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Use of antihypertensive medications and risk of adverse breast cancer outcomes in a SEER-Medicare population

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Abstract

Background—It is unclear if use of common antihypertensive medications influences the risk of adverse breast cancer outcomes.

Methods—Using the linked Surveillance, Epidemiology and End-Results (SEER)-Medicare database, we identified 14,766 women between ages 66 and 80 years diagnosed with incident stage I/II breast cancer between 2007–2011. Medicare Part D data were obtained to characterize women's post-cancer use of various antihypertensive medications. Outcomes included a second breast cancer event (SBCE, a composite outcome defined as the first of a recurrence or a second contralateral primary breast cancer), breast cancer recurrence, and breast-cancer specific mortality. Time-varying Cox proportional hazard models were used to estimate hazard ratios (HRs) and their associated 95% confidence intervals (CIs).

Results—There were 791 SBCEs, 627 breast cancer recurrences, and 237 breast cancer deaths identified over a median follow-up of 3 years. Use of diuretics (n=8,517) after breast cancer diagnosis was associated with 29% (95% CI: 1.10–1.51), 36% (95% CI: 1.14–1.63) and 51% (95% CI: 1.11–2.04) higher risks of a SBCE, recurrence, and breast cancer death, respectively. Compared to nonusers, β-blockers users (n=7,145) had a 41% (95% CI: 1.07–1.84) higher risk of breast cancer death. Use of angiotensin II receptor blockers, calcium channel blockers and angiotensin-converting enzyme inhibitors were not associated with risks of breast cancer outcomes.

Conclusions—Use of diuretics and β-blockers may be associated with increased risk of breast cancer outcomes among older women.

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Impact—Most antihypertensive medications are safe with respect to breast cancer outcomes, but more research is needed for diuretics and β-blockers.

Introduction

Hypertension is the most prevalent chronic condition among older Americans, affecting 61% of women enrolled in Medicare (1). As a result, antihypertensive drugs are the most commonly prescribed class of medications in the U.S (2).

Angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), β-blockers (BB), calcium channel blockers (CCBs) and diuretics are the most commonly used classes of medications to treat hypertension. Certain types of antihypertensive medications, namely thiazides (3,4) and beta-blockers (5), have been hypothesized to influence cancer cell growth through different mechanisms, providing rationale for their possible associations with breast cancer. A number of epidemiological studies have also been conducted to assess their possible influence on breast cancer incidence and outcomes. With respect to incident breast cancer, the results of prior studies are mixed, with some (6–11), but not all (12–16), observing use of CCBs and diuretics to be associated with an increase in risk. Neither of the two studies of these two classes of medications observed an association with breast cancer outcomes (17,18). Use of BBs was associated with 48–81% lower risks of breast cancer specific mortality (19–22) and 48–57% lower risks of breast cancer recurrence/distant metastases (19,21). However these studies were all limited by small sample sizes (number of BB users: n=43–102) and their findings have not been confirmed in more recent studies with larger sample sizes (17,23,24). ACEI use has been associated with 56–66% higher risks of recurrence (24) and second primary breast cancer (17) in some prior studies, but not associated with risks of either breast cancer recurrence (17,25) or breast cancer death in several other studies (24,26,27).

In this study, we assessed associations between use of different classes of antihypertensive medications after breast cancer diagnosis and risk of a second breast cancer events (SBCE, a recurrence or a second primary breast cancer), breast cancer recurrence, and breast cancer mortality using the linked Surveillance, Epidemiology and End-Results (SEER)-Medicare database.

Methods and materials

Population

A retrospective cohort was created using persons in the linked SEER-Medicare database, which contains claims data as well as cancer registry data for Medicare beneficiaries diagnosed with cancer living in the catchment areas of the 18 SEER cancer registries located throughout the U.S (28). Medicare provides hospital insurance (Part A), medical insurance (Part B), and prescription drug coverage (Part D, initiated in 2006) for individuals aged 65 or older in the U.S. We used the data from SEER-Medicare linked database from January 1, 2007 (the beginning year of Part D data) to December 31, 2012 (the latest year at the time of data request). The SEER data were used to identify breast cancer cases from 2007–2011 (2012 cases were excluded, so all included cases had at least 1 year of follow-up) with

information on patients' demographic characteristics, cancer stage, tumor hormone receptor status, diagnosis date, surgery and radiation treatment received within 4 months of diagnosis, vital status and cause of death. Medicare Parts A, B and D claims data from January 1, 2007 to December 31, 2012 were retrieved for breast cancer patients identified in SEER, including Medicare enrollment information as well as dates and types of medical services women received during this time period. The study protocol was approved by the Fred Hutchinson Cancer Research Center's institutional review board.

