Research Article

Cancer Epidemiology, Biomarkers & Prevention

Use of Statin Medications Following Diagnosis in Relation to Survival among Women with Ovarian Cancer

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Abstract

Background: It has been suggested that the likelihood of survival among women with ovarian cancer could be increased by postdiagnosis statin use. This study examines the potential association between postdiagnosis statin use and cancer-specific mortality among women with ovarian cancer.

Methods: This cohort study used SEER-Medicare data on women ≥66 years of age diagnosed with ovarian cancer during 2007 to 2012 who were enrolled in Medicare parts A, B, and D during the year after diagnosis. Statin use was defined as two or more fills for a statin during the year after diagnosis. Ovarian cancer–specific death was assessed starting 1 year after diagnosis. Marginal structural Cox models were used, adjusting for the inverse probability of treatment weighting and censoring weighting. Treatment weights and censoring weights were calculated using logistic regression models with *a priori*–defined covariates.

Results: Among 2,195 women with ovarian cancer, 489 (22%) used statins within 1 year after their diagnosis. Over a mean follow-up of 2.2 years, 796 (36%) women died from ovarian cancer. The adjusted HR for ovarian cancer mortality comparing statin users to nonusers was 0.74 (95% confidence interval, 0.61–0.91).

Conclusions: Findings from this and prior work suggest statin use following a diagnosis with ovarian cancer is associated with a lower risk of cancer death.

Impact: Because, in most women, statin administration has limited side effects, a randomized trial of statins among patients with ovarian cancer may be warranted.

Introduction

At the present time, administration of statins is the mainstay of treatment of dyslipidemia, and there are reasons to believe that these drugs may have the potential to reduce the risk of cancer (1). Results of prior studies also suggest that use of statins is associated with improved survival from breast (2), colorectal (3), and ovarian cancer (4). These medications have been postulated to reduce cancer growth and progression via several mechanisms. First, they inhibit a major rate-limiting enzyme of the mevalonate pathway, resulting in reduced levels of mevalonate and corresponding downstream products, which are necessary for imperative cellular functions such as cell signaling, protein synthesis, and cell-cycle action (5). Statins have also been shown to promote apoptosis in ovarian cancer cell lines specifically (1). This occurs via several intrinsic and extrinsic cascades, which result in caspase-mediated apoptosis (6). Lastly, statins may have important anti-inflammatory properties (7), which may oppose inflammation-driven ovarian tumorigenesis and cancer progression (8). Mechanistic nuances based on lipophilicity of statins have been proposed, suggesting that lipophilic statins ought to diminish gynecologic tumor progression to a relatively greater degree. Hydrophilic statins are more hepatoselective, whereas lipophilic statins show activity in nonhepatic tissues as well (9). This results in a differential action of statins in gynecologic tissues (10). In addition, ovarian cancer is a heterogeneous disease and the histologic types are frequently perceived as distinctive diseases with differing pathogenesis and treatment responses (11). As such, associations between statin use and histologic subtype may vary (12).

To date, there have been no randomized trials of statin administration in women with ovarian cancer. Nonrandomized studies are limited by the potential for confounding (statins preferentially used by women with a relatively more favorable prognosis) and immortal time bias (survival up to the time of initiation of a statin postdiagnosis inappropriately not being credited to statin nonusers). The aim of this study was to examine the potential association between postdiagnosis statin use and cancer-specific mortality among women with ovarian cancer, using design and analytic strategies that attempt to minimize sources of bias. We also sought to address the possibility of a difference in the impact of statins based on their lipophilicity, and to see whether the presence or magnitude of any association differed according to ovarian cancer histologic type.

Materials and Methods

Population

This was a retrospective cohort study of women in the linked Surveillance Epidemiology, and End Results (SEER)–Medicare database. This database contains claims data as well as cancer

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registry data for Medicare beneficiaries diagnosed with cancer living in the catchment areas of the 18 United States–based SEER cancer registries (12), which enumerate incident cancer cases from approximately 28% of the U.S. population (13, 14). The Medicare program provides hospital insurance (Part A), medical insurance (Part B), and prescription drug coverage (Part D, available 2006-onward) for individuals ages 65 or older in the United States.

