Hypertension and diabetes treatments and risk of adverse outcomes among breast cancer patients

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Abstract

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Background:

Hypertension and diabetes are two common chronic conditions affecting 2.9 million breast cancer survivors in the U.S. Despite generally good safety profiles of widely used antihypertensive medications and diabetes treatments, few studies have examined their relationships with adverse breast cancer outcomes. In particular, metformin, a first line diabetes treatment, is hypothesized to lower the risk of incident breast cancer, but it is unclear whether metformin influences breast cancer progression. The purpose of this dissertation was to characterize how commonly prescribed classes of antihypertensive medications and diabetes treatments relate to adverse breast cancer outcomes.

Methods:

We conducted a retrospective cohort study of women between ages 66 and 80 years newly diagnosed with stage I or II breast cancer during 2007-2011. A total of 14,766 eligible women were identified in the linked Surveillance, Epidemiology and End-Results (SEER)-Medicare database. Medicare Part D Prescription Drug Event data were obtained to characterize women's use of commonly used antihypertensive medications (angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), β-blockers, calcium channel blockers and diuretics) and diabetes treatments (metformin, sulfonylureas, insulin therapy and other diabetes treatments) after their breast cancer diagnosis. Primary outcomes were any second breast cancer events (SBCEs, recurrence or second primary breast cancer, n=791), recurrence per se (n=627), and breast cancer-specific mortality (n=327). Time varying Cox proportional hazard models, adjusted for demographic characteristics, tumor characteristics, first course treatment and a history of diabetes and hypertension, were used to estimate hazard ratios (HRs) and their associated 95% confidence intervals (CIs).

Results:

Use of diuretics (n=8,517) after breast cancer diagnosis was associated with 40% (95% CI: 1.20-1.64), 41% (95% CI: 1.18-1.67) and 78% (95% CI: 1.32-2.40) higher risks of a SBCE, recurrence and breast cancer death, respectively, compared to nonusers of diuretics. Use of β-

blockers (n=7,145) was associated with a 1.63-fold (95% CI: 1.24-2.13) higher risk of breast cancer death compared to women who did not use this class of drug. Use of ARBs was associated with 1.26-fold (95% CI: 1.08-1.48) higher risk of a SBCE. Use of calcium channel blockers and ACEIs were generally not associated with an altered risk of adverse breast cancer outcomes. With respect to diabetes treatments, use of metformin after breast cancer (n=2,558) was associated with 22% (95% CI: 0.62-0.98), 26% (95% CI: 0.57-0.96), and 40% (95% CI: 0.40-0.90) lower risks of a SBCE, breast cancer recurrence, and breast cancer death, respectively, compared to metformin nonusers. Use of sulfonylureas and insulin were associated with 1.58 (95% CI: 1.08-2.30) and 2.64-fold (95%CI: 1.78-3.92) higher risks of breast cancer death, respectively, than women who did not use these drugs.

Conclusions:

Use of certain types of antihypertensive medications after breast cancer diagnosis, including diuretics and β-blockers, may increase risk of adverse breast cancer outcomes among older women while use of metformin is associated with reduced risks of adverse outcomes. Additional research is warranted to clarify these potential associations.

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DEDICATION

For my parents, Ruisheng Chen and Huizhu Zhu, for their continual love and encouragement.

CHAPTER 1:

Use of antihypertensive medications and risk of adverse breast cancer outcomes: A population-based study using SEER-Medicare

Abstract

Background: Antihypertensive drugs are the most commonly prescribed category of medications in the U.S. Despite the generally good safety profile of widely used antihypertensive medications, few studies have examined their relationships with adverse breast cancer outcomes.

Methods: We conducted a retrospective cohort study of women between ages 66 and 80 years diagnosed with incident stage I or II breast cancer during 2007-2011. A total of 14,766 eligible women were identified in the linked Surveillance, Epidemiology and End-Results (SEER)-Medicare database. Medicare Part D Prescription Drug Event data were obtained to characterize women's use of commonly used antihypertensive medications after their breast cancer diagnosis. Our primary outcomes of interest were any second breast cancer event (SBCE, recurrence or second primary breast cancer, n=791), recurrence per se (n=627), and breast cancer-specific mortality (n=327). Time varying Cox proportional hazard models, adjusted for demographic characteristics, tumor characteristics, first course treatment and a history of diabetes and hypertension, were used to estimate hazard ratios (HRs) and their associated 95% confidence intervals (CIs).

Results: Use of diuretics (n=8,517) after breast cancer diagnosis was associated with 40% (95% CI: 1.20-1.64), 41% (95% CI: 1.18-1.67) and 78% (95% CI: 1.32-2.40) higher risks of a SBCE, recurrence and breast cancer death, respectively, compared to nonusers of diuretics. Use of β-blockers (n=7,145) was associated with a 1.63-fold (95% CI: 1.24-2.13) higher risk of breast cancer death compared to women who did not use this class of drug. Use of angiotensin II receptor blockers was associated with 1.26-fold (95% CI: 1.08-1.48) higher risk of a SBCE. Use of calcium channel blockers and angiotensin-converting enzyme inhibitors were generally not associated with an altered risk of adverse breast cancer outcomes.

Conclusion: Use of certain types of antihypertensive medications after breast cancer diagnosis, including diuretics and β-blockers, may increase risk of adverse breast cancer outcomes among older women. Additional research is warranted to clarify these potential associations.

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 category of medications in the U.S.,[2] and almost half of individuals diagnosed with hypertension require at least two different antihypertensive agents to control their blood pressure.[3]

Angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), β-blockers, calcium channel blockers and diuretics are the most commonly used classes of medications to treat hypertension. There is some evidence that some of these medications may influence risk of adverse breast cancer outcomes. Use of β-blockers has been associated with 48-81% lower risks of breast cancer specific mortality [4–7] and 48-57% lower risks of breast cancer recurrence/distant metastases.[4,6] However these studies were all limited by small sample sizes (number of β-blockers users: n=43-102) and their findings have not been confirmed in more recent studies with larger sample sizes.[8–10] ACEIs was associated with a 56-66% higher risk of recurrence[10] and second primary breast cancer[8] in some prior studies, but not associated with altered risks of either breast cancer recurrence[8,11] or breast cancer death in several other studies.[10,12,13] Although positive associations between use of calcium channel blockers (particularly long term use) and diuretics on risk of incident breast cancer have been noted by some,[14–19] but not all prior studies,[20–24] evidence is scarce regarding how they relate to breast cancer outcomes with only two studies reporting null associations for these two classes of drugs.[8,25]

Here we assessed the relationships between use of different classes of antihypertensive medications and risk of a second breast cancer event (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. Given the widespread use of antihypertensive medications and the 2.9 million and growing breast cancer survivors in the U.S., evaluating potential associations between these drugs and risks of adverse breast cancer outcomes is of both clinical and public health importance.

Methods

We conducted a retrospective cohort study of the risk of adverse outcomes among elderly women diagnosed with early stage breast cancer. Participants were identified from the linked SEER-Medicare database, a linkage between two population-based data sources providing claims data as well as cancer registry data for Medicare beneficiaries with cancer living in the catchment areas of the SEER registries located throughout the U.S. [26] The SEER program is sponsored by the National Cancer Institute and currently consists of 18 population-based cancer registries covering 28% of the entire U.S. population. Medicare is a social health insurance program that provides hospital insurance (Part A), medical insurance (Part B), and prescription drug coverage (Part D) for 97% of individuals aged 65 or older in the U.S. Medicare Part D was initiated in 2006 and approximately 60% of Medicare beneficiaries chose to enroll in the Part D in 2008. The SEER-Medicare linked database used in this study included SEER data from January 1, 2007 to December 31, 2011, providing 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 frame. All data were fully de-identified and the study protocol was approved by the Fred Hutchinson Cancer Research Center's institutional review board.