A total of 16,397 women diagnosed with incident primary stage I/II breast cancer between the ages 66 to 80 years from 2007 to 2011, and enrolled in Medicare Parts A/B/D at the time of diagnosis with no concurrent enrollment in a Medicare HMO were identified. (See Supplement Figure 1 for our study population inclusion/exclusion flow chart. Comparisons between included and excluded women on select characteristics are presented in Supplement Table 1). Since the algorithm used to identify SBCEs and recurrence in this study uses information on breast cancer directed surgical treatment, women who did not undergo surgery or with missing surgical data were excluded (n=426). All subjects were required to be cancer-free for at least 180 days post incident cancer diagnosis, and thus those who had a SEER record of a second primary breast cancer (n=577) or who died (n=80) within 180 days of the first breast cancer were excluded. Finally, 548 women without at least 12 months of continuous enrollment in Medicare Parts A, B, and D (unless died) were excluded. The final sample hence included 14,766 women.

Exposure

Our primary exposures of interest, post-cancer use of ACEIs, ARBs, BBs, CCBs and diuretics, were ascertained through Medicare Part D data. Ever use of each of these medications after breast cancer was compared to no use in the primary analyses. A user of a given medication was defined at the time of their first filled prescription of that drug after breast cancer diagnosis. A user was not allowed to go back to the unexposed group once she had a dispensing of a given drug. Common subclasses of some of these medications were also examined, including dihydropridines CCBs vs. non-dihydropridines CCBs, β1 vs. β1/β2 blockers, and loop vs. thiazide vs. other diuretics. In subclass analyses, users of a particular subclass were compared to women who never used that entire class of antihypertensive medications after cancer diagnosis.

To mitigate confounding by indication, we explored associations between each medication exposure and adverse breast cancer outcomes among women with a diagnosis of hypertension and were only using one type of antihypertensive drug (monotherapy users) and among hypertensive women who were using multiple classes of drugs (polytherapy users). These monotherapy/polytherapy-user sub-cohorts were created using a time-varying approach. Women became monotherapy users when they first filled a prescription of an antihypertensive medication after breast cancer and their follow-up time was censored at the time they filled a prescription of another class of antihypertensive medications. Women were defined as polytherapy users when they first filled a prescription of a second class of antihypertensive medications. Analyses restricted to monotherapy users compared use of

other antihypertensive medications against use of diuretics, while ever use of one given medication was compared to no use of that medication in analyses among polytherapy users.

Outcomes

Primary outcomes of interest were a SBCE (defined as the first of a breast cancer recurrence or a second contralateral primary breast cancer), recurrence, and breast cancer related mortality. We used a previously validated algorithm to identify SBCEs and recurrence. The development of the algorithm with detailed diagnosis and procedure code lists and its validation process against medical chart abstraction have been published elsewhere (29,30). Briefly, the algorithm uses procedures codes, diagnoses codes, frequency and timing of these events that may be indicative of a SBCE in conjunction with SEER cancer records to identify a SBCE (sensitivity=89%, specificity=99%) and breast cancer recurrence (sensitivity =69%, specificity=99%). Breast cancer death was ascertained through SEER which routinely abstracts cause of death from death certificates for all patients. Assessment of all outcomes started 180 days post cancer diagnosis. To assess the potential bias due to misclassification of cause of death, we conducted a sensitivity analysis in which deaths were attributed to breast cancer only if they were preceded by a SBCE (n=140).

Statistical analyses

Associations between use of various types of antihypertensive medications after breast cancer and risk of each adverse breast cancer outcome were estimated by cause-specific time-varying Cox proportional hazard models using SAS statistical software version 9.3 (SAS Institute Inc, Cary, NC). Medication exposures after breast cancer were modeled in a time-varying fashion such that time at risk before one becomes a user contributed to the nonuser category. We modeled time from the incident breast cancer to adverse breast cancer outcomes with a delayed entry of 180 days post diagnosis. Women were followed until the first of SBCE/recurrence, disenrollment in any of Medicare Part A, B or D, end of the study, or death. Stratified analyses were conducted based on timing of medication initiation in relation to cancer diagnosis among a subset of 11,494 women (77.8%) who were enrolled in Medicare Parts A/B/D for ≥12 months prior to their breast cancer diagnosis. Women were then categorized into those who used the drug only before cancer diagnosis (dropped from further analysis as it was not the focus of the study), those who used medications of interest both in the year prior to cancer diagnosis and after cancer diagnosis (continuous users), those who began using medications after cancer diagnosis and those who never used medications of interest (nonusers). Separate time-varying Cox models were used to compare each of the categories to nonusers.

