Commonly used medications and survival from ovarian cancer

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A dissertation
submitted in partial fulfillment of the
requirements for the degree of
Doctor of Philosophy

University of Washington
2019

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ABSTRACT

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Background:

Ovarian cancer is the 5th leading cause of cancer-related death among women in the United States. Typically diagnosed as a late stage disease, it follows an aggressive clinical course resulting in 5-year survival proportions of less than 50% for all stages and less than 30% for advanced stage disease. Current treatment for ovarian cancer consists of surgery plus chemotherapy and has largely remained unchanged in recent years, resulting in little improvement in survival. Identifying novel therapeutic approaches to combat ovarian cancer progression is vital to improving ovarian cancer survivorship. Pre-clinical and early-stage epidemiologic work has provided evidence in support of using antihypertensives and statins as possible therapies to improve survival for women with this disease. Both medication classes have been shown to reduce cancer progression and proliferation on a cellular level. Epidemiologic studies show a possible extension of survival length among antihypertensive or statin users. However, these studies have been limited by methodologic issues.

Methods:

These cohort studies utilized SEER-Medicare data on women 66+ years of age diagnosed with ovarian cancer during 2007-2012 who were enrolled in Medicare parts A, B and D during the

year after diagnosis. Use of the medications of interest (statins, antihypertensives [including angiotensin converting enzyme inhibitors (ACEIs), beta blockers (BBs), calcium channel blockers (CCBs) and thiazide diuretics (TDs)]) was defined as two or more fills for a given medication class during the year after diagnosis. Ovarian cancer-specific death was assessed starting one year after diagnosis. Cox proportional hazards regression models were used, adjusting for participant demographics, tumor-specific factors, and comorbidities.

Results: A total of 2,195 women who were 66+ years of age at diagnosis with ovarian cancer during 2007-2012 met inclusion criteria. Of these women, 489 (22%) used statins, 18 (33%) used a TD, 690 (31%) used an ACEI, 521 (24%) used a BB and 154 (7%) used a CCB. During a mean follow-up of 2.2 years, 796 (36%) women died from ovarian cancer. Ovarian cancer-specific mortality was found to be lower among women who used a statin (compared to non-users), adjusted hazard ratio (aHR) 0.74, 95% confidence interval (CI) 0.60-0.91. Reductions in ovarian cancer-specific mortality were also found among women who used an ACEI (aHR 0.76, 95% CI 0.63-0.92), a TD (aHR 0.82, 95%CI 0.68-0.99), or a non-selective beta-blocker (NSBB) (aHR 0.60, 95%CI 0.43-0.83), but no such association was found in women who took a selective beta-blocker (SBB) or CCB.

Conclusions:

The use of statins and certain types of antihypertensive medications after ovarian cancer diagnosis is associated with reduced risks of mortality. Because statins have a relatively good safety profile coupled with findings from prior work reporting similar reductions in death among statin users, a randomized trial with statins as a therapeutic option may be warranted. Additional research of antihypertensive medication use and ovarian cancer-specific survival is warranted to confirm potential associations with certain types of antihypertensive medications.

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ACKNOWLEDGEMENTS

I would like to thank my chair, Noel Weiss, for being extremely generous with his time to consult, review, and mentor me through this project. I often reflect that convincing him to be my dissertation chair was the smartest decision I made in graduate school.

I would also like to thank Chris Delaney, a committee member and a generally outstanding person who is engaged not only in my academic achievement, but also in supporting my achievement of a happy, wholesome life.

I would also like to acknowledge that this dissertation research used the linked SEER-Medicare database. The interpretation and reporting of these data are the sole responsibility of the authors. The authors acknowledge the efforts of the National Cancer Institute; the Office of Research, Development and Information, CMS; Information Management Services (IMS), Inc.; and the Surveillance, Epidemiology, and End Results (SEER) Program tumor registries in the creation of the SEER-Medicare database.

DEDICATION

For my parents, David and Lisa Harding and my partner, Leon Simcha, who provided endless encouragement and support.

CHAPTER 1**: Use of statin medications following diagnosis in relation to survival among women with ovarian cancer**

Abstract:

Background: It has been suggested that the likelihood of survival among women with ovarian cancer could be increased by post-diagnosis statin use. This study examines the potential association between post-diagnosis 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 2007-2012 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 one 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 one year after their diagnosis. Over a mean follow-up of 2.2 years, 796 (36%) women died from ovarian cancer. The adjusted hazard ratio (aHR) for ovarian cancer mortality comparing statin users to non-users was 0.74 (95% CI 0.60-0.91).

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. Because, in most women, statin administration has limited side effects, a randomized trial of statins among ovarian cancer patients 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 action 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 non-hepatic tissues as well [9]. These properties result in a differential action of statins in gynecologic tissues [10]. Additionally, 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 sub-type may vary [12].

To date, there have been no randomized trials of statin administration in women with ovarian cancer. Non-randomized 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 post-diagnosis inappropriately not being credited to statin non-users). The aim of the present study was to examine the potential association between post-diagnosis statin use and cancer-specific mortality among women with ovarian cancer, using design and analytic strategies that attempt to minimize sources of bias. The study also sought to address the possibility of a difference in the impact of statins based on their lipophilicity, and to see if the presence or magnitude of any association differed according to ovarian cancer histologic type.

Methods:

Population:

This study 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 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 US 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 EOC patients identified in SEER, as well as dates and types of medical services women received

during this period. For the present 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. The study 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 (Figure 1.1). These requirements 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 (IRB File #8607).

Exposure:

The primary exposure of interest was post-ovarian cancer diagnosis use of statins. In the 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. A one year fixed baseline period was applied during which exposure was defined in order 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 these possibilities, 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.

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 3 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.

The study also used Medicare data to identify chemotherapy use, Charlson comorbidity index (Deyo-Charlson adaptation) [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 hazard ratios (HRs) and associated 95% confidence intervals (CIs) [27]. The time scale in Cox models was time since one 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]. Treatment weights were estimated 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 Supplemental Figure 1). 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]. Censoring weights were also estimated 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 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, the distribution of weights was examined in order 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 standard deviations 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: (1) "sick stopper" bias; (2) the impact of prevalent statin use prior to baseline; and (3) "healthy user" bias. 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 since 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 and beyond so that one year of statin use prior to diagnosis date could be measured. The third sensitivity analysis addressed concerns of healthy user bias. This analysis measured the association between glaucoma medication use and cancer specific mortality. Glaucoma medications, like statins, are similarly used less among older, sicker adults [35], and glaucoma medications almost certainly do not lead to a reduced ovarian cancer case-fatality. Comparing results from the analyses of glaucoma and statin medications may help to assess the potential bias resulting from statin users having an inherently better prognosis than their non-using 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 1.1 provides baseline characteristics of all study participants. Compared to women who did not use statins, those who did had on average a greater burden of comorbidity (Table 1.1). 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 hazard ratio (aHR) from the marginal structural Cox model of a death from ovarian cancer comparing statin users to non-users 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 1.2). Estimates from a traditional Cox model produced comparable results (Supplemental Table 1).