The SEER data were used to identify all epithelial ovarian cancer (EOC) cases diagnosed during 2007–2012. Borderline tumors were not included. A total of 19,931 women 65 years or older were diagnosed with histologically confirmed malignant primary EOC, determined by ICD-oncology 3rd edition codes (C56.9). Medicare enrollment information and Medicare Parts A, B, and D claims data from January 1, 2007, to December 31, 2012 were retrieved for all patients with EOC identified in SEER, as well as dates and types of medical services women received during this period. For the current analysis, all subjects were required to be 66 years of age or above at the time of diagnosis and to not have a prior history of cancer. We further excluded those whose EOC diagnosis came from autopsy or death certificate alone and those who were missing complete information on date of diagnosis. Additional exclusions were made for those enrolled in a health maintenance organization (HMO) for 1 or more months during the first year after baseline and for those not continuously enrolled in Medicare parts A, B, and D during the first year (Fig. 1). This resulted in an eligible cohort of 2,195 women.

The study protocol was approved by the Fred Hutchinson Cancer Research Center's Institutional Review Board.

Exposure

The primary exposure of interest was postovarian cancer diagnosis use of statins. In our main analyses, women were considered users of statins if they had two or more fills for a statin medication during the first year following ovarian cancer diagnosis. We applied a 1-year fixed baseline period during which exposure was defined to avoid immortal time bias (15). In addition, because of how reimbursement for part D is done, participants may fall into a coverage gap during which they bear the brunt of medication costs. A lack of financial assistance in the coverage gap has been associated with the discontinuation of medications (16). Patients may switch Medicare plans, which may result in their drug use no longer being covered or available in Medicare data files (17). Because of this, requiring all women to be enrolled in part D for an entire year during which drug use can be ascertained equally for all women is a reliable approach to measuring exposure for all women (18). Statins were classified as either lipophilic or hydrophilic to examine potential differences based on lipophilicity (9, 10). The former includes atorvastatin, simvastatin, lovastatin, and fluvastatin, while the latter includes pravastatin and rosuvastatin (19).

Outcome

The primary outcome was ovarian cancer–specific death, as determined using underlying cause of death in the SEER files. SEER records cause of death from death certificate data. Women were considered to have died from ovarian cancer if the reported underlying cause of death was ovarian cancer.