Analyses were adjusted for age at diagnosis, year of diagnosis, cancer stage, estrogen receptor (ER) /progesterone receptor (PR) status, receipt of complete first course treatment (whether or not a woman received either a total mastectomy or a breast conserving surgery with radiation), receipt of chemotherapy, use of adjuvant hormone therapy, baseline diabetes, baseline hypertension at breast cancer diagnosis and use of other classes of antihypertensive medications. Categorizations of these covariates are shown in Table 1. Women were considered as having received chemotherapy if there was any chemotherapy related claims within 180 days after cancer diagnosis. Use of adjuvant hormone therapy was defined at the

first dispensing of a hormonal therapy drug and was modeled as a unidirectional, time-varying covariate as other medications of interest. Women with two diagnosis codes of hypertension or diabetes within 180 days after breast cancer diagnosis were classified as having the respective condition at baseline. Other potential confounders evaluated were race/ethnicity and marital status, which minimally changed the results and thus were not included in our final models. We assessed potential effect modification by breast cancer ER status using a Wald test, but none of the interaction terms were statistically significant at $p<0.05$, and thus are not shown.

Results

During a median follow-up of 3 years, 791 out of 14,766 women experienced a SBCE, 627 had a breast cancer recurrence, and 237 died from breast cancer (outcomes were not mutually exclusive). Women with a SBCE, recurrence, or breast cancer death were in general less likely to be non-Hispanic white, to have ER+/PR+ tumors, and to be on adjuvant hormonal therapy among those with ER+ breast cancers, and more likely to be older, to be diagnosed with stage II disease, to have had chemo therapy, and to have diabetes or hypertension compared to women in general (Table 1).

Use of diuretics after breast cancer (n=8,517) was associated with 29%, 36% and 51% higher risks of SBCE (95% CI: 1.10–1.51), recurrence (95% CI: 1.14–1.63), and breast cancer death (95% CI: 1.11–2.04), respectively (Table 2). Ever use of BBs (n=7,145) after cancer diagnosis was associated with 41% (95% CI: 1.07–1.84) higher risk of breast cancer death, but not an increased risk of SBCE or recurrence. Use of ARBs, ACEIs and CCBs after breast cancer was not associated with risk of adverse breast cancer outcomes. Results regarding breast cancer death changed minimally when breast cancer deaths restricted to the 140 cases who had a SBCE prior to death.

Similar associations were observed across subclasses of medications (Figure 1). Ever use of loop, thiazide or other types of diuretics after breast cancer were similarly associated with elevated risks of SBCE and recurrence. However, only use of loop diuretics was associated with a 2.53-fold (95%CI: 1.81–3.53) higher risk of breast cancer death. None of the subtypes of CCBs or BBs was significantly associated with risk of adverse breast cancer outcomes.

When stratified by timing of initiation, no consistent pattern was observed (Figure 2). Women who began using BBs after cancer diagnosis, but not those who used them before and after diagnosis, had a 2.33-fold higher risk of breast cancer death (95% CI: 1.34–4.03). There was no corresponding excess risk of a SBCE or recurrence. Those who continuously used ARBs had a 1.28-fold (95% CI: 1.02–1.61) higher risk of a SBCE, but not of any other outcomes. Continuous users of diuretics had a 1.33–1.52-fold higher risk of a SBCE/breast cancer recurrence while only those who began using diuretics after cancer had an elevated risk of breast cancer death.

Among 2,494 hypertensive women who were using only one class of antihypertensive drugs, there were no significant differences in risks of SBCEs and recurrences comparing users of

other antihypertensive medications with diuretic users (Table 3). Results on breast cancer deaths were not presented for monotherapy users due to small numbers of cases. Results of analysis among 7,721 polytherapy users were very similar to the primary analysis where use of diuretics was associated with 39% higher risks of SBCE (95% CI: 1.07–1.80) and use of BBs was associated with 1.26-fold and 1.71-fold (95%CI: 1.18–2.47) higher risk of recurrence and breast cancer death, respectively.