Among all women with serous cancer, statin-use was associated with an aHR of 0.71(95% CI 0.54-0.92) (Table 1.3) 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 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) (Figure 1.2).

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) (Supplemental Table 2). 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)] (Supplemental Table 2). Finally, glaucoma medication use was not associated with a reduced risk of death from ovarian cancer (aHR 1.15 (0.86-1.53)), arguing against the hypothesis of an underlying lower risk of death among women taking another medication for disease prevention (e.g. a statin) (Supplemental Table 3).

Discussion:

In this large, population-based cohort study, a 9-39% reduction in the risk of ovarian cancer-specific mortality was observed among women prescribed statins during the year following an ovarian cancer diagnosis. Because the prognosis of ovarian cancer is poor, there is an interest in discovering novel therapeutic options. In recent years, some new developments in chemotherapy have been made including two Poly(ADP-ribose) polymerase (PARP) inhibitors, olaparib and rucaparib, which have been approved by the US Food and Drug Administration (FDA) for the treatment of ovarian cancer as well as a third PARP inhibitor, niraparib, which has been approved as maintenance therapy following platinum-based chemotherapy for recurrent ovarian cancer [38]. Still, the prognosis from ovarian cancer remains poor.

There are several potential threats to the validity of studies of post-diagnostic statin use in relation to ovarian cancer mortality. These include immortal time bias [15, 39] and confounding by disease severity. Immortal time bias was avoided 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 [40]. Though the 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 this study include the lack of information on whether maximal cytoreduction was achieved, a strong predictor of mortality in ovarian cancer patients [41, 42]. Second, the study relied on medication use defined from prescription records, without information on adherence, which may not be an accurate assessment of medication used if patents are prescribed but do not take their medications. Third, although adjustments were made for the presence of hyperlipidemia, the study did not have information on severity of hyperlipidemia. Fourth, though surgery and chemotherapy receipt were adjusted for in analyses, the information available from our data source did not indicate if this treatment was according to guideline recommendations, simply that some level of surgery and chemotherapy were utilized. Fifth, this analysis considers statin use only after diagnosis and does not take into account whether patients had used these medications prior to their diagnosis and if so, for how long, however our sensitivity analysis adjusting for prevalent statin use produced results similar to those from the primary analysis and finally, residual confounding may exist due to the observational study design.

Post-diagnostis statin use in relation to survival among women with epithelial ovarian cancer has been studied previously. Among 30-84 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 statin non-users 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 non-statin drugs, history of comorbidities, education, income and marital status [43]. 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 to non-users, 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 [44].

A third study investigating post-diagnostic statin use among women with ovarian cancer was conducted by Vogel et al. [4], utilizing a SEER-Medicare population of EOC patients during 2007-2009 (a portion of the population included in this 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 this study and that of Vogel et al: 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 correctly credited to the experience of non-users.) In this 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 the analytic choice made for this study 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 et al. defined exposed participants as those with one or more medication fill, while this study 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.

Though some prior work has suggested differences in cancer outcomes based on the lipophilicity of statins [9, 10], in this 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 et al. 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 et al. 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 [44]. Taken together, there appears to be little difference in the association between post-diagnosis statin use and mortality from ovarian cancer based on statin lipophilicity.

The results of this study may not apply to women during the first year following diagnosis. While the focus on statin use during the first post-diagnosis 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 [45]. A further consideration is that EOC is a heterogeneous disease with each of the histologic sub-types exhibiting a different disease profile. This 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 non-serous tumors prevented the examination of associations among other specific histologic subgroups. Finally, as this study included only women above the age of 66, we cannot conclude with certainty if findings would be the same for younger women who are non-Medicare enrolls.

Overall, findings from this and prior work suggest that post-diagnosis statin use among women with ovarian cancer confers some reduction in the risk of cancer death. However, 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.

Table 1.1: 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)		Statin nonusers (n= 1,706)	
	n	%	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.
[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+ 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 non-statin users, and these are the denominators used for calculating percentages in this row of the table.

Table 1.2: Risk of cancer-specific mortality associated with statin use					
				Hazard Ratio (95% Confidence Interval)	
	Follow-up time (person-years)	Number of ovarian cancer deaths	Incidence (Per 1,000 person-years)	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

Table 1.3: Risk of cancer-specific mortality associated with statin use stratified by serous histologic sub-type and stage		
	Hazard Ratio (95% Confidence Interval)	
	Crude	Marginal Structural Model Estimate[a]
All histologic type, all stages	0.78 (0.66-0.92)	0.74 (0.61-0.91)
Serous histologic type	0.76 (0.56-0.95)	0.71 (0.54-0.92)
Low-grade serous	0.30 (0.09-0.98)	0.31 (0.11-0.92)
High-grade serous	0.88 (0.66-1.10)	0.81 (0.62-1.06
Unknown grade	0.79 (0.48-1.19)	0.58 (0.36-0.94)
Stage		
Stage I-II	0.71 (0.45-1.15)	0.71 (0.43-1.18)
Stage III-IV	0.80 (0.67-0.96)	0.76 (0.61-0.95)

[a]Main model uses inverse probability weighting

Figure 1.1: Flow chart of selection of population for inclusion in ovarian cancer and statin use 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.