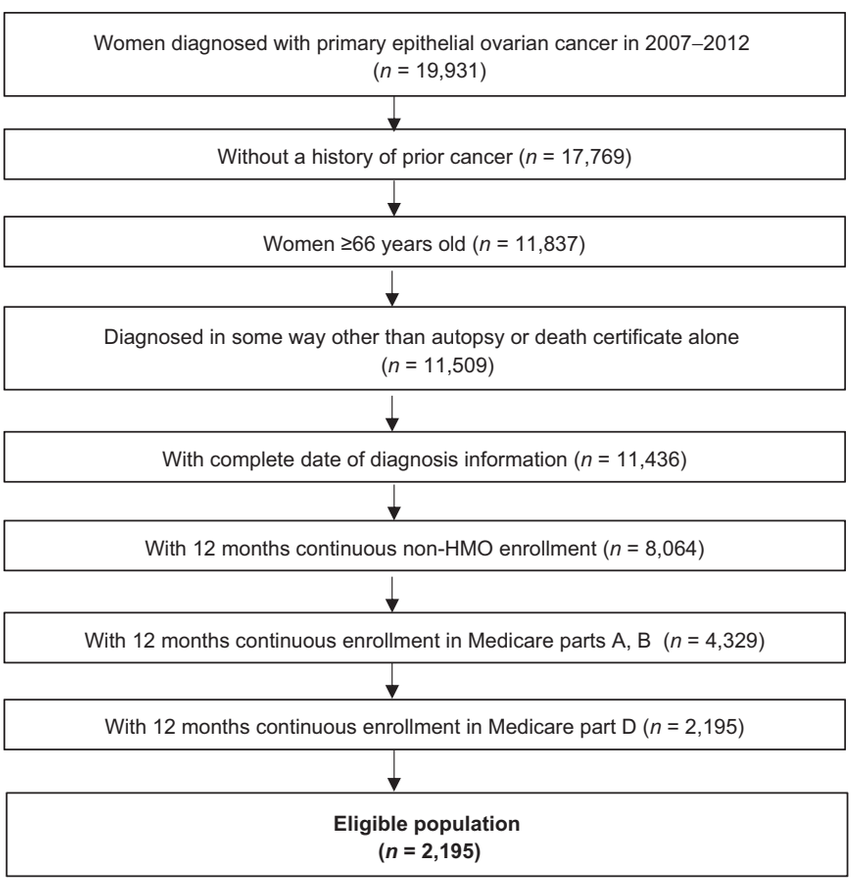

Figure 1.
Flow chart of selection of population for inclusion in study. Eligible women were those who had a primary diagnosis of epithelial ovarian cancer during the study years. Exclusions were made for those with a prior cancer, those <66 years of age, those diagnosed by autopsy or death alone, those with missing information on date of diagnosis, those without 12 months of continuous enrollment in Medicare part A, B, or D after diagnosis, or those who were enrolled in an HMO during some or all of the year following diagnosis.

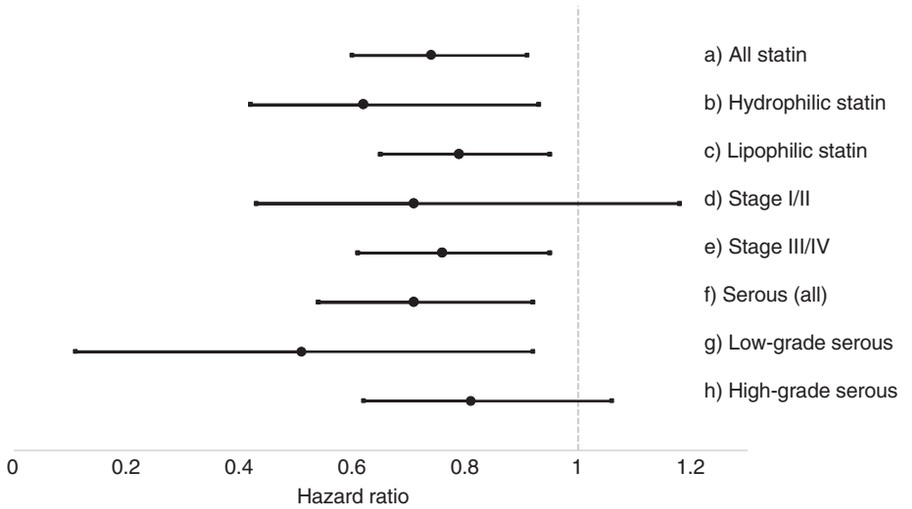

Figure 2.
Associations between statin use and risk of ovarian cancer mortality. The aHRs and corresponding 95% CIs for the risk of mortality are shown for the following comparisons: a) statin use versus no statin use, b) hydrophiic statin use versus no statin use, c) lipophilic statin use versus no statin use, d) statin use versus no statin use among women with grade I–II ovarian cancer, e) statin use versus no statin use among women with stage III–IV ovarian cancer, f) statin use versus no statin use among women with tumors of serous histology, g) statin use versus no statin use among women with tumors of low-grade serous histology, and h) statin use versus no statin use among women with tumors of high-grade serous histology.

Covariates

Information on potential confounders including demographic, cancer-specific, and other health-related factors was collected from SEER or Medicare data. Demographic factors, including the year of diagnosis, age at diagnosis, race and ethnicity, marital status, census tract poverty level, and location of residence were available from SEER. Census tract poverty level was categorized into three groups based on the percentage of residents living below the poverty level: 0–<10% 10–<20% or ≥20% (20). This measure has been consistently associated with the presence of various diseases using different spatial scales, and has implications for access to treatment and other health- care–related outcomes (21, 22). Location of residence was defined as either urban or rural, using Rural Urban Continuum Codes based on the population size and proximity to metropolitan areas (23). In addition to demographic factors available in SEER at the time of diagnosis, information on cancer-related factors was also collected including tumor histology, tumor stage and grade at diagnosis, and surgical treatment receipt. Women were considered to have undergone surgery only if the operation was done as part of the initial work-up or first course of therapy.