Discussion

In this large population-based cohort of older women with early stage breast cancer, we observed that certain types of antihypertensive medications taken after breast cancer diagnosis were associated with risks of adverse breast cancer outcomes. Use of diuretics after cancer diagnosis, including both loop and thiazide diuretics, were associated with a higher risk of SBCE, recurrence, and breast cancer death. Although we adjusted for baseline hypertension and observed similar elevations in risks of adverse breast cancer outcomes among diuretics users in primary analyses and in sensitivity analyses restricted to hypertensive women, the possibility of confounding by indication cannot be completely ruled out. One alternative explanation is that diuretic users might be less healthy and appeared to have higher risks of adverse outcomes either because they did not tolerate breast cancer treatment well (e.g., less intensive chemotherapy) or their SBCEs or recurrence were more completely captured using claims data-based algorithm due to more frequent medical visits. Only one prior study has assessed associations between use of diuretics (number of diuretic users=1,770) and risk of SBCEs and recurrence, and found no associations (17). With respect to incident breast cancer risk, while a 40–70% higher risk of breast cancer was reported for diuretic users compared to nonusers in two studies (6,9), the majority of prior studies are null (8,10,12,14,15). Diuretics have been long used to manage hypertension and act on blood pressure via increasing urinary sodium and water losses. Certain subtypes of diuretics, namely thiazides, may be associated with increased insulin resistance (3,4), and insulin resistance is an established risk factor for breast cancer (31), providing a some potential mechanism for the relationship observed here for this specific subtype, although it cannot explain the elevated risks observed across subtypes of diuretics in our study. While this is the largest study of the association between diuretics and adverse breast cancer outcomes, we believe that our results require confirmation and should be interpreted with caution.

BBs compete with norepinephrine and epinephrine for available beta-adrenoceptors and may be involved in multiple cellular processes relevant to cancer through stress response pathways (5). Contrary to some smaller prior studies either reporting favorable results for BBs (19–22) or no associations (24), our study observed a higher risk of breast cancer death associated with use of BBs after breast cancer diagnosis but not SBCEs or recurrence. The associations were similar across β1 and β1/β2 blockers. Our results are based on a much larger sample size than prior studies (n=7,145 for β-blocker users) and are consistent with two recent larger studies in Denmark (n=3,660 for β-blocker users) and in the U.S. (n=1,501 for β-blocker users) where a 29–30% higher risk of breast cancer recurrence was noted for users of β-blockers compared to nonusers (17,25). Of note, together these two studies and ours did not observe any clear patterns with respect to timing, duration, or dose, and no

corresponding excess risk was observed for SBCEs or among women using β-blockers alone.

We observed post cancer use of ARBs were associated with higher risks of SBCEs among women who have also used the drug before cancer diagnosis, but this could be a chance finding given no elevated risk of adverse breast cancer outcomes was observed in all other analyses examining ARBs. Our findings that use of ARBs, CCBs and ACEIs after breast cancer generally were not associated with risks of adverse breast cancer outcomes were consistent with those obtained in most prior studies,(17,24–27) although two studies observed 56–66% higher risk of recurrence (n=137 for ACEI users) and second contralateral breast cancer (n=1,515 for ACEI users) associated with use of ACEIs.(17,24) However, of note, no clear trend was observed in the only prior study that examined duration of use of ACEI (17).

There are several important limitations that should be considered when interpreting results from this study. We did not have data on a number of established risk factors for breast cancer progression that are also related to use of antihypertensive medications. Overweight/obese women are known to have a higher risk of both poor breast cancer outcomes (32,33) and hypertension (34), but obesity status was not available through claims or registry data and thus was not adjusted for in our study. Given the potential positive association between obesity and both breast cancer outcomes and use of antihypertensive medications, our observed risk estimates may be falsely exaggerated. The identification of some of our outcomes, namely SBCE and recurrence, rely on a claims-data based algorithm which may be subject to misclassification in outcome status. This algorithm has been previously validated against medical records review data and showed good performance when this algorithm was recently evaluated in a new set of breast cancer patients (35). Although we did sensitivity analyses restricted to breast cancer death preceded by a SBCE and observed similar results, misclassification of cause of death on breast cancer is possible and may be the reason that we observed the stronger associations with breast cancer mortality compared to other outcomes. If women with hypertension and treated with these medications were sicker and more likely to die, more deaths would be misclassified as breast cancer death among users than nonusers, result in spuriously higher risks of breast cancer death associated with use of these medications in the absence of true association. This may also partly explain the association with breast cancer death only seen among new users of BBs and diuretics but not established users as initiation of these medications may be a marker of worsening cardiovascular health. In light of an aging population where competing risks due to death may interfere with estimating true risks for cancer-specific outcomes, we used cause-specific hazard models to address this issue (36). Of note, only 5.8% of the entire cohort died of all causes during the study period, limiting its impact on the observed results. Also, some of the positive findings could be due to chance given multiple comparisons. We did not have power to detect differences by subtypes within these medication classes or certain combinations of medications. Last but not least, the follow-up time in our cohort is also relatively short, limiting our ability to examine the impact of long-term use of these medications or the trend in the association by duration of use.