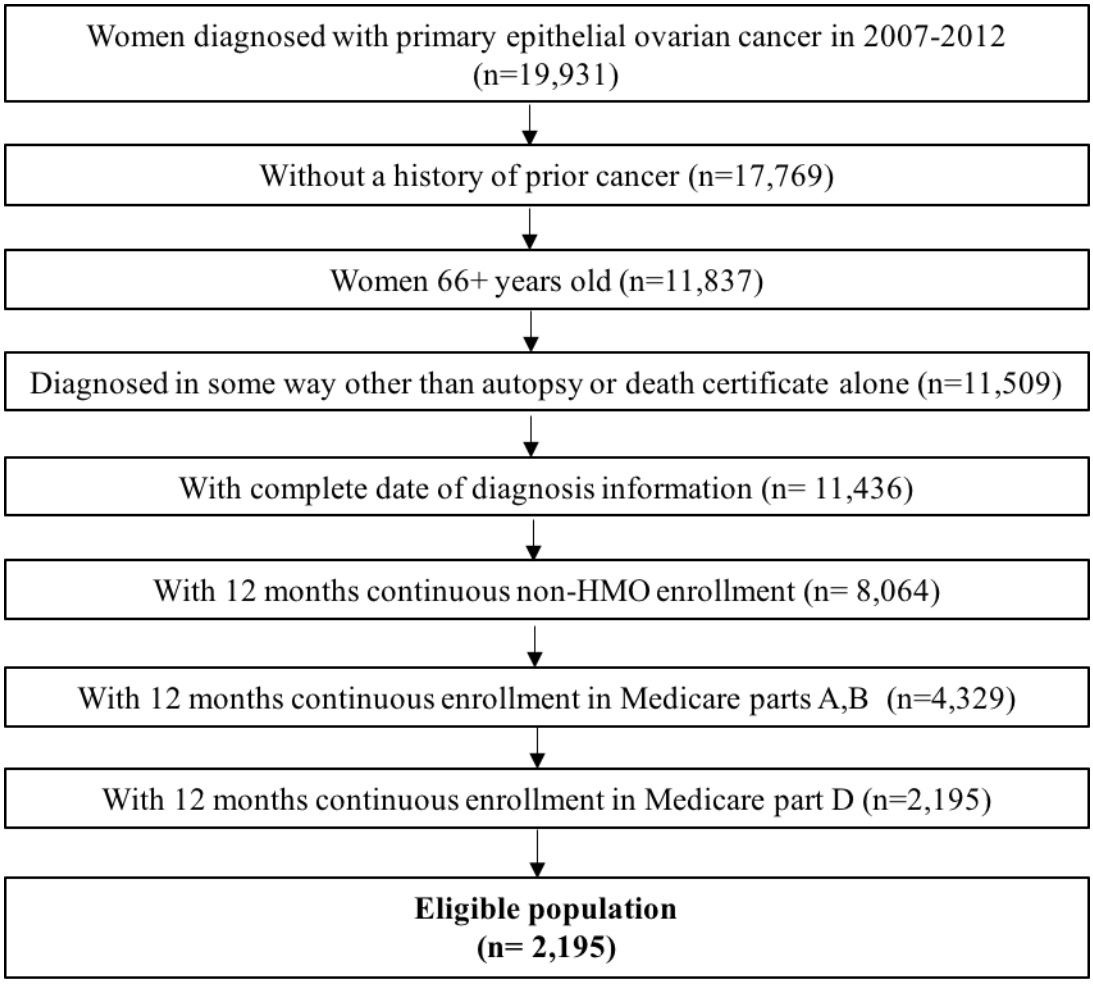
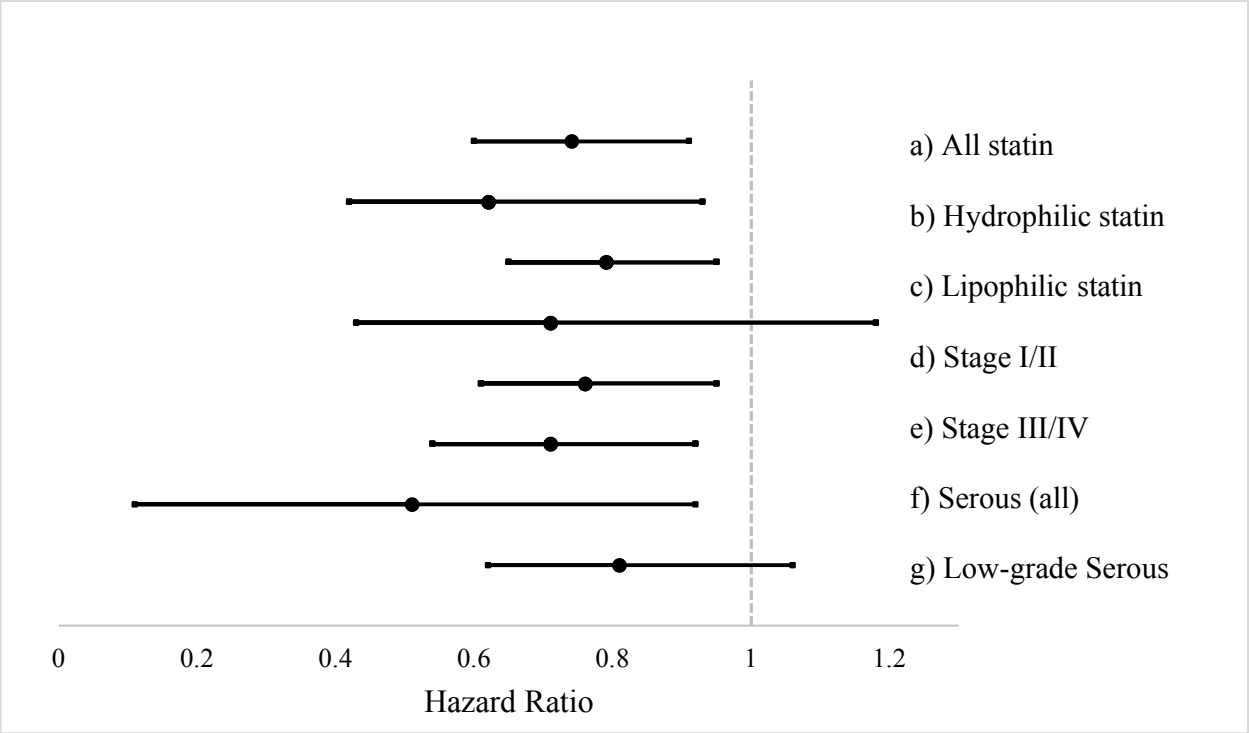


Figure 1.2: Associations between statin use and risk of ovarian cancer mortality. The adjusted hazard ratios and corresponding 95% confidence intervals for the risk of mortality are shown for the following comparisons a) statin use versus no statin use, b) hydrophilic statin use versus no statin use, c) lipophilic statin use versus no statin use, d) statin use versus no statin use among women with stage I-II ovarian cancer, d) statin use versus no statin use among women with stage III-IV ovarian cancer, e) statin use versus no statin use among women with tumors of serous histology, f) statin use versus no statin use among women with tumors of low-grade serous histology and g) statin use versus no statin use among women with tumors of high-grade serous histology.



CHAPTER 2**: Post-diagnosis use of antihypertensive medications and the risk of death from ovarian cancer**

Abstract:

Background: While antihypertensive (AH) use following the diagnosis of some forms of cancer appears to be associated with a reduced case-fatality rate, information is limited on the impact of such use among women with ovarian cancer. This study examines associations between post-diagnosis use of thiazide diuretics (TDs), angiotensin converting enzyme inhibitors (ACEIs), beta blockers (BBs, both selective [SBB] and non-selective [NSBB]) and calcium channel blockers (CCBs) and ovarian cancer-specific survival.

Methods: This cohort study used SEER-Medicare data on 2,195 women 66+ years of age who were diagnosed with ovarian cancer during 2007-2012 and who survived for at least 12 months. Use of an AH class was defined as two or more fills during the year after diagnosis. Ovarian cancer-specific death was assessed starting one year after diagnosis and continued through the end of 2013. Associations between AH use and ovarian cancer-specific mortality were assessed using Cox proportional hazard models, comparing users of a given class of AH to non-AH users.

Results: Overall, 718 (33%), 690 (31%), 521 (24%), 154 (7%) of women used a TD, ACEI, BB, or CCB, respectively, with some women (48%) using more than one class of drug. Ovarian cancer-specific mortality was found to be lower among women who used an ACEI (adjusted hazard ratio [aHR] 0.76, 95% confidence interval [CI] 0.63-0.92), a TD (aHR 0.82, 95%CI 0.68-0.99), or an NSBB (aHR 0.60, 95%CI 0.43-0.83), but no such association was seen in women who took an SBB or a CCB.