We also used Medicare data to identify chemotherapy use, Charlson comorbidity index (Deyo–Charlson adaptation; ref. 24), the presence of diabetes and information on hyperlipidemia, hypertension or glaucoma. Receipt of chemotherapy was defined as any chemotherapy-related claims within 180 days after cancer diagnosis. The Charlson comorbidity index was created by compiling information from Medicare utilization records during the 1-year baseline period between diagnosis and the beginning of follow-up. Diabetes was defined using International Disease Code 9th Revision (ICD-9) codes for diabetes found during the year following diagnosis of ovarian cancer in Medicare claims. The Medicare chronic conditions flag files (25) were used to determine whether women had hyperlipidemia, hypertension, or glaucoma.

Statistical analysis

The association between statin use and cancer-specific mortality was modeled using marginal structural Cox models with a robust sandwich variance estimator (26) to produce HRs and associated 95% confidence intervals (CI; ref. 27). The time scale in Cox models was time since 1 year after diagnosis (index date). Person-time that accrued and deaths that occurred among women who died during the first year following diagnosis were not considered. Inverse probability weighting was used to adjust for confounders of the association of interest between statin use and ovarian cancer mortality (28). We estimated treatment weights for each participant, proportional to the inverse probability of statin use conditional on the following covariates: year of diagnosis, age at diagnosis, race/ethnicity, marital status, census tract poverty level, location of residence, tumor histology, tumor stage, tumor grade, surgical treatment receipt, chemotherapy receipt, Charlson comorbidity score, diabetes, hyperlipidemia, and hypertension (29). Weights were calculated using a logistic regression model with *a priori*–defined covariates including known confounders as well as variables known to be associated with ovarian cancer–specific mortality regardless of their association with the exposure of interest. The addition of these "precision" variables has been shown to improve precision estimates through the control of imbalances of risk factors across treatment groups (30). We also estimated censoring weights to adjust for potentially informative censoring (31). The product of the treatment weights and the censoring weights were included in models to calculate the association between statin use and cancer-specific mortality. No additional covariates were added to the weighted cox models.

To improve our statistical efficiency, the inverse probability weights were stabilized by setting the numerator of the weight equal to the probability of statin exposure conditional on the covariates detailed above (32, 33). To check model assumptions, we examined the distribution of weights to ensure the mean of the stabilized weights was one (28).

Cohort characteristics were presented stratified according to statin use during the year following baseline, with means and SDs for continuous variables and frequencies and proportions for categorical variables. Complete case analysis methods were used. Data management and analyses were completed using SAS version 9.4 and Stata version 14.0.

Sensitivity analyses

Three sensitivity analyses were conducted to evaluate the presence of: (i) "sick-stopper" bias; (ii) the impact of prevalent statin use prior to baseline; and (iii) healthy user bias.

Table 1. Baseline[a] characteristics of women diagnosed with ovarian cancer during 2007–2012, by statin use during the first year after diagnosis[b] ($N = 2,195$)