A total of 48,785 women diagnosed with incident primary stage I and II breast cancer between the ages 66 to 80 years from 2007 to 2011 were identified. Women with an unknown cancer diagnosis month (n=105) were excluded. To obtain complete claims data, the cohort was restricted to the 16,397 Medicare beneficiaries enrolled in Parts A, B, and D at the time of diagnosis without concurrent enrollment in a Medicare HMO. Since the algorithm used to identify SBCE and recurrence in this study relies on surgery treatment received for the initial breast cancer in classifying outcomes, women who did not undergo surgery or with missing data on surgical treatment were excluded (n=426). All subjects were required to be cancer free for 180 days post 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, yielding a final sample of 14,766 women.

Our primary exposures of interest, use of ACEIs, ARBs, β-blockers, calcium channel blockers and diuretics, were ascertained through Medicare Part D Prescription Drug Event data. Common subclasses of some of these medications were also examined, including dihydropridines vs. non-dihydropridines calcium channel blockers, β1 vs. β2 blockers, and loop vs. thiazide vs. other diuretics. In our primary analyses, we compared ever use of a given antihypertensive medication to no use of that medication after breast cancer diagnosis. A user of a given medication was defined at the time of their first filled prescription of that drug after breast cancer diagnosis. 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 assess confounding by indication, we explored associations between each medication exposure and adverse breast cancer outcomes among women who only used one type of antihypertensive drug (monotherapy users) and among women who were using two or more classes of drugs to manage hypertension (polytherapy users, a proxy for those with women with more severe/more difficult to control hypertension). Women became a monotherapy user when she first filled a prescription of any antihypertensive medications after breast cancer diagnosis and would be censored at the time she filled a prescription of another class of antihypertensive medications. Similarly, women were defined as a polytherapy user when she first filled a prescription of a second class of antihypertensive medications. Women would not enter the risk sets for monotherapy or polytherapy users until they met the definition for each sub-cohort.

Primary outcomes of interest were a second breast cancer event (SBCE, defined as the first of a breast cancer recurrence or a second contralateral primary breast cancer), recurrence, and breast cancer death. We used a previously validated algorithm to identify SBCEs and

recurrence which used both claims data and SEER data to classify outcomes based on whether women had diagnoses of and/or received typical treatments for secondary malignancies, or had a second breast cancer record in SEER after their initial breast cancer diagnosis.[27,28] The algorithm offers various modes with varying levels of sensitivity and specificity for different applications. As illustrated in previous studies with hypothetical examples and simulation data,[29,30] bias in risk estimates increases with decreasing specificity when relying on an algorithm to classify outcomes even with perfect sensitivity. Alternatively, bias due to misclassification could be minimized with a high specificity even if sensitivity is not perfect but nondifferential to the exposure status. Therefore, we chose modes that prioritize specificity and positive predictive values (PPV) (sensitivity=89%, specificity=99%, PPV=90% for the SBCE algorithm, sensitivity=69%, specificity=99% and PPV=86% for the recurrence algorithm).[30] 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. We also conducted a sensitivity analysis restricted to breast cancer deaths preceded by a SBCE (n=140) to assess the potential bias due to misclassification of cause of death.

Associations between use of various types of antihypertensive medications after breast cancer and risk of each adverse breast cancer outcome were estimated by separate time-varying Cox proportional hazard models using SAS statistical software version 9.3 (SAS Institute Inc, Cary, NC). Therefore, all medication exposures after breast cancer were modeled in a time-varying fashion such that time at risk time before one becomes a user contributes 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. To explore recency of medication use, we conducted stratified analyses based on timing of medication initiation among a subset of 11,494 women (77.8%) who were enrolled in Medicare Parts A/B/D for at least 12 months prior to their initial breast cancer diagnosis. Women were then categorized into those who used the drug only before cancer diagnosis (dropped from further analysis as they were not the focus of our study), those who used it both before and after cancer diagnosis (continuous users), and those who began using it after cancer diagnosis (new users) and those who never used the drug. As the exposure status did not vary with time for those who continuously used the drug, time-fixed Cox models were used to compare continuous users against never users. Time-varying models were used for the comparison between those who started using after cancer diagnosis and never users.

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 (defined as having received either a total mastectomy or breast conserving surgery with radiation), receipt of chemotherapy, use of adjuvant hormone therapy, history of diabetes, and history of hypertension. Categorizations of these covariates are shown in Table 1. Women were considered as having received chemotherapy if there was any chemotherapy related claims in their records within 180 days of cancer diagnosis. Use of adjuvant hormone therapy was defined at the first filled prescription of any of the commonly used drugs for hormonal therapy (e.g., tamoxifen, raloxifene, toremifene , anastrozole, letrozole, exemestane, leuprolide, or goserelin) and was modeled as a time-varying covariate. History of diabetes and hypertension

was determined by any diagnosis of these diseases in Medicare claims. 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 ER status of the first breast cancer using a Wald test, but none of the interactions between ER status and medication exposure were statistically significant at $p<0.05$, and thus none are shown.

Results

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, and to have a history of diabetes or hypertension compared to women who did not experience one of these outcomes (Table 1.1).

Use of diuretics after breast cancer diagnosis was associated with 40%, 41% and 78% higher risks of SBCE (95% CI: 1.20-1.64), recurrence (95% CI: 1.18-1.67), and breast cancer death (95% CI: 1.32-2.40), respectively (Table 1.2). Ever use of β-blockers or calcium channel blockers after cancer diagnosis was associated with 63% (95% CI: 1.24-2.13) and 39% (95% CI: 1.06-1.82) higher risk of breast cancer death, respectively, but not other outcomes. A 26% higher risk (95% CI: 1.08-1.48) of a SBCE was observed among women ever used ARBs after breast cancer. There was a suggestion for a positive association (HR: 1.51, 95% CI: 0.91-2.51) between use of ARBs and risk of second contralateral breast cancer in a post-hoc sensitivity analysis restricting to 89 second contralateral breast cancer cases. Use of ACEIs was not associated with an altered risk of any of the adverse breast cancer outcomes examined. Results regarding breast cancer death changed minimally when restricted to the 140 cases who had a SBCE prior to breast cancer death. As nonusers of a particular antihypertensive medication were allowed to have used one or more different antihypertensive agents and the large majority of them did so in the stratum of women with hypertension, we did not adjust for concurrent use of other antihypertensive medications in our primary analysis. Besides, no material changes in results were observed in a sensitivity analysis where we additionally adjusted for use of other types of antihypertensive medications as time-varying covariates when analyzing for one particular type.

In general, similar associations were observed across subclasses of medications (Table 1.3). Ever use of loop, thiazide or other types of diuretics after breast cancer were similarly associated with elevated risks of SBCE, recurrence, and breast cancer death. However, there was some variability in the magnitude of these associations, as a 2.90-fold (95%CI: 2.09-4.01) higher risk of breast cancer death was observed among loop diuretic users, but only 1.27 (95% CI: 0.92-1.75) to 1.39-fold (95% CI: 0.91-2.12) higher risks were observed among users of other types of diuretics. A 45-60% higher risk of breast cancer death was observed for women using either β1-blockers (95% CI: 1.08-1.94) or β1/β2-blockers (95% CI: 1.12-2.29). Neither use of dihydropridines nor use of non-dihydropridines calcium channel blockers was associated with the risk of any adverse breast cancer outcome.