Conclusions: It was observed that women who took certain forms of an AH medication during the year following a diagnosis of ovarian cancer were thereafter at a relatively reduced risk of dying from their disease. However, the potential for residual confounding by disease severity argues for a cautious interpretation.

Introduction:

The majority of women who are diagnosed with ovarian cancer die as a result of this disease [46, 47]. While it has been suggested that use of some antihypertensive (AH) medications is associated with an improved likelihood of survival from some forms of cancer [48, 49], information is limited on the impact of use among women with ovarian cancer.

Preclinical studies have elucidated mechanisms whereby some AHs might disrupt tumor progression. The results of molecular and *in vivo* studies suggest that angiotensin converting enzyme inhibitors (ACEIs) could alter the behavior of malignancy by inhibiting RAS-related cellular proliferation, invasion, migration, and metastasis [46, 50]. Use of ACEIs may also alter angiogenesis and other mitogenic actions through changes in vascular endothelial growth factor expression [51]. Administration of CCBs can target energy metabolism and interrupt mitochondrial respiration in cancer cells, a crucial factor in tumor progression [52, 53]. Pre-clinical work has shown that multiple types of voltage-activated calcium channels are aberrantly expressed in cancer cells, including ovarian cancer cell lines. As a result, inhibition of these channels by calcium channel blockers (CCBs) interrupts cell cycle progression, reduces proliferative potential and enhances cell death [54-56]. The use of beta blockers (BBs), antagonists of norepinephrine and epinephrine, may affect progression of cancer by impeding the harmful effects of these catecholamines [57], including increased tumor invasive potential [58], oxidative stress [59], and chemoresistance of tumor cells [60]. BBs can block signaling in cancer cells that otherwise could directly affect tumor cell survival, motility, and invasion by way of Src activation [61]. There are two types of BBs, selective BBs (SBBs) and non-selective BBs (NSBBs). NSBBs, which block both beta-1 and beta-2 receptors, affect a wider range of tissues than SBBs, which target only beta-1 receptors and mainly act on heart tissue [62]. Research has shown that tumor growth is mediated predominantly by beta-2 or beta-3 adrenergic receptors, which NSBBs would be able to influence to a greater degree [63].

Because the prognosis of advanced ovarian cancer is relatively poor, plus there has been recent interest in non-cancer medications that may have anticancer properties [18], it is worthwhile to study the relationship between commonly used medications and ovarian cancer survival. The present study sought to examine the association between post-diagnosis use of AH medications and ovarian cancer-specific survival.

Methods:

Population:

This retrospective cohort study included women in the linked Surveillance, Epidemiology, and End Results (SEER)–Medicare database. This database contains claims data as well as cancer 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 US population [14]. For individuals 65 years of age and above in the United States, the Medicare program provides hospital insurance (Part A), medical insurance (Part B), and prescription drug coverage (Part D, available 2006-onward).

The SEER data were used to identify all epithelial ovarian cancer (EOC) cases diagnosed during 2007-2012 with histologically confirmed malignant primary EOC, determined by ICD-oncology 3rd edition codes (C56.9). Borderline tumors were not included. Medicare enrollment information and Medicare Parts A, B, and D claims data from January 1, 2007, to December 31, 2012 were retrieved for all EOC patients identified in SEER. For the present analysis, women

were required to be 66 years of age or above at the time of diagnosis and to have no history of prior cancer. Potential cases whose EOC diagnosis came solely from an autopsy report or death certificate were excluded, as well as those who were missing complete information on the date of diagnosis. Further 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 (Figure 2.1). These requirements 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 (IRB File #8607).

Exposure:

The primary exposure of interest was post-diagnosis use of antihypertensive medications, categorized into the following major classes: (a) angiotensin converting enzyme inhibitors, (b) beta blockers, (c) calcium channel blockers, and (d) thiazide diuretics.

Women were considered users of a given type of AH medication if they had two or more fills for a drug in that AH class during the first year following cancer diagnosis. To avoid immortal time bias [15], a one year fixed baseline period was applied during which exposure was defined and after which person-time and events were counted. In addition, because of how reimbursement for part D is done, participants may fall into a coverage gap. A lack of financial assistance in the coverage gap has been associated with the discontinuation of medications [16]. Also, patients may switch Medicare plans, which may result in their drug use no longer being covered or available in Medicare data files [17]. By restricting the analysis to women who were enrolled in part D for the entirety of the first year following their diagnosis of ovarian cancer, completeness of ascertainment of AH use was maximized [18].

Outcome:

The primary outcome was ovarian cancer-specific death, as determined using the underlying cause of death found in the SEER files, beginning in the second year after ovarian cancer diagnosis with follow-up through the end of 2013. Women who died during follow-up from a non-ovarian cancer-specific cause were censored at the time of death.

Covariates:

Information on potential confounders including demographic, cancer-specific, and other health-related factors was collected from SEER and/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 3 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 collected, including tumor histology, stage and grade at diagnosis, and receipt of surgical treatment. Women were considered to have undergone surgery only if the operation was done as part of the first course of therapy (indicated in the treatment plan and performed prior to disease progression).

Medicare data were used to identify chemotherapy use, defined as any chemotherapy related claims within 180 days after cancer diagnosis. The Charlson comorbidity index [24] was calculated 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 Classification of Diseases, Ninth Edition (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 which women had been diagnosed with hypertension. The chronic condition variables are developed from algorithms in Medicare data [64-66]. The validity of hypertension defined from combinations of claims and hospitalization codes in administrative data is good, with an estimated positive predictive value of 88% (95%CI 85-90%) and specificity of 95% (95%CI 94-96%) [64].

Statistical analysis:

The association between AH use and cancer-specific mortality was modeled using Cox proportional hazards regression models to produce hazard ratios (HRs) and associated 95% confidence intervals (CIs). The time scale in Cox models was time beginning one 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.

The main analysis compared users of a particular AH drug (ACEI, BB, CCB or TD) to women who did not use AH medications during the year after diagnosis. Women using AH medications in more than one class were included in multiple analyses. This approach allowed for the inclusion of women who use combination AH therapies, which is common among women in this population (48% of AH users). Comparisons were also made based on BB selectivity. In addition, a secondary analysis was conducted, which restricted to monotherapy AH users, and compared monotherapy users of a particular AH class to non-AH users as the reference. The primary and secondary analyses adjusted for age at diagnosis, year of diagnosis, race/ethnicity, marital status, census tract poverty level, location of residence, tumor histology, stage at diagnosis, receipt of surgery, receipt of chemotherapy, Charlson comorbidity score, and diagnosis of diabetes and of hypertension. Complete case analysis methods were used. (approximately 8% were missing data on baseline covariates).

