunotherapy, depression, cardiovascular disease (myocardial infarction, heart failure, stroke, or peripheral vascular disease), hyperlipidemia, hypertension, and diabetes.

[4] Only statin users included in the trend analysis

Supplemental Table 3. Association of post-diagnosis statin use with cancer-specific mortality by statin solubility[1 2 3]

	Solubility	Follow-up time (person-years)	Number of cancer deaths	HR (95% CI)
No use as the reference group				
Prostate cancer	No use	124,096	779	ref
	Hydrophilic	8,939	61	1.02 (0.78, 1.34)
	Lipophilic	28,689	173	0.89 (0.75, 1.06)
Colorectal cancer	No use	68,590	2163	ref
	Hydrophilic	3,425	76	0.91 (0.72, 1.14)
	Lipophilic	10,695	254	0.92 (0.80, 1.05)
Lung cancer	No use	40731	6146	ref
	Hydrophilic	2615	172	**0.75 (0.64, 0.87)**
	Lipophilic	7265	543	**0.83 (0.76, 0.91)**
Bladder cancer	No use	16,922	1,006	ref
	Hydrophilic	930	34	1.01 (0.71, 1.44)
	Lipophilic	2,643	86	0.83 (0.66, 1.04)
Pancreatic cancer	No use	5,708	2,363	ref
	Hydrophilic	123	28	0.69 (0.47, 1.01)
	Lipophilic	504	83	**0.73 (0.58, 0.91)**
Non-Hodgkin lymphoma	No use	11,050	302	ref
	Hydrophilic	558	16	1.33 (0.79, 2.24)
	Lipophilic	1,858	50	1.27 (0.92, 1.76)
Lipophilic use as the reference group				
Prostate cancer	Lipophilic	28,689	173	ref
	Hydrophilic	8,939	61	1.16 (0.87, 1.56)
Colorectal cancer	Lipophilic	10,695	254	ref
	Hydrophilic	3,425	76	0.98 (0.76, 1.27)
Lung cancer	Lipophilic	7265	543	ref
	Hydrophilic	2615	172	0.90 (0.75, 1.07)
Bladder cancer	Lipophilic	2,643	86	ref
	Hydrophilic	930	34	1.22 (0.80, 1.86)
Pancreatic cancer	Lipophilic	504	83	ref
	Hydrophilic	123	28	0.84 (0.52, 1.35)
Non-Hodgkin lymphoma	Lipophilic	1,858	50	ref
	Hydrophilic	558	16	1.16 (0.65, 2.07)

Abbreviations: HR=hazard ratio, CI=confidence interval

[1] Only patients without pre-diagnosis use were included in the analyses.

[2] Exposure lagged by 6 months for prostate cancer, colorectal cancer, bladder cancer, and non-Hodgkin lymphoma; lagged by 1 month for lung cancer and pancreatic cancer.

[3] All models were adjusted for age at diagnosis, sex, race, year of diagnosis, tumor stage and grade, receipt of surgery, chemotherapy, radiotherapy, hormone therapy and immunotherapy, depression, cardiovascular disease (myocardial infarction, heart failure, stroke, or peripheral vascular disease), hyperlipidemia, hypertension, and diabetes.

Supplemental Table 4. Sensitivity analyses[1 2 3]

Patients without pre-diagnosis use defined as either those with fewer than 2 prescription fills or those with no prescription fills in the year prior to diagnosis*

		Among those without pre-diagnosis use (<2 prescription fills)			*Among those without pre-diagnosis use (0 prescription fills)*		
		Follow-up time (person-years)	**Number of cancer deaths**	**HR (95% CI)**	**Follow-up time (person-years)**	**Number of cancer deaths**	**HR (95% CI)**
Prostate cancer	No use	124,096	779	ref	118,128	753	ref
	Ever use	37,628	234	0.92 (0.79, 1.08)	26,060	168	0.92 (0.77, 1.10)
Colorectal cancer	No use	68,590	2,163	ref	65,399	2,067	ref
	Ever use	14,119	330	0.92 (0.81, 1.03)	9,752	234	0.96 (0.84, 1.11)
Lung cancer	No use	40,731	6,146	ref	38,247	5,762	ref
	Ever use	9,880	715	**0.81 (0.74, 0.88)**	6,705	472	**0.82 (0.74, 0.91)**
Bladder cancer	No use	16,922	1,006	ref	15,927	948	ref
	Ever use	3,572	120	0.87 (0.71, 1.07)	2,534	78	0.88 (0.69, 1.13)
Pancreatic cancer	No use	5,708	2,363	ref	5,273	2,191	ref
	Ever use	627	111	**0.72 (0.59, 0.87)**	365	52	**0.70 (0.53, 0.93)**
Non-Hodgkin lymphoma	No use	11,050	302	ref	10,472	292	ref
	Ever use	2,416	66	1.29 (0.96, 1.72)	1,690	46	1.21 (0.86, 1.70)

Abbreviations: HR=hazard ratio, CI=confidence interval

[1] Only patients without pre-diagnosis use were included in the analyses.

[2] Ever use = ever use of statins post-diagnosis.

[3] All models were adjusted for age at diagnosis, sex, race, year of diagnosis, tumor stage and grade, receipt of surgery, chemotherapy, radiotherapy, hormone therapy and immunotherapy, depression, cardiovascular disease (myocardial infarction, heart failure, stroke, or peripheral vascular disease), hyperlipidemia, hypertension, and diabetes.

* Exposure lagged by 6 months.

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