When stratified by timing of initiation, no consistent pattern was observed (Table 1.4). Women who began using β-blockers after cancer diagnosis, but not those who had used them both before and after diagnosis, had a 2.27-fold higher risk of breast cancer death (95% CI: 1.30-3.91), there was no corresponding excess risk of a SBCE or recurrence. Those who continuously used ARBs had a 1.42-fold (95% CI: 1.15-1.74) higher risk of a SBCE, but not of any other outcome. Continuous users of diuretics had a 1.51-fold (95% CI: 1.21-1.89) higher risk of a SBCE and 1.57-fold higher risk (95% CI: 1.21-2.03) of a breast cancer recurrence while those who began using diuretics after cancer had a 2.39-fold higher risk (95% CI: 1.35-4.23) of breast cancer death.

Among women who only used one type of antihypertensive medication, only use of diuretics was associated with 1.65-fold (95% CI: 1.11-2.47) higher risk of breast cancer death (Table 1.5). Results on breast cancer deaths were not presented for monotherapy users due to a small number of cases (n=41). Among 9,642 women using two or more different classes of antihypertensives, use of diuretics again was associated with 35-40% higher risks of SBCE (HR: 1.40, 95% CI: 1.10-1.77) and recurrence (HR: 1.35, 95% CI: 1.04-1.76). Use of β-blockers and calcium channel blockers were associated with 1.66-fold (95%CI: 1.19-2.31) and 1.41 -fold (95% CI: 1.04-1.90) higher risks of breast cancer death, respectively, among these polytherapy users.

Discussion

In this large population-based cohort of elderly women with early stage breast cancer, we observed that most commonly used forms of antihypertensive medications taken after diagnosis are not associated with risks of adverse breast cancer outcomes. However, our results suggest use of diuretics after cancer diagnosis, including both loop and thiazide diuretics, is associated with a higher risk of SBCE, recurrence, and breast cancer death. This relationship is unlikely to be entirely due to confounding by indication, as we adjusted for a history of high blood pressure and observed similar elevations in risks of adverse breast cancer outcomes among diuretics users in analyses restricted to monotherapy and polytherapy users of antihypertensives. Only one prior study has assessed associations between use of diuretics (number of diuretic users=1,770 vs. 8,517 in the current study) and breast cancer outcomes, and found no impact on risk of SBCE among women who took diuretics (HR: 1.08, 95% CI: 0.88-1.31). 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,[14,17] the majority of prior studies are null.[16,18,20,22,23] 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,[31,32] and insulin resistance is an established risk factor for breast cancer,[33] providing a potential mechanism for the relationship observed here. While this is the largest study of the impact of diuretics on adverse breast cancer outcomes, we believe that our results require confirmation and should be interpreted with caution.

β-blockers compete with norepinephrine and epinephrine for available beta-adrenoceptors and may be involved in multiple cellular processes relevant to cancer through stress response pathways.[34] Contrary to some smaller prior studies either reporting favorable results for β-

blockers[4–7] or no associations,[10] our study observed a higher risk of breast cancer death associated with use of β-blockers after breast cancer diagnosis. The associations were similar across β1 and β1/β2 blockers. Our results are based on a much larger sample size than any prior studies (n=7145 for β-blocker users) and are consistent with two recent larger studies in Denmark (n=3660 for β-blocker users) and in the U.S. (n=1501 for β-blocker users) where a 29-30% higher risk of breast cancer recurrence was noted for users of β-blockers compared to nonusers.[8,11] 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 among women using β-blockers alone.

We also observed a higher risk of SBCEs but not recurrence or breast cancer death among women who ever used ARBs after cancer diagnosis. Two previous studies found that use of ARBs was not related to risk of breast cancer recurrence or breast cancer specific mortality.[11,13] Our observed association between use of ARBs and risk of SBCE seemed to be primarily driven by a relationship with risk of second contralateral breast cancer rather than with risk of recurrence. No prior studies have assessed the relationship between ARB use and the incidence of contralateral breast cancer. Similarly, we observed a higher risk of breast cancer death among women using calcium channel blockers but this could be a spurious finding as we did not see a pattern when examined by time of initiation and the only prior study assessed calcium channel blockers found no association with breast cancer recurrence.[8]

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[35,36] and hypertension,[37] but obesity status was not available through claims or registry data and thus was not adjusted for in our study. This is addressed, though, to some extent in our analyses restricted to antihypertensive monotherapy and polytherapy. 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. However, this algorithm has been previously validated against medical records review data and the two specificity-prioritized modes applied in our study showed best performance when this algorithm was recently evaluated in a new set of breast cancer patients (SBCE algorithm: sensitivity=80%, specificity=98%, PPV=89%; recurrence algorithm: sensitivity=75%, specificity=97%, PPV=85%).[38] 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.

Our results provide some reassurance that majority of the commonly prescribed antihypertensive medications are safe with respect to breast cancer outcomes in a cohort of older women with early stage breast cancer. 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.

Table 1.1: Characteristics of women diagnosed with stage I or II breast cancer during 2007-2011

	All	Women with SBCE	Women with recurrence	Women died from breast cancer
	(n=14766)	(n=791)	(n=627)	(n=237)
	n (%)	n (%)	n (%)	n (%)
Demographic factors				
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	2944 (19.9)	119 (15.0)	96 (15.3)	23 (9.7)
2011	3093 (20.9)	59 (7.5)	49 (7.8)	2 (0.8)
Age at diagnosis				
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)	9 (3.8)
American Indian/Native American	49 (0.3)	6 (0.8)	5 (0.8)	3 (1.3)
Unknown	82	3	2	0
Marital status				
Married	6895 (48.7)	358 (46.9)	288 (47.4)	91 (39.4)
Widowed	4043 (28.5)	216 (28.3)	172 (28.3)	84 (36.4)
Single/Unmarried	1368 (9.7)	70 (9.2)	55 (9.1)	24 (10.4)
Separated/Divorced	1863 (13.1)	120 (15.7)	92 (15.2)	32 (13.9)
Missing	597	27	20	6
Tumor characteristics of the first breast cancer				
Stage at diagnosis				
I	9410 (63.7)	294 (37.2)	203 (32.4)	60 (23.2)
II	5356 (36.3)	497 (62.8)	424 (67.6)	199 (76.8)
ER/PR status				
ER+/PR+	10413 (73.7)	394 (51.8)	303 (50.2)	75 (33.8)
ER-/PR-	1908 (13.5)	239 (31.4)	201 (33.3)	109 (49.1)
ER+/PR-	1707 (12.1)	122 (16.0)	95 (15.8)	33 (14.9)
ER-/PR+	103 (0.7)	6 (0.8)	4 (0.7)	5 (2.3)
Unknown	635	30	24	15
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)
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				
History of diabetes				
No	9304 (63.0)	471 (59.5)	372 (59.3)	126 (53.2)
Yes	5462 (37.0)	320 (40.5)	255 (40.7)	111 (46.8)
History of hypertension				
No	2203 (14.9)	95 (12.0)	67 (10.7)	25 (10.5)
Yes	12563 (85.1)	696 (88.0)	560 (89.3)	212 (89.5)

Table 1.2: Antihypertensive medications and risk of adverse breast cancer among women diagnosed with stage I/II breast cancer, 2007-2011