Tumor grade was not adjusted for in the main analyses because a) tumor grade was missing for a sizeable portion of the women in this study (35% of women) and b) it is unlikely that grade is strongly associated with antihypertensive use and therefore was unlikely to be a confounder of the association of interest. However, since grade is an important prognostic factor, two sensitivity analyses were undertaken to investigate the impacts of adjusting for this variable. In the first, grade was added to the set of adjustment variables and complete case methods were used (36% were missing data on baseline covariates when grade was included). Then, in a second sensitivity analysis, multiple imputation with chained equations (MICE) [67] were applied to generate 10 sets of complete data with imputed values for missing grade [68]. In order to avoid bias, the imputation model included all variables used in the primary model [69]. It was assumed that data were missing at random. Because grade at diagnosis is an ordered categorical variable, it was treated as an ordinal variable when imputing values. Quantile-quantile plots were generated as a diagnostic tool for the imputed values. The analysis was run on the imputed data and produced pooled summary results from these 10 complete datasets.

The assumption of proportional hazards was tested with Schoenfeld residuals. Cohort characteristics were presented stratified according to AH use during the year following baseline.

Data management and analyses were completed using SAS version 9.4 and Stata version 14.0.

Results:

This study included a total of 2,195 women whose median age was 74 years at the time of diagnosis (interquartile range [IQR] 70-80) and of whom 1,302 (59%) had two or more prescription fills for at least one of the antihypertensive medications of interest during the year following diagnosis. Cohort characteristics are presented in Table 2.1. Compared to women who did not use antihypertensive medications, those who did were older, less often non-Hispanic white, and had on average a greater burden of comorbidity (Table 2.1). Cancer-specific characteristics were similar between those who used antihypertensive medications and those who did not. Among women who used different classes of antihypertensive medications, characteristics were similar, with slight differences in the distribution of race/ethnicity. Over a mean follow-up of 2.2 years (beginning one year following diagnosis), 796 (36%) women died as a result of ovarian cancer.

Relative to ovarian cancer-specific mortality in women who had not taken an AH, modest reductions were seen for users of ACEIs (aHR 0.76, 95% CI 0.63-0.92) and users of TDs (aHR 0.82, 95% CI 0.68-0.99). While the use of BBs overall had little association with cancer-specific mortality (aHR 0.89, 95%CI 0.72-1.10), NSBB users had a reduction in cancer-specific mortality (aHR 0.60, 95% CI 0.43-0.83) while SBB users did not (aHR 1.03, 95% CI 0.82-1.30). No association was found for CCB use (aHR 0.95, 95% CI 0.70-1.30). (Table 2.2). Restriction of the analysis to women who used just one AH gave similar results (Table 2.3).

Results from sensitivity analyses including adjustment for grade produced HRs similar to those from the primary analysis. (Table 2.4)

Discussion:

There are several important considerations when interpreting the results of non-randomized, retrospective studies of post-diagnosis AH use in relation to ovarian cancer mortality. First, the study relied on medication use defined from prescription records, without information on adherence, which may not be an accurate assessment of medication used if patents are prescribed but do not take their medications. Second, although adjustments were made for the presence of hypertension, the study did not have information on severity of hypertension. Third, though surgery and chemotherapy receipt were adjusted for in analyses, the information available from our data source did not indicate if this treatment was according to guideline recommendations, simply that some level of surgery and chemotherapy were utilized. Fourth, this analysis considers AH use only after diagnosis and does not take into account whether patients had used these medications prior to their diagnosis and if so, for how long. The present study sought to prevent immortal time bias [15, 39] by implementing a fixed exposure assessment period which occurred prior to the accrual of deaths and follow-up time. Still, there may have been residual confounding due to one or more reasons. First, as AH medications are generally prescribed for high blood pressure, a known risk factor of many comorbidities, confounding by indication is of concern. However, AH medications are not indicated for ovarian cancer-specific reasons [70], prior work has failed to show an association between hypertension and ovarian cancer [71], and adjustment for this characteristic had no material bearing on any of the results. Therefore, the likelihood of confounding by indication having a large impact on the study findings is small.

Of greater concern is the presence of confounding by disease severity, which may exist if among women with hypertension, those expected to have a relatively more aggressive

malignancy are less likely to continue to use AH medications during the year following diagnosis [40]. Though the data source allowed for assessment of stage and grade of disease at the time of diagnosis, stage and grade are broadly defined and do 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 AH use was ascertained. If such an incomparability in cancer severity between AH users and non-users had been present, a spuriously low estimate of the relative mortality among AH users would have occurred. Conceivably, the modest reductions in case-fatality associated with use of ACEIs and TDs could be due to confounding from this source.

In contrast, the finding of a favorable impact of NSBB use is suggestive of an association beyond the presence of confounding given the relatively large association seen (a 40% reduction in case-fatality) and the lack of any such reduction among women who used SBBs. Further support for this hypothesis comes from the results of a study involving the administration of an NSBB at the time of ovarian cancer surgery and extending for one week following surgery, in which (after adjustment for prognostic characteristics) there was a 32% (95% CI 1-54%) reduction in mortality compared to that observed among women with ovarian cancer treated at another institution in which peri-operative NSBB administration did not take place [41]. In addition, two clinical trials of NSBB use among women with ovarian cancer are underway [72, 73] to assess the efficacy of concurrent beta-blocker administration with chemotherapy.

In conclusion, although in recent years, some new developments in chemotherapy have been made including two Poly(ADP-ribose) polymerase (PARP) inhibitors, olaparib and rucaparib, which have been approved by the US Food and Drug Administration (FDA) for the treatment of ovarian cancer as well as a third PARP inhibitor, niraparib, which has been approved as maintenance therapy following platinum-based chemotherapy for recurrent ovarian cancer [38], the prognosis of this disease is still poor, which calls for research into potential novel adjuvant therapies. In this study a reduced case-fatality was observed associated with the use of several anti-hypertensive agents (especially NSBBs) among women who have been diagnosed with ovarian cancer. At present, these results should be interpreted cautiously while awaiting the results of further research in which there is a greater ability to distinguish cause from confounding.

Table 2.1: Baseline characteristics of women diagnosed with ovarian cancer during 2007–2012 based on antihypertensive use during follow-up (N=2,195)