Our results provide some reassurance that majority of the commonly prescribed antihypertensive medications are safe with respect to breast cancer outcomes for older breast cancer survivors. Further efforts are needed to clarify and confirm the positive associations between use of diuretics and β-blockers and risks of adverse breast cancer outcomes observed in this study. Given the increasing number of available antihypertensive medications, characterization of potential relationships between use of these medications and adverse breast cancer outcomes may help clinicians and women with breast cancer weigh the benefits and risks of different treatment options when managing hypertension.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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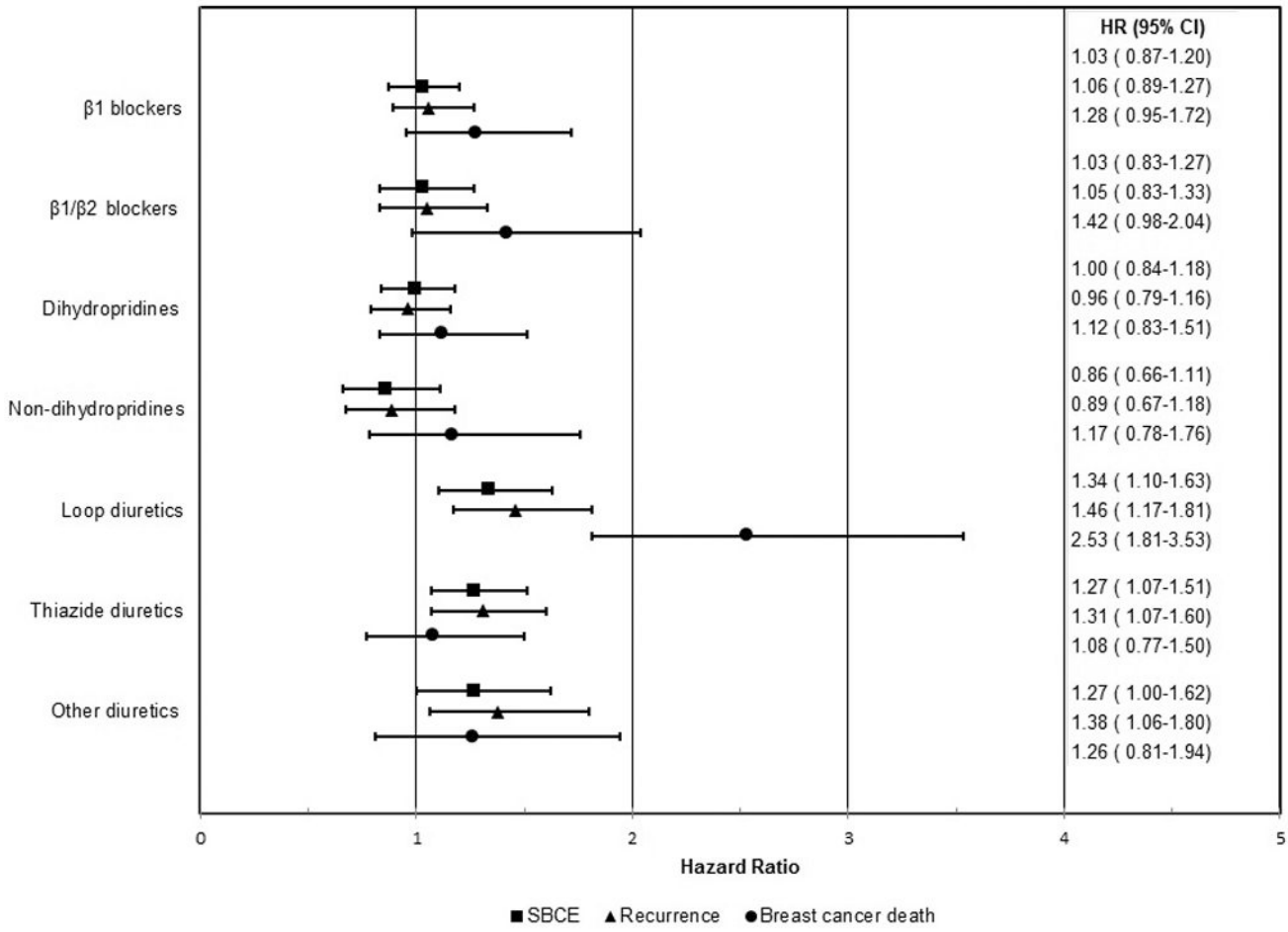

Figure 1. Risk of adverse breast cancer outcomes by different antihypertensive subclasses

Users of each subclass of a given antihypertensive medication were compared to nonusers of the entire class in separate time-varying Cox models. Hazard ratio (HR) adjusted for age at diagnosis, year of diagnosis, AJCC stage, ER/PR status, receipt of complete first course treatment, receipt of any chemotherapy, use of adjuvant hormonal therapy (time-varying), hypertension at breast cancer diagnosis, diabetes at breast cancer diagnosis and use of other classes of antihypertensive medications.