Ever use after breast cancer diagnosis	All women n=14766	SBCE n=791			Recurrence n=627			Breast cancer death n=237		
	n (%)[a]	n (%)[a]	HR[b]	95% CI	n (%)[a]	HR[b]	95% CI	n (%)[a]	HR[b]	95% CI
Angiotensin-converting enzyme inhibitors										
No	8866 (60.0)	437 (55.2)	Reference		352 (56.1)	Reference		131 (55.3)	Reference	
Yes	5900 (40.0)	354 (44.8)	1.03	0.89-1.20	275 (43.9)	0.98	0.83-1.16	106 (44.7)	1.22	0.93-1.60
Angiotensin II receptor blockers										
No	10526 (71.3)	521 (65.9)	Reference		426 (67.9)	Reference		168 (70.9)	Reference	
Yes	4240 (28.7)	270 (34.1)	1.26	1.08-1.48	201 (32.1)	1.15	0.96-1.37	69 (29.1)	1.03	0.76-1.40
β *blockers*										
No	7621 (51.6)	360 (45.5)	Reference		279 (44.5)	Reference		102 (43.0)	Reference	
Yes	7145 (48.4)	431 (54.5)	1.11	0.96-1.28	348 (55.5)	1.13	0.96-1.33	135 (57.0)	1.63	1.24-2.13
Calcium channel blockers										
No	9193 (62.3)	467 (59.0)	Reference		372 (59.3)	Reference		134 (56.5)	Reference	
Yes	5573 (37.7)	324 (41.0)	1.02	0.88-1.19	255 (40.7)	0.97	0.82-1.16	103 (43.5)	1.39	1.06-1.82
Diuretics										
No	6249 (42.3)	256 (32.4)	Reference		193 (30.8)	Reference		74 (31.2)	Reference	
Yes	8517 (57.7)	535 (67.6)	1.40	1.20-1.64	434 (69.2)	1.41	1.18-1.67	163 (68.8)	1.78	1.32-2.40

[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 intial 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 non-user 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 hormonal therapy (time-varying), hypertension, and diabetes.

Table 1.3: Subclasses of selected antihypertensive medications and risk of adverse breast cancer outcomes

Ever use after breast cancer diagnosis	All women	SBCE			Recurrence			Breast cancer death		
	n=14766	n=791			n=627			n=237		
	n (%)[a]	n (%)[a]	HR[b]	95% CI	n (%)[a]	HR[b]	95% CI	n (%)[a]	HR[b]	95% CI
Beta blockers										
None users of any beta blockers	7621 (51.6)	360 (45.5)	Reference		279 (44.5)	Reference		102 (43.0)	Reference	
Ever use of β1 blockers [c]	5408 (36.6)	332 (42.0)	1.09	0.93-1.28	268 (42.7)	1.10	0.92-1.32	96 (40.5)	1.45	1.08-1.94
Ever use of β1/β2 blockers [c]	2664 (18.0)	168 (21.2)	1.04	0.84-1.29	133 (21.2)	1.10	0.89-1.35	47 (19.8)	1.60	1.12-2.29
Calcium channel blockers										
None users of any calcium channel blockers	9193 (62.3)	467 (59.0)	Reference		372 (59.3)	Reference		134 (56.5)	Reference	
Ever use of dihydropridines [c]	4422 (29.9)	266 (33.6)	1.08	0.92-1.27	206 (32.9)	1.01	0.84-1.21	77 (32.5)	1.28	0.96-1.72
Ever use of non-dihydropridines [c]	1501 (10.2)	85 (10.7)	1.10	0.89-1.35	70 (11.2)	0.93	0.70-1.23	30 (12.7)	1.29	0.86-1.93
Diuretics										
None users of any diuretics	6249 (42.3)	256 (32.4)	Reference		193 (30.8)	Reference		74 (31.2)	Reference	
Ever use of loop diuretics [c]	3435 (23.3)	261 (33.0)	1.42	1.17-1.72	225 (35.9)	1.51	1.23-1.86	99 (41.8)	2.90	2.09-4.01
Ever use of thiazide diuretics [c]	6532 (44.2)	392 (49.6)	1.40	1.18-1.66	311 (49.6)	1.37	1.13-1.66	100 (42.2)	1.27	0.92-1.75
Ever use of other diuretics [c]	2073 (14.0)	128 (16.2)	1.31	1.04-1.66	107 (17.1)	1.38	1.07-1.79	33 (13.9)	1.39	0.91-2.12

[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 non-user category. The percentages may add up >100% because women could take one or more subclasses of a given drug after cancer diagnosis.

[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 hormonal therapy (time-varying), hypertension, and diabetes.

[c] Users of each subclass of a given antihypertensive medication was compared to nonusers in separate time-varying cox models.

Table 1.4: Antihypertensive medications and risk of adverse breast cancer outcomes by time of initiation

Ever use after breast cancer diagnosis	All women n=11494	SBCE n=537			Recurrence n=414			Breast cancer death n=134		
	n (%)[a]	n (%)[a]	HR[b]	95% CI	n (%)[a]	HR[b]	95% CI	n (%)[a]	HR[b]	95% CI
Angiotensin-converting enzyme inhibitors										
Never users	6207 (54.0)	275 (51.2)	Reference		217 (52.4)	Reference		66 (49.3)	Reference	
Continuous users [c]	3286 (28.6)	152 (28.3)	0.98	0.79-1.21	113 (27.3)	0.88	0.69-1.12	46 (34.3)	1.00	0.67-1.49
Began using after cancer diagnosis [d]	1120 (9.7)	70 (13.0)	0.96	0.69-1.33	50 (12.1)	0.76	0.52-1.13	14 (10.4)	1.28	0.70-2.33
Angiotensin II receptor blockers										
Never users	7849 (68.3)	331 (61.6)	Reference		266 (64.3)	Reference		93 (69.4)	Reference	
Continuous users [c]	2389 (20.8)	144 (26.8)	1.42	1.15-1.74	105 (25.4)	1.24	0.98-1.57	24 (17.9)	0.71	0.45-1.12
Began using after cancer diagnosis [d]	771 (6.7)	36 (6.7)	1.05	0.69-1.61	21 (5.1)	0.81	0.49-1.35	8 (6.0)	1.20	0.57-2.51
β-*blockers*										
Never users	5651 (49.2)	240 (44.7)	Reference		184 (44.4)	Reference		52 (38.8)	Reference	
Continuous users [c]	4148 (36.1)	196 (36.5)	1.08	0.88-1.32	157 (37.9)	1.09	0.87-1.37	57 (42.5)	1.30	0.88-1.94
Began using after cancer diagnosis [d]	1230 (10.7)	85 (15.8)	1.18	0.87-1.61	63 (15.2)	1.11	0.78-1.58	20 (14.9)	2.27	1.32-3.92
Calcium channel blockers										
Never users	6780 (59.0)	302 (56.2)	Reference		236 (57.0)	Reference		67 (50.0)	Reference	
Continuous users [c]	3130 (27.2)	149 (27.7)	1.00	0.81-1.23	111 (26.8)	0.92	0.73-1.16	46 (34.3)	1.18	0.79-1.75
Began using after cancer diagnosis [d]	1086 (9.4)	64 (11.9)	1.18	0.85-1.65	50 (12.1)	1.11	0.77-1.61	15 (11.2)	1.69	0.94-3.03
Diuretics										
Never users	4327 (37.6)	159 (29.6)	Reference		114 (27.5)	Reference		38 (28.4)	Reference	
Continuous users [c]	5237 (45.6)	278 (51.8)	1.51	1.21-1.89	217 (52.4)	1.57	1.21-2.03	69 (51.5)	1.03	0.67-1.58
Began using after cancer diagnosis [d]	1200 (10.4)	71 (13.2)	1.23	0.88-1.71	59 (14.3)	1.29	0.89-1.86	20 (14.9)	2.39	1.35-4.23

[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 intial cancer diagnosis. The percentages may not add up to 100% as women who stopped taking a given medication were excluded from analyses on that particular class of drug.
[b] 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, and hypertension.
[c] Time-fixed cox models were used to calculate HRs and associated 95% CIs comparing continuous users vs. never users.
[d] Time-varying cox models were used to calculate HRs and associated 95% CIs comparing ever use (yes vs. no) after breast cancer diagnosis among new users and never users such that at risk time before one became a user contributes to the non-user category.