	Non-AH users (n= 893)		ACEI users (n=690)		BB users (n=521)		CCB users (n=154)		TD users (n=718)	
	n	%	n	%	n	%	n	%	n	%
Year of diagnosis										
2007	130	14.6%	85	12.3%	78	15.0%	18	11.7%	99	13.8%
2008	166	18.6%	117	17.0%	94	18.0%	29	18.8%	118	16.4%
2009	152	17.0%	116	16.8%	94	18.0%	42	27.3%	130	18.1%
2010	146	16.3%	127	18.4%	78	15.0%	20	13.0%	124	17.3%
2011	125	14.0%	141	20.4%	87	16.7%	25	16.2%	120	16.7%
2012	174	19.5%	104	15.1%	90	17.3%	20	13.0%	127	17.7%
Age at diagnosis (years)										
65-69	250	28.0%	146	21.2%	102	19.6%	28	18.2%	141	19.6%
70-74	256	28.7%	223	32.3%	150	28.8%	39	25.3%	216	30.1%
75-79	184	20.6%	146	21.2%	124	23.8%	33	21.4%	164	22.8%
80-84	203	22.7%	175	25.4%	145	27.8%	54	35.1%	197	27.4%
Marital status										
single	84	9.4%	75	10.9%	58	11.1%	15	9.7%	74	10.3%
married	406	45.5%	287	41.6%	202	38.8%	53	34.4%	285	39.7%
separated, divorced or widowed	403	45.1%	328	47.5%	261	50.1%	86	55.8%	359	50.0%
Race/ethnicity										
non-Hispanic white	763	85.4%	544	78.8%	395	75.8%	103	66.9%	561	78.1%
non-Hispanic black	24	2.7%	54	7.8%	52	10.0%	26	16.9%	67	9.3%
Hispanic	58	6.5%	60	8.7%	37	7.1%	11	7.1%	56	7.8%
Asian/Pacific Islander	44	4.9%	23	3.3%	33	6.3%	14	9.1%	31	4.3%
Surgery	730	81.7%	537	77.8%	405	77.7%	112	72.7%	570	79.4%
Chemotherapy	467	52.3%	326	47.2%	250	48.0%	61	39.6%	338	47.1%
Tumor histology										
serous	497	55.7%	371	53.8%	272	52.2%	84	54.5%	369	51.4%
mucinous	18	2.0%	29	4.2%	16	3.1%	[e]	[e]	29	4.0%
endometrioid	71	8.0%	58	8.4%	41	7.9%	[e]	[e]	54	7.5%
clear cell	31	3.5%	17	2.5%	14	2.7%	[e]	[e]	22	3.1%
other	276	30.9%	215	31.2%	178	34.2%	48	31.2%	244	34.0%
Stage at diagnosis										

I	146	16.3%	123	17.8%	99	19.0%	32	20.8%	133	18.5%
II	97	10.9%	82	11.9%	54	10.4%	16	10.4%	65	9.1%
III	376	42.1%	266	38.6%	185	35.5%	58	37.7%	266	37.0%
IV	212	23.7%	166	24.1%	121	23.2%	38	24.7%	183	25.5%
missing	62	6.9%	53	7.7%	62	11.9%	10	6.5%	71	9.9%
Grade										
1	36	4.0%	23	3.3%	19	3.6%	[e]	[e]	26	3.6%
2	93	10.4%	67	9.7%	61	11.7%	26	16.9%	76	10.6%
3	307	34.4%	222	32.2%	168	32.2%	49	31.8%	247	34.4%
4	164	18.4%	122	17.7%	94	18.0%	[e]	[e]	121	16.9%
missing	293	32.8%	256	37.1%	179	34.4%	60	39.0%	248	34.5%
SES Poverty Indicator										
<10% poverty	489	54.8%	335	48.6%	233	44.7%	69	44.8%	357	49.7%
10-<20% poverty	246	27.5%	182	26.4%	156	29.9%	39	25.3%	196	27.3%
20-100% poverty	146	16.3%	165	23.9%	122	23.4%	45	29.2%	156	21.7%
Urban/rural										
urban	804	90.0%	593	85.9%	455	87.3%	139	90.3%	620	86.4%
rural	89	10.0%	97	14.1%	66	12.7%	15	9.7%	98	13.6%
Deyo-Charlson comorbidity score[d]										
0	422	47.3%	241	34.9%	168	32.2%	49	31.8%	254	35.4%
1	230	25.8%	151	21.9%	111	21.3%	33	21.4%	168	23.4%
2+	241	27.0%	298	43.2%	242	46.4%	72	46.8%	296	41.2%
Diabetes	72	8.1%	102	14.8%	76	14.6%	23	14.9%	93	13.0%
Hypertension	264	29.6%	616	90.1%	478	92.1%	144	94.1%	655	91.9%

[a]Includes only women who survived during the first year of follow-up after diagnosis.
[b]Columns of antihypertensive medication use are not mutually exclusive. Those using combination antihypertensives are included in multiple columns.
[c]Antihypertensive use during the year following diagnosis. Women considered users if they had 2+ claims for a fill during this year.
[d] All variables are measured at the time of diagnosis using SEER data except for comorbidity score which was measured during the first year following diagnosis.
[e] Cannot be displayed due to restrictions regarding the publication of small cells in the data use agreement.
Abbreviations: ACEI, angiotensin converting enzyme inhibitors; BB, beta blockers; CCB, calcium channel blockers; TD, thiazide diuretics

Table 2.2: Risk of ovarian cancer mortality among users of four major classes of antihypertensive medications (n=2,027) with complete covariate information)

				Hazard Ratio (95% Confidence Interval)	
	Follow-up time (person-years)	Number of ovarian cancer deaths	Rate (per 100 person-years)	Unadjusted	Adjusted[a]
No AH	1,730	307	17.7	1.00 (ref)	1.00 (ref)
ACEI	1,396	206	14.8	0.83 (0.70-0.99)	0.76 (0.63-0.92)
CCB	319	56	17.6	1.00 (0.75-1.33	0.95 (0.70-1.30)
TD	1,470	226	15.4	0.87 (0.74-1.04)	0.82 (0.68-0.99)
BB	1,025	172	16.8	0.96 (0.79-1.15)	0.89 (0.72-1.10)
NSBB	406	49	12.1	0.70 (0.51-0.94)	0.60 (0.43-0.83)
SBB	669	126	18.8	1.07 (0.87-1.32)	1.03 (0.82-1.30)

[a]Adjusted for: age at diagnosis, year of diagnosis, race/ethnicity, marital status, census tract poverty level, location of residence, tumor histology, stage at diagnosis, receipt of surgery, receipt of chemotherapy, Charlson comorbidity score, and diagnosis of diabetes and of hypertension

Abbreviations: TD, thiazide diuretics; ACEI, angiotensin converting enzyme inhibitors; BB, beta blockers; CCB, calcium channel blockers; NSBB, non-selective beta blockers; SBB, selective beta blockers.

Table 2.3: Risk of ovarian cancer mortality among monotherapy users of antihypertensive medications

				Hazard Ratio (95% Confidence Interval)	
	Follow-up time (person-years)	Number of ovarian cancer deaths	Rate (per 100 person-years)	Unadjusted	Adjusted[a]
No AH	1,730	307	17.7	1.00	1.00
ACEIs	483	64	13.3	0.73 (0.56-0.96)	0.69 (0.52-0.91)
CCBs	61	9	14.8	0.86 (0.44-1.67)	1.01 (0.51-2.01)
TDs	489	71	14.5	0.83 (0.64-1.08)	0.78 (0.60-1.03)
BBs	362	59	16.3	0.96 (0.72-1.27)	0.95 (0.70-1.28)
NSBB	110	11	10.0	0.60 (0.33-1.09)	0.46 (0.24-0.86)
SBB	231	46	19.9	1.17 (0.86-1.59)	1.30 (0.93-1.81)

[a]Adjusted for: age at diagnosis, year of diagnosis, race/ethnicity, marital status, census tract poverty level, location of residence, tumor histology, stage at diagnosis, receipt of surgery, receipt of chemotherapy, Charlson comorbidity score, and diagnosis of diabetes and of hypertension