	Statin users[c] ($n = 489$) n (%)	Statin nonusers ($n = 1,706$) n (%)
Year at diagnosis		
2007	55 (11.2%)	257 (15.1%)
2008	85 (17.4%)	310 (18.2%)
2009	94 (19.2%)	290 (17.0%)
2010	87 (17.8%)	275 (16.1%)
2011	80 (16.4%)	275 (16.1%)
2012	88 (18.0%)	299 (17.5%)
Age at diagnosis (years)		
65–69	102 (20.9%)	429 (25.1%)
70–74	139 (28.4%)	502 (29.4%)
75–79	121 (24.7%)	349 (20.5%)
80–84	127 (26.0%)	426 (25.0%)
Race/ethnicity		
Non-Hispanic white	387 (79.1%)	1,384 (81.1%)
Non-Hispanic black	30 (6.1%)	103 (6.0%)
Hispanic	34 (7.0%)	134 (7.9%)
Asian/Pacific Islander	30 (6.1%)	85 (5.0%)
Marital status		
Never married	45 (9.2%)	173 (10.1%)
Married	212 (43.4%)	716 (42.0%)
Separated/divorced	209 (42.7%)	763 (44.7%)
Widowed	23 (4.7%)	54 (3.2%)
Surgical treatment received	393 (80.4%)	1,353 (79.3%)
Chemotherapy received	269 (55.0%)	976 (57.2%)
Tumor histology		
Serous	248 (50.7%)	926 (54.3%)
Low-grade	20 (8.1%)	100 (10.9%)
High-grade	173 (69.8%)	601 (65.3%)
Unknown grade	55 (22.2%)	220 (23.9%)
Mucinous	19 (3.9%)	49 (2.9%)
Endometrioid	43 (8.8%)	132 (7.7%)
Clear cell	15 (3.1%)	57 (3.3%)
Other	164 (33.5%)	542 (31.8%)
Stage at diagnosis		
I	109 (22.2%)	285 (16.7%)
II	34 (7.0%)	169 (9.9%)
III	196 (40.1%)	693 (40.6%)
IV	113 (23.1%)	426 (25.0%)
Missing	37 (7.5%)	133 (7.8%)
Grade		
I	21 (4.3%)	60 (3.5%)
II	52 (10.6%)	185 (10.8%)
III	166 (34.0%)	568 (33.3%)
IV	86 (17.6%)	293 (17.2%)
Missing	164 (33.5%)	600 (35.2%)
Census tract poverty level		
<10% poverty	240 (49.7%)	885 (52.5%)
10–<20% poverty	131 (27.1%)	469 (27.8%)
>20–100% poverty	112 (23.2%)	332 (19.7%)
Location of residence		
Urban	422 (86.3%)	1,521 (89.2%)
Rural	67 (13.7%)	185 (10.8%)
Deyo–Charlson comorbidity score		
0	180 (36.8%)	706 (41.4%)
1	113 (23.1%)	418 (24.5%)
2+	196 (40.1%)	582 (34.1%)
Diabetes	192 (39.3%)	426 (25.0%)
Hyperlipidemia	399 (81.6%)	745 (43.7%)
Hypertension	420 (85.9%)	1,195 (70.0%)
Glaucoma	54 (11.0%)	207 (12.1%)
Prior statin use[d]	374 (86.2%)	167 (11.5%)

[a]All variables are measured at the time of diagnosis using SEER data with the exception of the comorbidity score, which was measured during the first year following diagnosis.

The first sensitivity analysis addressed concerns that advancing disease could confound results if it led to a discontinuation of statin medication (34). In the main analysis, stage at diagnosis is adjusted for. However, with rapidly advancing disease, baseline covariate adjustment may be inadequate. The available data do not allow for time-updated adjustment because data values in SEER are only assessed at diagnosis without update according to disease progression. This analysis limited the medication exposure window to 6 months after diagnosis, at which point disease status was likely to be relatively more similar to each woman's status at the time of diagnosis, and so adjustment for baseline characteristics will more completely control confounding. In this analysis, follow-up for mortality began 6 months following diagnosis. The second sensitivity analysis addressed the possible influence of statin use prior to ovarian cancer diagnosis. This analysis limited the patient population to those who were diagnosed in 2008 or after, so that 1 year of possible prior use could be measured. The third sensitivity analysis addressed concerns of healthy user bias by comparing ovarian cancer mortality between users of drugs prescribed for treatment of glaucoma—medications that are similarly used less among older, sicker adults (35), and which are not associated with ovarian cancer mortality. Comparing the findings among this group of patients with glaucoma to statin users may help assess the potential bias resulting from statin users being relatively more health-care seeking, more closely engaged in care, or more adherent to screening, and/or other preventive recommendations than their nonusing counterparts (36, 37).

Results

There was a total of 2,195 women with median age of 74 years [interquartile range (IQR) 70–80], which comprised 489 (22%) statin users. Table 1 provides baseline characteristics of all study participants. Compared with women who did not use statins, those who did had on average a greater burden of comorbidity (Table 1). Cancer characteristics among both groups of women were similar. Over a mean follow-up of 2.2 years, 796 (36%) women died as a result of ovarian cancer.

The adjusted HR (aHR) of a death from ovarian cancer comparing statin users to nonusers was 0.74 (95% CI, 0.61–0.91). Lipophilic statin use was associated with an aHR of 0.79 (95% CI, 0.65–0.95), and hydrophilic statin use was associated with an aHR of 0.62 (95% CI, 0.42–0.93; Table 2).

Among all women with serous cancer, statin-use was associated with an aHR of 0.71 (95% CI, 0.54–0.92). Stratified further into low- or high-grade serous tumors, the aHR for low-grade serous was 0.51 (95% CI, 0.11–0.92) and the aHR for high-grade serous was 0.81 (95% CI, 0.62–1.06). The limited number of women with other histologic types precluded further analyses by

[b]The table includes only women who survived during the first year of follow-up after diagnosis.