Table 1.5: Risk of adverse breast cancer outcomes among monotherapy and polytherapy users of antihypertensive medications

Ever use after breast cancer diagnosis	All women	SBCE			Recurrence			Breast cancer death		
	n (%)[a]	n (%)[a]	HR[b]	95% CI	n (%)[a]	HR[b]	95% CI	n (%)[a]	HR[b]	95% CI
Monotherapy users [c]										
	n=4436	n=133			n=109			n=41		
Angiotensin-converting enzyme inhibitors										
No	3491 (78.7)	108 (81.2)	Reference		89 (81.7)	Reference		32 (78.0)		NA
Yes	945 (21.3)	25 (18.8)	0.83	0.53-1.29	20 (18.3)	0.80	0.49-1.31	9 (22.0)		
Angiotensin II receptor blockers										
No	4012 (90.4)	115 (86.5)	Reference		96 (88.1)	Reference		38 (92.7)		NA
Yes	424 (9.6)	18 (13.5)	1.57	0.95-2.61	13 (11.9)	1.41	0.78-2.54	3 (7.3)		
β-blockers										
No	3130 (70.6)	104 (78.2)	Reference		87 (79.8)	Reference		35 (85.4)		NA
Yes	1306 (29.4)	29 (21.8)	0.68	0.45-1.03	22 (20.2)	0.61	0.38-0.97	6 (14.6)		
Calcium channel blockers										
No	3779 (85.2)	114 (85.7)	Reference		94 (86.2)	Reference		35 (85.4)		NA
Yes	657 (14.8)	19 (14.3)	0.95	0.58-1.55	15 (13.8)	0.93	0.54-1.61	6 (14.6)		
Diuretics										
No	3332 (75.1)	91 (68.4)	Reference		70 (64.2)	Reference		24 (58.5)		NA
Yes	1104 (24.9)	42 (31.6)	1.37	0.95-2.00	39 (35.8)	1.65	1.11-2.47	17 (41.5)		
Polytherapy users [d]										
	n=9642	n=529			n=425			n=178		
Angiotensin-converting enzyme inhibitors										
No	4267 (44.3)	224 (42.3)	Reference		186 (43.8)	Reference		81 (45.5)	Reference	
Yes	5375 (55.7)	305 (57.7)	0.97	0.81-1.15	239 (56.2)	0.93	0.77-1.12	97 (54.5)	0.95	0.70-1.28
Angiotensin II receptor blockers										
No	5642 (58.5)	288 (54.4)	Reference		243 (57.2)	Reference		112 (62.9)	Reference	
Yes	4000 (41.5)	241 (45.6)	1.16	0.98-1.38	182 (42.8)	1.06	0.88-1.29	66 (37.1)	0.98	0.72-1.34
β-*blockers*										
No	3283 (34.0)	160 (30.2)	Reference		125 (29.4)	Reference		49 (27.5)	Reference	
Yes	6359 (66.0)	369 (69.8)	1.12	0.94-1.34	300 (70.6)	1.19	0.97-1.46	129 (72.5)	1.66	1.19-2.31
Calcium channel blockers										

	No	4434 (46.0)	241 (45.6)	Reference		201 (47.3)	Reference		81 (45.5)	Reference	
	Yes	5208 (54.0)	288 (54.4)	0.95	0.81-1.13	224 (52.7)	0.92	0.76-1.10	97 (54.5)	1.41	1.04-1.90
Diuretics											
	No	1804 (18.7)	66 (12.5)	Reference		55 (12.9)	Reference		32 (18.0)	Reference	
	Yes	7838 (81.3)	463 (87.5)	1.40	1.10-1.77	370 (87.1)	1.35	1.04-1.76	146 (82.0)	1.11	0.75-1.63

[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 intial 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 non-user 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 and hypertension.

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 if they ever used more than 1 class after breast cancer diagnosis. Users of each class were compared to non-users of any antihypertensive medications in separate time-varying cox models.

[d] Polytherapy users were defined in a time-varying fashion such that women entered the cohort on the day they first received more than 1 class of antihypertensive medications.

CHAPTER 2:

Diabetes treatment and risks of adverse breast cancer outcomes among elderly breast cancer patients: A SEER-Medicare analysis

Abstract

Background: Metformin, a first line diabetes treatment, is hypothesized to lower the risk of incident breast cancer, but it is unclear whether metformin (and other forms of treatment for diabetes) influences the likelihood of adverse breast cancer outcomes.

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Methods: A retrospective cohort study was conducted using the linked Surveillance, Epidemiology and End-Results (SEER)-Medicare database. Diabetic and nondiabetic women were included if they were aged 66-80 years, newly diagnosed with stage I or II breast cancer, and enrolled in Medicare Parts A, B and D during 2007-2011. Information on filled diabetes treatment prescriptions was obtained from Medicare Part D claims data. Our primary outcomes of interest were a second breast cancer event (SBCE, recurrence or second primary breast cancer) 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: Among 14,766 women included in the study, 791 were identified as having had a second breast cancer event, 627 had a recurrence, and 237 died from breast cancer. Use of metformin after breast cancer (n=2,558) was associated with a 22% (HR: 0.78, 95% CI: 0.62-0.98), 26% (HR: 0.74, 95% CI: 0.57-0.96), and 40% (HR: 0.60, 95% CI: 0.40-0.90) lower risk of a SBCE, breast cancer recurrence, and breast cancer death, respectively, compared to metformin nonusers. Use of sulfonylureas and insulin were associated with 1.58 (95% CI: 1.08-2.30) and 2.64-fold (95%CI: 1.78-3.92) higher risks of breast cancer death, respectively, than women who did not use these drugs. In assessing potential confounding by indication, similar patterns were observed in analyses restricted to pharmacologically-treated diabetic patients.

Conclusion: We observed variation in the relationship between different diabetes medications and risk of adverse breast cancer outcomes, with metformin associated with reduced risks and sulfonylureas and insulin with increased risks. Pending confirmation of these results, metformin may be a preferred treatment for diabetes among breast cancer survivors, and further research examining its benefits among non-diabetic patients may be warranted.

Introduction

Type 2 diabetes is a common chronic condition characterized by hyperglycemia, insulin resistance and impaired insulin secretion. There are approximately 29.1 million diabetics in the United States, with 17.9 million currently using prescription medications to manage their disease.[39]

Metformin, a biguanide used as a first line treatment for type 2 diabetes, has been at the center of recent investigations for its potential as a breast cancer chemopreventive agent. Recent meta-analyses report a 13-17% lower risk of incident breast cancer associated with metformin use,[40,41] but relatively few studies have assessed metformin in relation to adverse breast cancer outcomes. A large Canadian study observed a modest reduction in case-fatality (9% per year of metformin use, but the results were statistically consistent with no true reduction). Three small U.S. studies[42–44] found that metformin use was associated with a lower risk of distant metastasis and breast cancer death and a higher likelihood of pathologic complete response, but another small U.S. study did not.[45,46] A key limitation of the U.S. studies was their small sample size (n=63-88 metformin users). Also, most lacked data on other outcomes, namely breast cancer recurrence and second primary breast cancer. Few studies have examined other diabetes treatments, such as sulfonylureas and insulin therapy, in relation to breast cancer progression.

The purpose of this study is to assess how use of different types of diabetes medications are related to risk of adverse breast cancer outcomes, including any second breast cancer event (recurrence or a second primary breast cancer), breast cancer recurrence per se, and breast cancer specific mortality in a cohort of elderly women enrolled in Medicare. Characterizing the potential associations between various diabetes treatment and risks of developing adverse breast cancer outcomes potentially is of both clinical and public health importance.