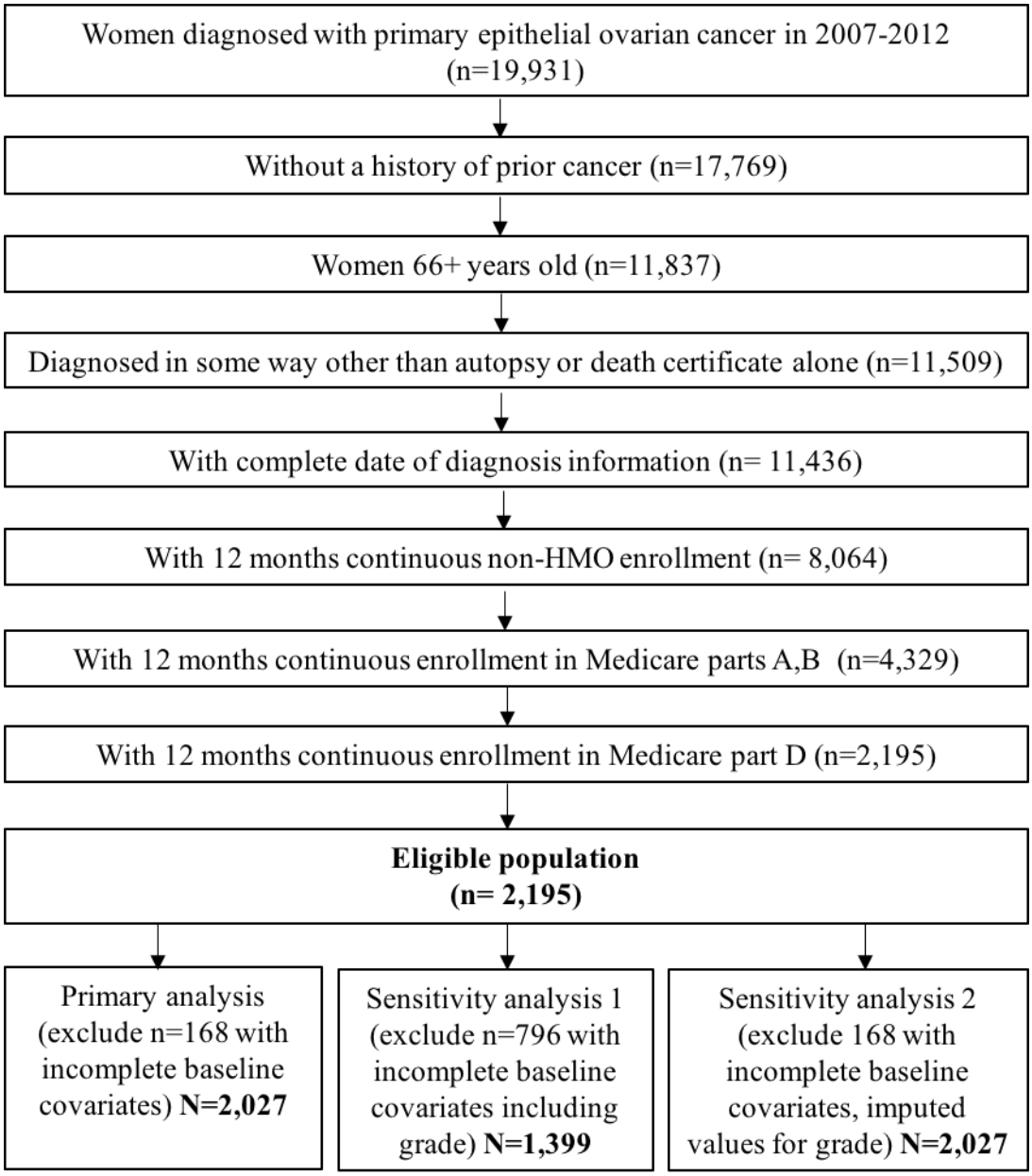
Abbreviations: TD, thiazide diuretics; ACEI, angiotensin converting enzyme inhibitors; BB, beta blockers; NSBB, non-selective beta blockers; SBB, selective beta blockers.

Table 2.4: Including grade in adjustments				
	Complete case analysis (n=1,399)		Multiple imputation for grade (n=2,027)	
	Hazard Ratio (95% Confidence Interval)		Hazard Ratio (95% Confidence Interval)	
	Unadjusted	Adjusted[a]	Unadjusted	Adjusted[a]
No AH	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
ACEIs	0.77 (0.62-0.97)	0.70 (0.54-0.89)	0.83 (0.70-0.99)	0.76 (0.63-0.93)
CCBs	0.91 (0.62-1.33)	0.87 (0.58-1.32)	0.99 (0.75-1.37)	0.94 (0.69-1.28)
TDs	0.80 (0.64-0.99)	0.73 (0.57-0.94)	0.87 (0.74-1.04)	0.82 (0.68-0.99)
BBs	0.95 (0.75-1.19)	0.85 (0.65-1.10)	0.96 (0.79-1.15)	0.89 (0.72-1.10)
NSBB	0.74 (0.51-1.07)	0.59 (0.40-0.88)	0.70 (0.51-0.94)	0.59 (0.43-0.82)
SBB	1.02 (0.79-1.33)	0.95 (0.71-1.28)	1.07 (0.87-1.32)	1.04 (0.82-1.30)

[a]Adjusted for: age at diagnosis, year of diagnosis, race/ethnicity, marital status, census tract poverty level, location of residence, tumor histology, stage at diagnosis, grade at diagnosis, receipt of surgery, receipt of chemotherapy, Charlson comorbidity score, and diagnosis of diabetes and of hypertension

Abbreviations: TD, thiazide diuretics; ACEI, angiotensin converting enzyme inhibitors; BB, beta blockers; NSBB, non-selective beta blockers; SBB, selective beta blockers.

Figure 2.1: Flow chart of selection of population for inclusion in ovarian cancer and antihypertensive use 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 at some point during the year following diagnosis. Additional numbers provided for sensitivity analyses including grade in adjustments.



SUPPLEMENTAL MATERIAL

Supplemental Table 1: Risk of cancer-specific mortality associated with statin use, comparing findings from traditional cox model to marginal structural model

				Hazard Ratio (95% Confidence Interval)		
	Follow-up time (person-years)	Number of ovarian cancer deaths	Incidence (Per 1,000 person-years)	Crude	Marginal Structural Model Estimate[a]	Traditional Cox Model[b]
All statins	1,543	153	99.2	0.78 (0.66-0.92)	0.74 (0.61-0.91)	0.79 (0.66-0.95)
Hydrophilic statin	232	21	90.5	0.62 (0.41-0.94)	0.62 (0.42-0.93)	0.77 (0.50, 1.19)
Lipophilic statin	1,325	134	101.1	0.80 (0.68-0.96)	0.79 (0.65-0.95)	0.82 (0.68, 0.99)

[a] Model incorporating inverse probability of treatment and censoring weighting.
[b] Adjusted for age at diagnosis, year of diagnosis, race/ethnicity, marital status, census tract poverty level, location of residence, tumor histology, stage at diagnosis, grade at diagnosis, receipt of surgery, receipt of chemotherapy, Charlson comorbidity score, diabetes, hyperlipidemia and hypertension.