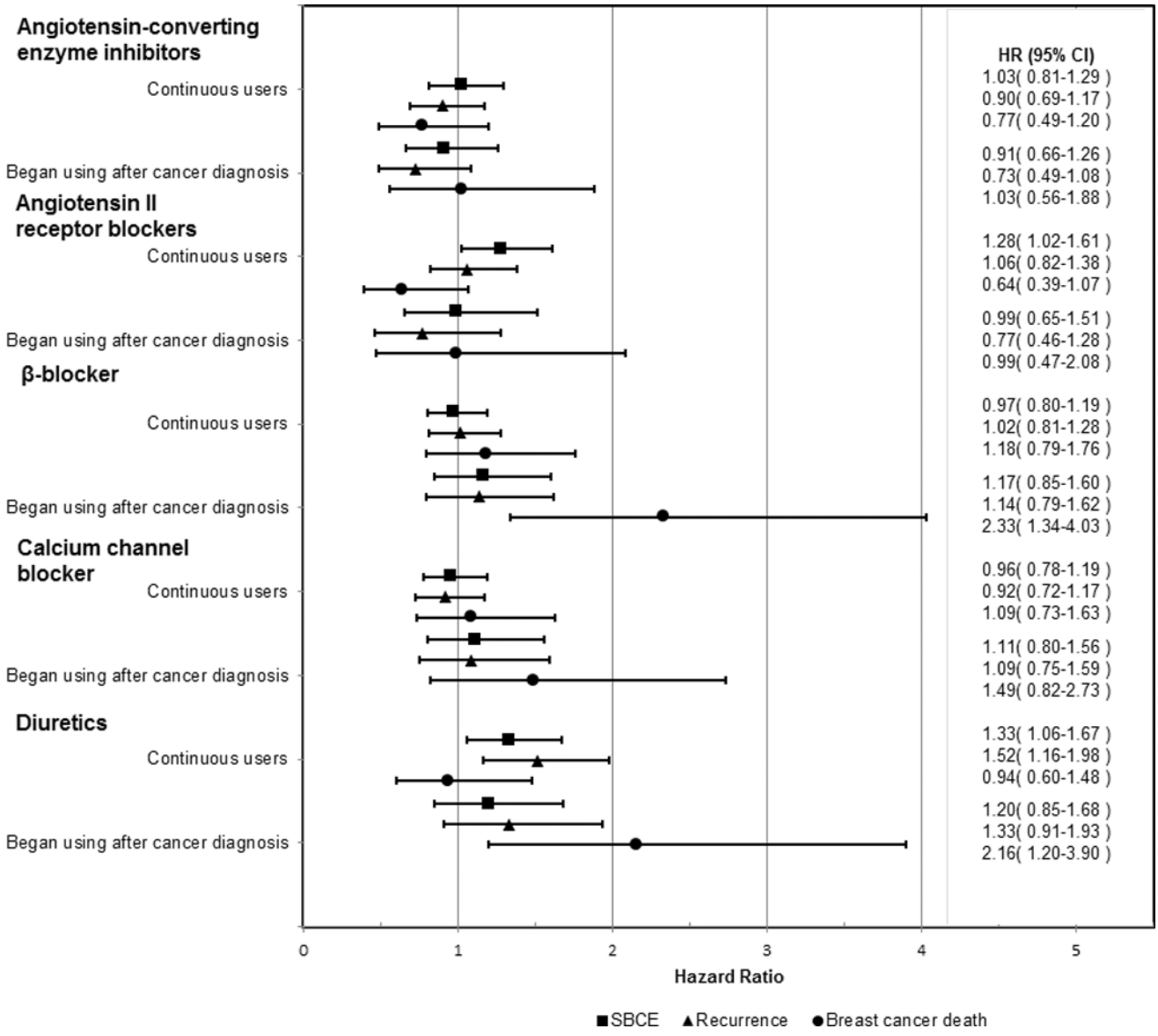

Figure 2. Risk of adverse breast cancer outcomes and use of antihypertensive medications stratified by time of initiation

ACEI: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin II receptor blocker; BB: β-blocker; CCB: calcium channel blocker.