Material and methods

We conducted a retrospective cohort study using the linked Surveillance, Epidemiology and End-Results (SEER)-Medicare data. The study was approved by the Institutional Review Board at the Fred Hutchinson Cancer Research Center. Details regarding the SEER-Medicare database have been described elsewhere.[26] Briefly, the SEER program of the National Cancer Institute consists of population-based tumor registries serving 18 geographic areas in the U.S., encompassing 28% of the U.S. population. These cancer registries routinely collect cancer incidence and survival data including patient demographic factors, primary tumor site, tumor characteristics (e.g., stage, estrogen receptor and progesterone receptor (ER/PR) status), surgical and radiation treatment received within 4 months of diagnosis, and vital status. Medicare provides health insurance to 97% of individuals 65 years or older in the U.S, covering inpatient care (Part A) as well as physician service and outpatient care (Part B). In 2006, Medicare Part D was initiated to provide prescription drug coverage for those who chose to enroll and approximately 60% of Medicare beneficiaries had Part D coverage in 2008. SEER data and Medicare data are then linked based on an algorithm involving social security number, name, sex and date of birth, providing rich health care utilization data for Medicare beneficiaries with cancer.

Patient population

The cohort consisted of both diabetic and nondiabetic women between 66 and 80 years of age newly diagnosed with stage I and II breast cancer during 2007-2011. Among a total of 48,785 breast cancer cases identified, women were excluded in a stepwise fashion if they had unknown month of diagnosis (n=105); were not enrolled in Part A, Part B and Part D or were enrolled in an HMO (HMO enrollees lack detailed claims data) at the time of diagnosis (n=32,283); were not documented to have had surgical treatment (n=426); had a SEER record of a second primary breast cancer (n=577) or died (n=80) within 180 days of the first breast cancer; or did not have at least 12 months of continuous enrollment of Part A/B/D after the initial breast cancer diagnosis (unless they died during the first 12 months) (n=548), leaving a final cohort of 14,766 women.

Exposure assessment

Use of metformin, a sulfonylurea, insulin, or other diabetes medications (meglitinides, glitazones, acarbose, exenatide, liraglutide, mglitol, pramlintide acetate, saxagliptin, sitagliptin and tolbutamide) after breast cancer diagnosis were our exposures of interest. Medicare Part D Prescription Drug Event data during 2007-2012 were obtained, including information on medications dispensed, prescription fill dates, and days of supply dispensed. Women were defined as a user of a given medication of interest if they had any dispensing of that drug after their initial breast cancer diagnosis date. Thus, a woman would be considered a user of a given medication beginning the day when she first filled a prescription for that drug after breast cancer diagnosis.

Outcome assessment

Second breast cancer events (SBCEs), recurrence, and breast cancer death were our primary outcomes of interest. SBCEs were defined as the first of a breast cancer recurrence or a second contralateral primary breast cancer. Both SBCEs and breast cancer recurrence were assessed using a previously validated administrative data based algorithm.[27,28] Using claims data on procedures, diagnoses, frequency and timing of these events that may be indicative of a second breast cancer event together with SEER cancer records, the algorithm identifies a second breast cancer event (sensitivity=89%, specificity=99%) and breast cancer recurrence (sensitivity =69%, specificity=99%) with high sensitivity and specificity when validated against medical records review data. Breast cancer death was determined using SEER data, which abstracted primary cause of death from death certificates. Date of death was obtained using Medicare data, which was reported to the Centers for Medicare & Medicaid Services by the Social Security Administration. The agreement of vital status between SEER and Medicare data were >99.0% for the study cohort. The assessment of all outcomes started 180 days after the initial breast cancer diagnosis. Due to availability of the data based on the most recent SEER-Medicare linkage at the time of analyses, the last day of follow-up was 12/31/2012 for SBCE and recurrence, and 12/31/2011 for breast cancer death.

Statistical analyses

Time-varying Cox proportional hazards models were used to estimate hazard ratios (HRs) and associated 95% confidence intervals (CIs) for the associations between various diabetes treatments and risk of adverse breast cancer outcomes. Each outcome was modeled separately with women censored at the earliest of disenrollment, end of follow-up, or death. In all models, the time axis was defined as the time since the initial breast cancer diagnosis with a delayed entry of 180 days post diagnosis. In addition to evaluating ever/current use after cancer diagnosis, we also evaluated timing of medication initiation among women who had at least one year of continuous enrollment in Medicare Part A/B/D in the year prior to their breast cancer diagnosis (n=11,494, 77.8%). These women were categorized into the following groups: those who never used the drug before or after cancer diagnosis, those who initiated using the drug after cancer diagnosis, and continuous users who used both before and after cancer diagnosis. Separate models were constructed to compare risks across these categories of women. Time-fixed Cox models were used to compare continuous users vs. never users as their exposure status after cancer diagnosis would not change with time (96-99% continuous users were truly continuously on a given diabetes treatment throughout their cancer diagnosis), whereas time-varying cox models were used to estimate risks associated with medication use comparing new users to never users.

All analyses were adjusted for age at diagnosis, year of diagnosis, cancer stage, ER/PR status, receipt of complete first course treatment, receipt of chemotherapy, use of adjuvant hormone therapy, history of diabetes, and history of hypertension (as grouped in Table 1). Since only stage I and II cases were included, women were considered to have had a complete first course of treatment if they received either a total mastectomy or breast conserving surgery with radiation, and those receiving primary treatments less than this were considered to have had an incomplete first course of treatment. Women were classified as having received chemotherapy if they had any related claims within 180 days of the initial breast cancer diagnosis. Use of adjuvant hormonal therapy was defined as having filled any prescriptions for tamoxifen, raloxifene, toremifene , anastrozole, letrozoles, exemestane, leuprolide, or goserelin after cancer and was modeled as a time-varying covariate (first use of these drugs after outcome events were not accounted). A woman with at least one diagnosis of diabetes or hypertension in any Medicare claims data was identified as having the condition respectively. Other potential confounders assessed were race/ethnicity and marital status, but neither materially changed the risk estimates and thus was not included in the final models. We assessed potential effect modification by ER status of women's first breast cancer using a Wald test while adjusting for all other covariates, but none of the interaction terms was statistically significant at $p<0.05$ and thus the interactions terms were dropped from final models.

A set of sensitivity analyses were conducted to further explore these associations. In order to evaluate potential confounding by indication, we restricted analyses to diabetic women who had used at least one of the antidiabetic agents after breast cancer diagnosis and compared risks of adverse breast cancer outcomes associated with using metformin, sulfonylureas and insulin relative to not using these medications while adjusting for the same set of covariates as in the primary analyses except for diabetes status. Similar analyses were repeated among diabetic women who were receiving diabetes treatments other than insulin since receipt of insulin is usually associated with more severe/poorly controlled diabetes. These subsets of women were

created in a time-varying fashion such that a woman would enter the treated diabetics subset when she first filled a prescription of any diabetes treatments examined in the study and would then leave the cohort at her first filled prescription of insulin for the analyses among treated diabetics excluding insulin users. Additionally, we did a sensitivity analysis restricted to breast cancer deaths preceded by a SBCE (n=140) to assess the potential bias due to misclassification of cause of death.

Results

Among 14,766 women included in the study, 791 were identified as having had a second breast cancer event, 627 had recurrences, and 237 died from breast cancer over a median follow-up of 3 years (Table 1.1). Compared to the overall cohort, women who had one of these outcomes were somewhat less likely to be non-Hispanic white, to have ER+/PR+ disease, and to be on adjuvant hormonal therapy if they had ER+ breast cancers. They were somewhat more likely to be older, to have stage II disease, to have received chemotherapy, to have a history of diabetes, and to have a history of hypertension.