Supplemental Table 2: Risk of cancer-specific mortality associated with statin use in sensitivity analyses		
	Hazard Ratio (95% Confidence Interval)	
	Crude	Adjusted
No statin use (reference)	1.00	1.00
Statin use during first 6 months after diagnosis (N=2,593)[a]	0.82 (0.73-0.96)	0.83 (0.71-0.98)[c]
Statin use adjusted for prevalent use (N=1,883)[b]	0.76 (0.63-0.92)	0.75 (0.59-0.95)[d]

[a]The 6-month sensitivity analysis included more women (2,593) than the primary analysis (2,195). More women were available for this sensitivity analysis who survived 6+ months following diagnosis and were able to contribute to follow-up time beginning 6-months after ovarian cancer diagnosis.

[b]Prior statin use was assessed among the 1,883 women diagnosed in 2008+ who were eligible for this study and who contributed data to the sensitivity analysis adjusting for statin use prior to diagnosis.

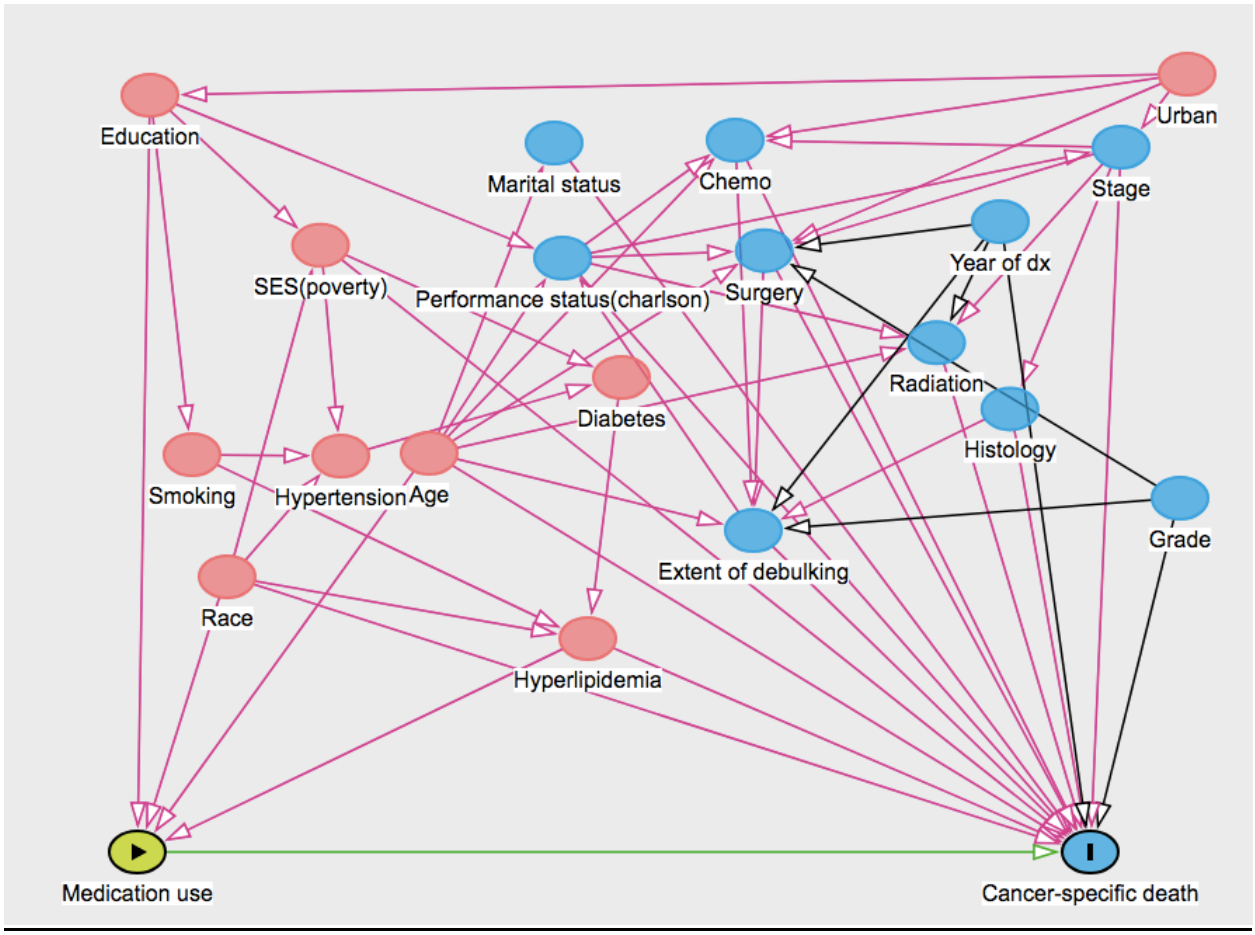
[c]Adjusted for: age at diagnosis, year of diagnosis, race/ethnicity, marital status, census tract poverty level, location of residence, tumor histology, stage at diagnosis, grade at diagnosis, receipt of surgery, receipt of chemotherapy, Charlson comorbidity score, diabetes, hyperlipidemia and hypertension.

[d]Adjusted for: prevalent statin use, age at diagnosis, year of diagnosis, race/ethnicity, marital status, census tract poverty level, location of residence, tumor histology, stage at diagnosis, grade at diagnosis, receipt of surgery, receipt of chemotherapy, Charlson comorbidity score, diabetes, hyperlipidemia and hypertension.

Supplemental Table 3: Risk of cancer-specific mortality associated with glaucoma medication use (N=2,195)					
				Hazard Ratio (95% Confidence Interval)	
	Follow-up time (person-years)	Number of ovarian cancer deaths	Incidence (Per 1,000 person-years)	Crude	Adjusted[a]
Glaucoma medication use (ref. non-glaucoma medication users	850	92	108.2	1.08 (0.83-1.40)	1.15 (0.86-1.53)
Statin use (ref. non-statin users)	1,543	153	99.2	0.78 (0.66-0.92)	0.79 (0.66- 0.95)

[a]Adjusted for: age at diagnosis, year of diagnosis, race/ethnicity, marital status, census tract poverty level, location of residence, tumor histology, stage at diagnosis, grade at diagnosis, receipt of surgery, receipt of chemotherapy, Charlson comorbidity score, diabetes, hyperlipidemia and hypertension.

Supplemental Figure 1: Directed acyclic graph showing relationships between key covariates and medication use and cancer-specific death. Included in this figure are confounders included in analyses of either a) statin-use and cancer-specific mortality or b) antihypertensive-use and cancer-specific use or both analyses. Also shown are variables including education, smoking and extent of debulking, which are important confounders which were unable to be addressed in either analysis due to the absence of this variable or a close proxy in the SEER-Medicare data.



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