[c]Statin use during the year following diagnosis. Women considered users if they had a claim for 2+ fills during this year.

[d]Prior statin use was assessed among the 1,883 women diagnosed in 2008 or after who were eligible for this study and who contributed data to the sensitivity analysis adjusting for statin use prior to diagnosis. In this sensitivity analysis, 434 women were statin users and 1,449 were nonstatin users, and these are the denominators used for calculating percentages in this row of the table.

Table 2. Risk of cancer-specific mortality associated with statin use

	Follow-up time (person-years)	Number of ovarian cancer deaths	Incidence (per 1,000 person-years)	HR (95% CI)	
				Crude	Marginal structural model estimate[a]
All statins	1,543	153	99.2	0.78 (0.66–0.92)	0.74 (0.61–0.91)
Hydrophilic statin	232	21	90.5	0.62 (0.41–0.94)	0.62 (0.42–0.93)
Lipophilic statin	1,325	134	101.1	0.80 (0.68–0.96)	0.79 (0.65–0.95)

[a]Main model uses inverse probability weighting.

histologic type. Statin use among those with stage I or II cancer was associated with an aHR of 0.71 (0.43–1.18), while among those with stage III or IV cancer it was associated with an aHR of 0.76 (95% CI, 0.61–0.95; Fig. 2).

In the sensitivity analysis examining statin exposure only within the 6 months following diagnosis and cancer-specific mortality beginning after 6 months following diagnosis, statin use was associated with an aHR of 0.83 (95% CI, 0.71–0.98). Adjusting for statin use prior to diagnosis, the aHR of ovarian cancer mortality was very similar [aHR 0.75 (95% CI, 0.59–0.95)]. In the subanalysis assessing cancer-specific mortality among patients with glaucoma, glaucoma medication use was associated with an aHR close to the null of 1.15 (0.86–1.53).

Discussion

In this large, population-based cohort study, we observed a 9%–39% reduction in the risk of ovarian cancer–specific mortality among women prescribed statins during the year following an ovarian cancer diagnosis.

There are several potential threats to the validity of studies of postdiagnosis statin use in relation to ovarian cancer mortality. These include immortal time bias (15, 38) and confounding by disease severity. We avoided immortal time bias by implementing a fixed exposure assessment period, which occurred prior to the accrual of deaths and follow-up time. Among women diagnosed with ovarian cancer, drugs such as statins, which are used in an attempt to reduce morbidity and mortality from conditions unrelated to the cancer, are likely to be prescribed selectively to those who are expected to have a relatively good prognosis (39). Although our data source allowed for assessment of stage of disease at diagnosis, stage is broadly defined and does not capture the full extent of disease severity. Also, there was no update of this information over the course of the year after diagnosis during which a statin may have been initiated. Therefore, some residual confounding by disease severity could have been present, leading to a spuriously low estimate of the mortality rate among statin users. Other limitations of our study include the lack of information on whether maximal cytoreduction was achieved, a strong predictor of mortality in patients with ovarian cancer (40, 41).

Postdiagnosis statin use in relation to survival among women with epithelial ovarian cancer has been studied previously. In 30- to 84-year-old Danish women who filled prescriptions for a statin during the first year after a diagnosis of ovarian cancer, there was a 10% reduction in all-cause mortality (aHR 0.90, 95% CI, 0.76–1.08) relative to that in statin nonusers during an average follow-up was 2.4 years. The investigators were able to adjust for age at diagnosis, year of diagnosis, stage, histology, receipt of chemotherapy and other nonstatin drugs, history of comorbidities, education, income, and marital status (42). In a Belgian study in which statin use was assessed beginning 6 months following diagnosis, the investigators observed an 19% reduction in all cause-mortality (aHR 0.81, 95% CI, 0.72–0.90) within 3 years after diagnosis among users of statins compared with nonusers, adjusting for age at diagnosis, year of diagnosis, grade, stage, histologic type, and cancer treatment (surgery, chemotherapy, radiotherapy) in the 9 months after diagnosis, as well as the presence of cardiovascular comorbidity and diabetes (43).