Ever use of metformin after breast cancer diagnosis was associated with lower risks of each adverse breast cancer outcome (Table 2.1). Specifically, metformin users had a 22%, 26%, and 40% lower risk of a SBCE (95% CI: 0.62-0.98), breast cancer recurrence (95% CI: 0.57-0.96) or breast cancer death (95% CI: 0.40-0.90) compared to nonusers, adjusting for demographic factors, tumor characteristics, hypertension, and diabetes status. Use of sulfonylurea or insulin was associated with 1.58 (95% CI: 1.08-2.30) and 2.64-fold (95% CI: 1.78-3.92) higher risk of breast cancer death, respectively. Use of other types of diabetes treatments was not associated with risks of adverse breast cancer outcomes. In a sensitivity analyses where we adjusted for concurrent use of other types of diabetes treatments as time-varying covariates, no material changes in results were observed. Results on breast cancer death were unchanged in a sensitivity analysis where only breast cancer death proceeded by a SBCE (n=140) was included (data not shown).

Similar patterns in these associations were observed in analyses aimed to assess confounding by indication that were restricted to diabetic women receiving any type of antidiabetic agents (Table 2.2). Use of metformin after breast cancer was again associated with 39%, 43% and 69% lower risks of a SBCE (95% CI: 0.46-0.82), recurrence (95% CI: 0.42-0.79), and breast cancer death (95% CI: 0.20-0.50), respectively, while use of insulin were associated with a 2.28-fold (95% CI: 1.44-3.60) higher risk of breast cancer death. Results were similar when the diabetic women on insulin therapy were excluded.

In analyses stratified by time of treatment initiation among the 11,494 women who had at least a year of data prior to breast cancer diagnosis, those who used metformin before their cancer diagnosis and continued using it afterwards had 21%, 32% and 67% lower risks of a SBCE (95% CI: 0.58- 1.08), recurrence (95% CI: 0.47- 0.99) and breast cancer death (95% CI: 0.24-0.77), respectively, compared to women who never used metformin (Table 2.3). There was some suggestion that risks were also lower among women who started using metformin after breast cancer, but these estimates were within limits of chance. We observed 1.56 to 3.15-fold higher risks of adverse breast cancer outcomes for women who started using a sulfonylurea

after breast cancer, but not among those who had been on sulfonylurea before cancer diagnosis. Similarly, new users of insulin therapy had 2.05 to 3.32-fold higher risks of all adverse outcomes compared to women who never used insulin. Continuous users of insulin also had a 2.21-fold higher risk (95% CI: 1.20- 4.06) of breast cancer death compared to never users of insulin.

Discussion

This large population based cohort study of elderly breast cancer patients adds to the preponderance of evidence from prior studies that metformin may confer some protection against adverse breast cancer outcomes among patients with early stage breast cancer. Our results suggest that the associations between metformin use and adverse breast cancer outcomes were strongest among women currently using metformin who had initiated use prior to their cancer diagnosis. Although incompletely understood, several biological mechanisms through which metformin could potentially influence breast cancer tumorigenesis and progression have been proposed. Metformin reduces glucose output by the liver and increases insulin sensitivity, and thus lowers blood glucose and circulating insulin levels. By changing the metabolic environment typical in diabetic patients, metformin may reduce tumor proliferation in breast cancers that are insulin-responsive.[47] This insulin mediated effect of metformin may not be limited to diabetic patients as some early phase clinical trials reported a decreased insulin level with administration of metformin to non-diabetic breast cancer patients.[48,49] Metformin may also exert anticancer effects directly through interfering with cellular energy processes through the activation of AMPK, a cellular energy sensor.[50] These proposed anticancer properties of metformin are supported by recent evidence from small-scale window-of-opportunity studies, in which reduced levels of tumor proliferation biomarkers were observed among non-diabetic women randomly assigned to receive metformin after breast cancer diagnosis, with the effect particularly evident among women with insulin resistance.[51–53]

Our study is first to report higher risks of adverse breast cancer outcomes, particularly breast cancer death, associated with the use of sulfonylureas and insulin. Different from metformin's mechanism of action, sulfonylureas increase insulin secretion without reducing insulin resistance. As insulin and insulin-like growth factor (IGF)-1 are thought to promote cancer proliferation and inhibit apoptosis,[47] there is some concern that diabetes treatments that increase circulating insulin may have carcinogenic effects. Overexpression of IGF-I and insulin receptors have been reported in breast cancer cells.[54,55] Furthermore, a higher level of fasting insulin level has been associated with a higher risk of breast cancer recurrence and death among early stage breast cancer patients without pre-existing diabetes.[56] However, direct evidence connecting sulfonylureas or insulin therapy with breast cancer progression is lacking, as no prior studies have evaluated these associations. It is also unclear why the associations between sulfonylureas/insulin and adverse breast cancer outcomes observed in the current study were strongest among patients who initiated these therapies after cancer diagnosis rather than those who had continuously used them.

Confounding by indication is a potential limitation of observational studies of medication use. Type 2 diabetes itself is an established risk factor for breast cancer progression, associated with 1.2-1.4-fold, a 1.3-2.3-fold and 4%-25% increased risks of breast recurrence,[57–59] second primary breast cancer[57,60] and breast cancer mortality,[57,58,61–63] respectively. We adjusted for diabetes history in our primary analysis, and observed similar results in a sensitivity analysis

where no adjustment for diabetes status was made. Nevertheless, confounding by diabetes status would result in spuriously positive associations given the direction of associations between diabetes and breast cancer outcomes, not an inverse association as we observed with metformin. Further, our sensitivity analyses restricted to treated diabetic women yielded results that were essentially equivalent to those observed in our primary analyses. However, confounding by severity of diabetes remains possible as metformin is the first line treatment for type 2 diabetes and those who use other diabetes medications may have more severe or longer duration of the disease. We assessed this to some degree by conducting a sensitivity analysis restricted to those treated diabetics who did not use insulin, since use of insulin is an indicator of more severe or less well controlled diabetes. Again though, quite similar associations were observed in this analysis compared to the overall analysis. Another limitation of this claims/registry-data based study is the lack of data on other important risk factors that correlate with both diabetes and breast cancer progression. Obesity is of particular importance, given its known positive correlations with both diabetes and poor breast cancer outcomes. [35,36] However, given these correlations, one would expect that any confounding resulting from obesity would yield a falsely weak association between use of metformin and more favorable breast cancer outcomes. Lastly, misclassification of SBCE and recurrence is possible with the use of a claims-data based algorithm. However, the algorithm has been previously validated against medical records review and there are various formulations of this algorithm designed for different applications.[27] We used the high-specificity algorithm to identify SBCE (sensitivity=89%, specificity=99%, positive predictive value (PPV)=90% in the original validation study) and the high-specificity/high-PPV algorithm (sensitivity=69%, specificity=99% and PPV=86%) to identify recurrence, as prioritizing specificity is desired to reduce bias in studies using algorithms to identify outcomes.[30] In addition, the two modes chosen in our study had the best performance (SBCE algorithm: sensitivity=80%, specificity=98%, PPV=89%; recurrence algorithm: sensitivity=75%, specificity=97%, PPV=85%) when recently tested in a new cohort of breast cancer patients.[38] Nevertheless, identification of SBCEs or recurrence using claims data requires medical encounters and these events may be missed if women did not seek care for signs associated with breast cancer progression. The follow-up time in our cohort is also relatively short, limiting our ability in examining the impact of long-term use of these medications

In summary, the results of this study suggest that among older women with breast cancer, use of metformin is associated with a lower risk of a SBCE, breast cancer recurrence and breast cancer death, and that use of sulfonylureas and insulin therapy is associated with a higher risk of breast cancer death. Further efforts to confirm these findings are necessary. Given challenges of assessing metformin use and breast cancer progression in observational designs (e.g., confounding by indication), evidence from randomized trials would be desirable. Several early phase randomized clinical trials evaluating the effect of metformin on breast cancer progression have been initiated, although most of them are limited by small sample sizes and the use of intermediate tumor biomarkers instead of breast cancer outcomes as endpoints. Only one Phase III randomized trial has been launched so far to assess metformin use and breast cancer survival, with a planned 9 years of follow-up. It may shed new insights on these relationships. Given the widespread use of diabetes treatments and growing number of breast cancer survivors with diabetes, characterization of potential relationships between use of these medications and risk of adverse breast cancer outcomes has the potential to help inform decision making around diabetes treatment. Furthermore, metformin has been clinically used for diabetes management for decades with a generally good safety profile, and may also have utility in improving outcomes among breast cancer survivors without diabetes pending confirmation of these results.