Continuous users and those who began using the medication after cancer diagnosis were compared to never users of that medication in separate Cox models. HRs were adjusted for age at diagnosis, year of diagnosis, AJCC stage, ER/PR status, receipt of complete first course of treatment, receipt of any chemotherapy, use of adjuvant hormonal therapy (time-varying) , diabetes at breast cancer diagnosis, hypertension at breast cancer diagnosis and use of other classes of antihypertensive medications.

Table 1

Characteristics of women diagnosed with stage I or II breast cancer during 2007–2011

	All (n=14766) n (%)	SBCE (n=791) n (%)	Recurrence (n=627) n (%)	Breast cancer death (n=237) n (%)
Demographic characteristics				
Year of diagnosis				
2007	2873 (19.5)	239 (30.2)	202 (32.2)	96 (40.5)
2008	2921 (19.8)	222 (28.1)	169 (27.0)	79 (33.3)
2009	2935 (19.9)	152 (19.2)	111 (17.7)	37 (15.6)
2010/2011*	6037 (40.8)	178 (22.5)	145 (23.1)	25 (10.5)
Age at diagnosis (years)				
66–70	5804 (39.3)	318 (40.2)	246 (39.2)	84 (35.4)
71–75	4937 (33.4)	251 (31.7)	196 (31.3)	67 (28.3)
76–80	4025 (27.3)	222 (28.1)	185 (29.5)	86 (36.3)
Race/Ethnicity				
Non-Hispanic white	11899 (81.0)	608 (77.2)	475 (76.0)	175 (73.8)
African American	1120 (7.6)	90 (11.4)	75 (12.0)	34 (14.3)
Hispanic white	887 (6.0)	36 (4.6)	33 (5.3)	16 (6.8)
Asian/Pacific Islander	729 (5.0)	48 (6.1)	37 (5.9)	*
American Indian/Native American	49 (0.3)	*	*	*
Unknown	82	*	*	*
Marital status				
Married	6895 (46.7)	358 (45.3)	288 (45.9)	91 (38.4)
Widowed	4043 (27.4)	216 (27.3)	172 (27.4)	84 (35.4)
Single/Unmarried	1368 (9.3)	70 (8.8)	55 (8.8)	24 (10.1)
Other	2460 (16.7)	147 (18.6)	112 (17.9)	38 (16.0)
Tumor characteristics of the first breast cancer				
Stage at diagnosis				
I	9410 (63.7)	294 (37.2)	203 (32.4)	54 (22.8)
II	5356 (36.3)	497 (62.8)	424 (67.6)	183 (77.2)
ER/PR status				
ER+/PR+	10413 (70.5)	394 (49.8)	303 (48.3)	75 (31.6)
ER−/PR−	1908 (12.9)	239 (30.2)	201 (32.1)	109 (46.0)
ER+/PR−	1707 (11.6)	122 (15.4)	95 (15.2)	33 (13.9)
ER−/PR+ or unknown	738 (5.0)	36 (4.6)	28 (4.5)	20 (8.4)
Treatment of the first breast cancer				
Receipt of complete first course treatment				
No	2550 (17.3)	151 (19.1)	97 (15.5)	46 (19.4)

	All (n=14766) n (%)	SBCE (n=791) n (%)	Recurrence (n=627) n (%)	Breast cancer death (n=237) n (%)
Yes	12216 (82.7)	640 (80.9)	530 (84.5)	191 (80.6)
Receipt of chemotherapy				
No	11512 (78.0)	477 (60.3)	357 (56.9)	138 (58.2)
Yes	3254 (22.0)	314 (39.7)	270 (43.1)	99 (41.8)
Ever use of hormone treatment since diagnosis (only among ER+ cases)				
No	1819 (15.0)	105 (20.3)	62 (15.6)	24 (22.2)
Yes	10301 (85.0)	411 (79.7)	336 (84.4)	84 (77.8)
Other co-morbidities at breast cancer diagnosis				
Diabetes				
No	11138 (75.4)	573 (72.4)	455 (72.6)	154 (65.0)
Yes	3628 (24.6)	218 (27.6)	172 (27.4)	83 (35.0)
Hypertension				
No	5357 (36.3)	234 (29.6)	184 (29.3)	59 (24.9)
Yes	9409 (63.7)	557 (70.4)	443 (70.7)	178 (75.1)

* Cannot be displayed or collapsed due to restrictions regarding the publication of small cells in the data use agreement.