A third study investigating postdiagnosis statin use among women with ovarian cancer was conducted by Vogel and colleagues (4), utilizing a SEER-Medicare population of patients with EOC during 2007–2009 (a portion of the population included in our study). They observed a reduction in all-cause mortality of 34% (95% CI, 19%–45%). Beyond the years of diagnosis of ovarian cancer and the outcome definition (all-cause mortality vs. mortality from ovarian cancer specifically), there is another difference between our study and that of Vogel and colleagues: in their study, statin use was defined as one or more fill taking place at any time following diagnosis, with follow-up for mortality beginning at the time such use began. (Person-time that accrued prior to the onset of statin use was credited to the experience of nonusers.) In our study, attention was restricted to statin use during the first year after diagnosis (or, in a sensitivity analysis, during the first six months). The rationale behind our analytic choice was based upon the nature of information used to control for potential confounding of disease severity, which was limited largely to that available at the time of diagnosis. As the time following a diagnosis of cancer grows, knowledge of disease severity at the time of diagnosis becomes less and less adequate to control for confounding. A final difference is that the study by Vogel and colleagues defined exposed participants as those with one or more medication fill, while we required two or more statin fills to reduce misclassification of exposure arising from people who may get a single prescription filled but take little or none of the medication.

Although some prior work has suggested differences in cancer outcomes based on the lipophilicity of statins (9, 10), in our study the estimated reductions in mortality from ovarian cancer were similar for each statin type [aHR lipophilic 0.79 (95% CI, 0.65–0.95), aHR hydrophilic 0.62 (95% CI, 0.42–0.93)]. Two other studies of women with ovarian cancer also observed no appreciable difference in survival according to lipophilicity. Vogel and colleagues reported an aHR of 0.66 (95% CI, 0.54–0.80) for use of lipophilic statins and an aHR of 0.71 (95% CI, 0.47–1.08) for use of hydrophilic statins (4), and Couttenier and colleagues reported an aHR of 0.87 (95% CI, 0.75–1.01) for use of lipophilic statins and an aHR of 0.80 (95% CI, 0.70–0.93) for use of hydrophilic statins (43). Taken together, there appears to be little difference in the association between postdiagnosis statin use and mortality from ovarian cancer based on statin lipophilicity.

Our results may not apply to women during the first year following diagnosis. Although our focus on statin use during

the first postdiagnosis year, with assessment of ovarian cancer mortality only after this time, prevented immortal time bias and allowed for the best adjustment for disease severity, it resulted in the exclusion of women who died relatively soon after diagnosis. However, the sensitivity analysis that limited the exposure ascertainment to 6 months obtained similar findings, and approximately 70% of women with ovarian cancer survived until this time (44). A further consideration is that EOC is clinically a heterogeneous disease with each of the four histologic subtypes having a different disease profile. Our study was large enough to analyze the association with statin use only among the subgroup of women with serous tumors. Small numbers of women with nonserous tumors prevented the examination of associations among other specific histologic subgroups. Finally, as this study included only women above the age of 66, findings may not generalize well to younger women with ovarian cancer.

Overall, findings from this and prior work suggest that postdiagnosis statin use among women with ovarian cancer confers some reduction in the risk of cancer death. In our opinion, these findings should not be viewed as definitive: despite the investigators' best efforts, concerns of confounding remain. Nonetheless, because in most women statin administration has few or limited side effects, a randomized trial of statins as a therapeutic strategy in women with ovarian cancer may be warranted.

Disclosure of Potential Conflicts of Interest

R.R. Urban has provided expert testimony for UpToDate, Inc. No potential conflicts of interest were disclosed by the other authors.

Disclaimer

This study used the linked SEER-Medicare database. The interpretation and reporting of these data are the sole responsibility of the authors.

Authors' Contributions

Conception and design: B.N. Harding, N.S. Weiss
Development of methodology: B.N. Harding, J.A. Delaney, R.R. Urban, N.S. Weiss
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): B.N. Harding
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): B.N. Harding, J.A. Delaney, R.R. Urban, N.S. Weiss
Writing, review, and/or revision of the manuscript: B.N. Harding, J.A. Delaney, R.R. Urban, N.S. Weiss
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): B.N. Harding
Study supervision: N.S. Weiss

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