Table 2.1: Diabetes treatments and risk of adverse breast cancer outcomes among women diagnosed with stage I/II breast cancer, 2007-2011

Ever use after breast cancer diagnosis	All women	SBCE			Recurrence			Breast cancer death		
	n=14766	n=791			n=627			n=237		
	n (%)[a]	n (%)[a]	HR[b]	95% CI	n (%)[a]	HR[b]	95% CI	n (%)[a]	HR[b]	95% CI
Metformin										
No	12208 (82.7)	661 (83.6)	Reference		524 (83.6)	Reference		205 (86.5)	Reference	
Yes	2558 (17.3)	130 (16.4)	0.78	0.62-0.98	103 (16.4)	0.74	0.57-0.96	32 (13.5)	0.60	0.40-0.90
Sulfonylureas										
No	13065 (88.5)	678 (85.7)	Reference		535 (85.3)	Reference		191 (80.6)	Reference	
Yes	1701 (11.5)	113 (14.3)	1.08	0.85-1.37	92 (14.7)	1.10	0.84-1.43	46 (19.4)	1.58	1.08-2.30
Insulin										
No	13667 (92.6)	703 (88.9)	Reference		552 (88.0)	Reference		199 (84.0)	Reference	
Yes	1099 (7.4)	88 (11.1)	1.21	0.91-1.60	75 (12.0)	1.30	0.96-1.77	38 (16.0)	2.64	1.78-3.92
Other diabetes treatment										
No	13533 (91.6)	713 (90.1)	Reference		570 (90.9)	Reference		215 (90.7)	Reference	
Yes	1233 (8.4)	78 (9.9)	0.85	0.64-1.12	57 (9.1)	0.75	0.55-1.05	22 (9.3)	0.83	0.52-1.33

[a] Ever use was defined as having at least one prescription of a given drug after diagnosis, but the cox models defined ever use as time-varying such that at risk time before one becomes a user contributes to the non-user 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, and diabetes.

Table 2.2: Diabetes treatments and risk of adverse breast cancer outcomes among treated diabetic women

Ever use after breast cancer diagnosis	All women	SBCE			Recurrence			Breast cancer death		
	n= 3460	n= 195			n= 156			n= 73		
	n (%)[a]	n (%)[a]	HR[b]	95% CI	n (%)[a]	HR[b]	95% CI	n (%)[a]	HR[b]	95% CI
Among all treated diabetic women										
Metformin										
No	988 (28.6)	75 (38.5)	Reference		62 (39.7)	Reference		43 (58.9)	Reference	
Yes	2472 (71.4)	120 (61.5)	0.61	0.46-0.82	94 (60.3)	0.57	0.42-0.79	30 (41.1)	0.31	0.20-0.50
Sulfonylureas										
No	1785 (51.6)	91 (46.7)	Reference		71 (45.5)	Reference		29 (39.7)	Reference	
Yes	1675 (48.4)	104 (53.3)	1.03	0.78-1.37	85 (54.5)	1.07	0.78-1.47	44 (60.3)	1.45	0.91-2.29
Insulin										
No	2380 (68.8)	116 (59.5)	Reference		88 (56.4)	Reference		37 (50.7)	Reference	
Yes	1080 (31.2)	79 (40.5)	1.15	0.85-1.57	68 (43.6)	1.27	0.90-1.78	36 (49.3)	2.28	1.44-3.60
Among all treated diabetic women excluding insulin users										
Metformin										
No	462 (19.4)	32 (27.6)	Reference		26 (29.5)	Reference		17 (45.9)	Reference	
Yes	1918 (80.6)	84 (72.4)	0.60	0.40-0.88	62 (70.5)	0.55	0.35-0.87	20 (54.1)	0.35	0.19-0.65
Sulfonylurea										
No	1219 (51.2)	51 (44.0)	Reference		40 (45.5)	Reference		12 (32.4)	Reference	
Yes	1161 (48.8)	65 (56.0)	1.10	0.76-1.60	48 (54.5)	1.05	0.68-1.60	25 (67.6)	1.90	0.99-3.64

[a] Ever use was defined as having at least one prescription of a given drug after diagnosis, but the cox models defined ever use as time-varying such that at risk time before one becomes a user contributes to the non-user 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 therapy (time-varying) and hypertension.

Table 2.3: Diabetes treatments and risk of adverse breast cancer outcomes by time of initiation

Ever use after breast cancer diagnosis	All women	SBCE			Recurrence			Breast cancer death		
	n=11494	n=537			n=414			n=134		
	n (%)[a]	n (%)[a]	HR[b]	95% CI	n (%)[a]	HR[b]	95% CI	n (%)[a]	HR[b]	95% CI
Metformin										
Never users	9277 (80.7)	438 (81.6)	Reference		338 (81.6)	Reference		110 (82.1)	Reference	
Continuous user [c]	1463 (12.7)	62 (11.5)	0.79	0.58-1.08	44 (10.6)	0.68	0.47-0.99	15 (11.2)	0.43	0.24-0.77
Began use after cancer diagnosis [d]	484 (4.2)	21 (3.9)	0.87	0.51-1.48	19 (4.6)	0.98	0.56-1.72	4 (3.0)	0.61	0.22-1.71
Sulfonylurea										
Never users	10010 (87.1)	457 (85.1)	Reference		351 (84.8)	Reference		100 (74.6)	Reference	
Continuous user [c]	976 (8.5)	50 (9.3)	1.10	0.80-1.54	38 (9.2)	1.08	0.74-1.58	18 (13.4)	1.14	0.64-2.02
Began use after cancer diagnosis [d]	289 (2.5)	21 (3.9)	1.56	0.92-2.62	18 (4.3)	1.79	1.04-3.08	11 (8.2)	3.15	1.59-6.25
Insulin										
Never users	10625 (92.4)	473 (88.1)	Reference		359 (86.7)	Reference		106 (79.1)	Reference	
Continuous user [c]	519 (4.5)	26 (4.8)	1.17	0.77-1.78	22 (5.3)	1.33	0.84-2.11	14 (10.4)	2.21	1.20-4.06
Began use after cancer diagnosis [d]	301 (2.6)	35 (6.5)	2.05	1.30-3.24	31 (7.5)	2.52	1.56-4.06	12 (9.0)	3.32	1.73-6.37

[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. Percentages may not add up to 100% as those who stopped using the treatment after cancer were dropped from the analyses on that particular type of treatment.

[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 hormone therapy (time-varying), hypertension, and diabetes.

[c] Time-fixed models were used to calculate HRs and associated 95% CIs comparing continuous users vs. never users.

[d] Time-varying cox models were used to calculate HRs and associated 95% CIs comparing those who began using the medication after cancer and never users such that at risk time before one became a user contributes to the non-user category.

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