Gynecologic Oncology 154 (2019) 426–431

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Post-diagnosis use of antihypertensive medications and the risk of death from ovarian cancer

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HIGHLIGHTS

- Prognosis of advanced ovarian cancer is poor.
- Interest lies in identifying medications with anti-cancer properties.
- This study investigates antihypertensive use, a commonly used medication, and ovarian cancer-specific survival.
- Non-selective beta-blockers were found to be associated with a reduction in case-fatality.

ARTICLE INFO

Article history:
Received 29 March 2019
Received in revised form 23 May 2019
Accepted 29 May 2019
Available online 7 June 2019

Keywords:
Ovarian cancer
Epidemiology
Antihypertensive medication
Cohort study

ABSTRACT

Objective. To examine associations between post-diagnosis use of antihypertensive (AH) medications including thiazide diuretics (TDs), angiotensin converting enzyme inhibitors (ACEIs), beta blockers (BBs) [both non-selective (NSBBs) and selective (SBBs)] and calcium channel blockers (CCBs) and ovarian cancer-specific survival.

Methods. This cohort study used SEER-Medicare data on 2195 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 a NSBB (aHR 0.60, 95%CI 0.43–0.83), but no such association was seen in women who took a SBB or CCB.

Conclusion. We 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.

1. Introduction

The majority of women who are diagnosed with ovarian cancer die as a result of this disease [1,2]. While prior studies suggest that use of some antihypertensive (AH) medications is associated with an improved likelihood of survival from some forms of cancer [3], 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 [1,4]. Use of ACEIs may also alter angiogenesis and other mitogenic actions through changes in vascular endothelial growth factor expression [5]. Administration of CCBs can target energy metabolism and interrupt mitochondrial respiration in cancer cells, a crucial factor in tumor progression [6,7]. Pre-

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https://doi.org/10.1016/j.ygyno.2019.05.030
0090-8258/

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 [8–10]. The use of beta blockers (BBs), antagonists of norepinephrine and epinephrine, may affect progression of cancer by impeding the harmful effects of these catecholamines [11], including increased tumor invasive potential [12], oxidative stress [13], and chemoresistance of tumor cells [14]. BBs can block signaling in cancer cells that otherwise could directly affect tumor cell survival, motility, and invasion by way of Src activation [15]. 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 [16]. Research has shown that tumor growth is mediated predominantly by beta2 or beta 3 adrenergic receptors, which NSBBs would be able to influence to a greater degree [17].

Because the prognosis of advanced ovarian cancer is relatively poor, coupled with 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.

2. Methods

2.1. 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 [19], which enumerate incident cancer cases from approximately 28% of the US population [20]. 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. 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. We excluded potential cases whose EOC diagnosis came solely from an autopsy report or death certificate, and 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 (Fig. 1). This resulted in an eligible cohort of 2195 women.

The study protocol was approved by the Fred Hutchinson Cancer Research Center's Institutional Review Board (IRB File #8607).

2.2. 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 [21], we applied a one year fixed baseline period 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 [22]. Also, patients may switch Medicare plans, which may result in their drug use no longer being covered or available in Medicare data files [23]. By restricting our analysis to women who were enrolled in part D for the entirety of the first year following their diagnosis of ovarian cancer, we were able to maximize completeness of ascertainment of AH use [24].

2.3. 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.

2.4. 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% [25] 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 [26,27]. 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 [28]. 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).

We used Medicare data to identify chemotherapy use, defined as any chemotherapy related claims within 180 days after cancer diagnosis. The Charlson comorbidity index [29] 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 [30] were used to determine which women had been diagnosed with hypertension. The chronic condition variables are developed from algorithms in Medicare data [31–33]. 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%) [31].

2.5. 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.