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Table 2

Risk of adverse breast cancer outcomes by antihypertensive medication use among women diagnosed with stage I/II breast cancer, 2007–2011

	All women n=14766	SBCE n=791			Recurrence n=627			Breast cancer death n=237		
Medication use after breast cancer diagnosis	**n (%)[a]**	**n (%)[a]**	**HR[b]**	**95% CI**	**n (%)[a]**	**HR[b]**	**95% CI**	**n (%)[a]**	**HR[b]**	**95% CI**
ACEIs										
No	8866 (60.0)	437 (55.2)	Reference		352 (56.1)	Reference		131 (55.3)	Reference	
Yes	5900 (40.0)	354 (44.8)	1.00	0.86–1.17	275 (43.9)	0.95	0.79–1.13	106 (44.7)	1.02	0.76–1.35
ARBs										
No	10526 (71.3)	521 (65.9)	Reference		426 (67.9)	Reference		168 (70.9)	Reference	
Yes	4240 (28.7)	270 (34.1)	1.16	0.98–1.37	201 (32.1)	1.05	0.87–1.26	69 (29.1)	0.96	0.71–1.30
BBs										
No	7621 (51.6)	360 (45.5)	Reference		279 (44.5)	Reference		102 (43.0)	Reference	
Yes	7145 (48.4)	431 (54.5)	1.03	0.89–1.19	348 (55.5)	1.08	0.91–1.27	135 (57.0)	1.41	1.07–1.84
CCBs										
No	9193 (62.3)	467 (59.0)	Reference		372 (59.3)	Reference		134 (56.5)	Reference	
Yes	5573 (37.7)	324 (41.0)	0.94	0.81–1.11	255 (40.7)	0.92	0.78–1.10	103 (43.5)	1.21	0.92–1.58
Diuretics										
No	6249 (42.3)	256 (32.4)	Reference		193 (30.8)	Reference		74 (31.2)	Reference	
Yes	8517 (57.7)	535 (67.6)	1.29	1.10–1.51	434 (69.2)	1.36	1.14–1.63	163 (68.8)	1.51	1.11–2.04

ACEI: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin II receptor blocker; BB: β-blocker; CCB: calcium channel blocker.
SBCE: second breast cancer event.

[a]Counts and percentages reflect ever use after cancer diagnosis, which was defined as having at least one prescription of a given drug after cancer diagnosis while the Cox models defined ever use as a time-varying exposure such that at risk time before one becomes a user contributes to the nonuser category.

[b]HRs were adjusted for age at diagnosis, year of diagnosis, AJCC stage, ER/PR status, receipt of complete first course treatment (yes vs no), receipt of any chemotherapy (yes vs no), use of adjuvant hormone treatment (time-varying), hypertension at breast cancer diagnosis, diabetes at breast cancer diagnosis, and use of other classes of antihypertensive medications.

Table 3

Risks of adverse breast cancer outcomes among monotherapy users of antihypertensive medications

Medication use after breast cancer diagnosis	All women n=2494		SBCE n=84		Recurrence n=65		
	n (%)[a]	n (%)[a]	HR[b]	95% CI	n (%)[a]	HR[b]	95% CI
ACEIs	610 (24.5)	17 (20.2)	0.83	0.41–1.67	13 (20.0)	0.78	0.35–1.70
ARBs	310 (12.4)	15 (17.9)	1.31	0.64–2.70	11 (16.9)	1.22	0.54–2.75
BBs	642 (25.7)	17 (20.2)	0.89	0.45–1.77	12 (18.5)	0.73	0.33–1.57
CCBs	430 (17.2)	17 (20.2)	1.12	0.57–2.20	13 (20.0)	0.99	0.47–2.09
Diuretics	502 (20.1)	18 (21.4)	Reference		16 (24.6)	Reference	

ACEI: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin II receptor blocker; BB: β-blocker; CCB: calcium channel blocker.

[a]Counts and percentages reflect ever use after cancer diagnosis, which was defined as having at least one prescription of a given drug after the initial cancer diagnosis while the Cox models defined ever use as time-varying such that at risk time before one becomes a user contributes to the nonuser category.

[b]HR adjusted for age at diagnosis, year of diagnosis, AJCC stage, ER/PR status, receipt of complete first course treatment, receipt of any chemotherapy, use of adjuvant hormone treatment (time-varying), diabetes at breast cancer diagnosis.

[c]Monotherapy users were defined in a time-varying fashion such that women entered the cohort on the day they first filled a prescription of antihypertensive medications and left the cohort on the day they started another antihypertensive medication. Users of each class were compared to diuretics users in separate time-varying cox models.