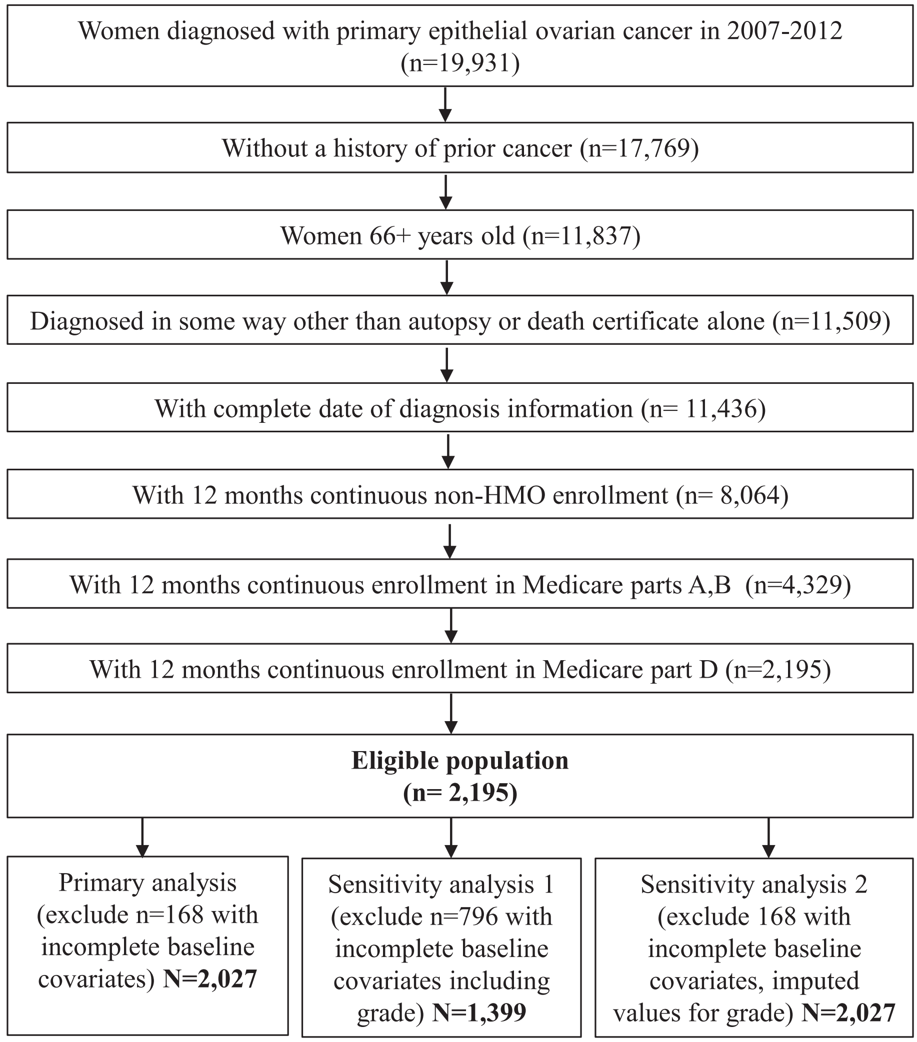

Fig. 1. Flow chart of selection of population for inclusion in study. Eligible women were those who had a primary diagnosis of epithelial ovarian cancer during the study years. Exclusions were made for those with a prior cancer, those <66 years of age, those diagnosed by autopsy or death alone, those 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 at some point during the year following diagnosis.

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 analysis because a) tumor grade was missing for a sizeable portion of the women in our 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, we undertook two sensitivity analyses 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, we applied multiple imputation with chained equations (MICE) [34] to generate 10 sets of complete data with imputed values for missing grade [35]. In order to avoid bias, the imputation model included all variables used in the primary model [36]. We assumed 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.

3. Results

This study included a total of 2195 women whose median age was 74 years at the time of diagnosis (interquartile range [IQR] 70–80) and of whom 1302 (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 1.

Table 1
Baseline characteristics of women diagnosed with ovarian cancer during 2007–2012 based on antihypertensive use during follow-up ($N = 2195$).[a]

Antihypertensive use[b]	Non-AH users ($n = 893$)		ACEI users[c] ($n = 690$)		BB users[c] ($n = 521$)		CCB users[c] ($n = 154$)		TD users[c] ($n = 718$)	
	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%

Abbreviations: ACEI, angiotensin converting enzyme inhibitors; BB, beta blockers; CCB, calcium channel blockers; TD, thiazide diuretics.
[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.

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 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). Restriction of the analysis to women who used just one AH gave similar results (Table 3).

Table 2
Risk of ovarian cancer mortality among users of four major classes of antihypertensive medications ($n = 2027$) with complete covariate information).

	Follow-up time (person-years)	Number of ovarian cancer deaths	Rate (per 100 person-years)	Hazard ratio (95% confidence interval)	
				Unadjusted	Adjusted[a]
No AH	1730	307	17.7	1.00 (ref)	1.00 (ref)
ACEI	1396	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	1470	226	15.4	0.87 (0.74–1.04)	0.82 (0.68–0.99)
BB	1025	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)

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.

[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.

Results from sensitivity analyses including adjustment for grade produced HRs similar to those from the primary analysis (Supplemental Table 1).

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, we 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 we adjusted for the presence of hypertension, we did not have information on severity of hypertension. Third, 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. In the present study, we sought to prevent immortal time bias [21,37] 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 [38], prior work has failed to show an association between hypertension and ovarian cancer [39], and adjustment for this characteristic had no material bearing on any of our results. Therefore, the likelihood of confounding by indication having a large impact on our 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 our 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 [42,43] to assess the efficacy of concurrent beta-blocker administration with chemotherapy.

In conclusion, in our study we observed a reduced case-fatality 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

Table 3
Risk of ovarian cancer mortality among monotherapy users of antihypertensive medications.

	Follow-up time (person-years)	Number of ovarian cancer deaths	Rate (per 100 person-years)	Hazard ratio (95% Confidence Interval)	
				Unadjusted	Adjusted[a]
No AH	1730	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)

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

[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.

awaiting the results of further research in which there is a greater ability to distinguish cause from confounding.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2019.05.030.

Declaration of Competing Interest

The authors certify that they have no conflicts of interest to disclose.

Acknowledgments

This study 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.

We acknowledge the assistance of Dr. Stephen M. Schwartz, Principal Investigator of the Fred Hutchinson Cancer Research Center's Cancer Surveillance System, who was instrumental in obtaining the data for this project.

Author contributions

Barbara N. Harding contributed to conception and design, development of study methodology, data acquisition, analysis and interpretation of data, and the writing and reviewing of the manuscript.

Joseph A. Delaney contributed to the development of study methodology, analysis and interpretation of data, and writing and reviewing of the manuscript.

Renata R. Urban contributed to development of study methodology and writing and reviewing of the manuscript.

Noel S. Weiss contributed to conception and design, development of study methodology, analysis and interpretation of data, writing and reviewing of the manuscript, and study supervision.

All authors have approved the final article.

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