Published OnlineFirst September 21, 2017; DOI: 10.1158/0008-5472.CAN-17-0687

Prevention and Epidemiology

Cancer Research

Diabetes Treatments and Risks of Adverse Breast Cancer Outcomes among Early-Stage Breast Cancer Patients: A SEER-Medicare Analysis

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Abstract

The widely prescribed diabetes medicine metformin has been reported to lower the risk of incident breast cancer, but it is unclear whether it affects malignant progression after diagnosis. In this study, we conducted a retrospective cohort study using the linked Surveillance, Epidemiology, and End-Results (SEER)-Medicare database. Women were included in the study if they were aged 66 to 80 years, newly diagnosed with stage I or II breast cancer, and enrolled in Medicare Parts A, B, and D during 2007 to 2011. Information on dispensed diabetes-related medications was obtained from Medicare Part D claims data. Our primary outcomes were second breast cancer events (SBCE), breast cancer recurrence, and breast cancer death. Time-varying Cox proportional hazard models were used to estimate HRs and their 95% confidence intervals (CI). Among 14,766 women included in the study, 791 experienced SBCE, 627 had a recurrence, and 237 died from breast cancer. Use of metformin (n = 2,558) was associated with 28% (95% CI, 0.57–0.92), 31% (95% CI, 0.53–0.90), and 49% (95% CI, 0.33–0.78) lower risks of an SBCE, breast cancer recurrence, and breast cancer death. Use of sulfonylureas or insulin was associated with 1.49- (95% CI, 1.00–2.23) and 2.58-fold (95% CI, 1.72–3.90) higher risks of breast cancer death. Further research may be warranted to determine whether metformin is a preferred treatment for diabetes among breast cancer survivors and whether it benefits breast cancer patients without diabetes. *Cancer Res; 77(21); 6033–41. ©2017 AACR.*

Introduction

Type II diabetes is a common chronic condition characterized by hyperglycemia, insulin resistance, and impaired insulin secretion. There are approximately 29.1 million people with diabetes in the United States, with 17.9 million currently using prescription medications to manage their disease (1). There are also an estimated 3.0 million breast cancer survivors in the United States (2), a growing and aging population frequently burdened with multiple chronic conditions including diabetes. Furthermore, diabetes itself is a risk factor for worse breast cancer progression: breast cancer patients with diabetes have 1.2- to 1.6-fold, 1.3- to 2.3-fold, and 1.16- to 1.25-fold higher risks of breast cancer recurrence (3, 4), second primary breast cancer (5, 6), and breast cancer death (7, 8) compared with those without diabetes.

Metformin, a biguanide used as a first-line treatment for type II diabetes, has been at the center of recent investigations for its potential as a breast cancer chemopreventive agent. Recent meta-analyses report a 13% to 17% lower risk of incident breast cancer associated with metformin use (9, 10), but relatively few studies have assessed metformin use after a diagnosis of breast cancer in relation to adverse breast cancer outcomes. Only one phase III trial on metformin and breast cancer survival has been initiated and is to be completed in 2020 (principal investigator: Pamela J. Goodwin, ClinicalTrials.gov identifier: NCT01101438). In terms of observational studies, a large Canadian cohort study (n = 1,094 for metformin users) observed a modest reduction in case fatality (9% per year of metformin use, but this reduction was not statistically significant; ref. 11). Three small U.S. studies (12–14) observed that metformin use was associated with a lower risk of distant metastasis and breast cancer death, and a better treatment response, but two recent U.S. studies did not (3, 15). A key limitation of the U.S. studies was their small sample size (n = 63–275 metformin users).

The purpose of this study was to assess how use of different types of diabetes medications is related to risk of different breast cancer outcomes.

Patients and Methods

We conducted a retrospective cohort study using 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 (Seattle, WA). Details regarding the SEER-Medicare database have been described

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Note: Supplementary data for this article are available at Cancer Research Online (http://cancerres.aacrjournals.org/).

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doi: 10.1158/0008-5472.CAN-17-0687

Published OnlineFirst September 21, 2017; DOI: 10.1158/0008-5472.CAN-17-0687

elsewhere (16). Briefly, the SEER program of the NCI consists of population-based tumor registries serving 18 geographic areas in the United States, encompassing 28% of the U.S. population. These cancer registries routinely collect cancer incidence and survival data including patient demographic and clinical factors. Medicare provides health insurance to 97% of individuals 65 years or older in the United States, covering inpatient care (Part A), physician service and outpatient care (Part B), and prescription drugs (Part D). SEER data and Medicare data are then linked on the basis of 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 women between 66 and 80 years of age, newly diagnosed with stage I/II breast cancer during 2007 to 2011 who were enrolled in Medicare Parts A/B/D at the time of diagnosis with no concurrent enrollment in a Medicare HMO (women who were not eligible for the study due to lack of enrollment to Medicare Part A/B/D or enrollment in a Medicare

Table 1. Characteristics of women diagnosed with stage I or II breast cancer during 2007–2011

	All ($n = 14,766$) *n* (%)	SBCE ($n = 791$) *n* (%)	Recurrence ($n = 627$) *n* (%)	Breast cancer death ($n = 237$) *n* (%)
Demographic factors				
Year of diagnosis				
2007	2,873 (19.5)	239 (30.2)	202 (32.2)	96 (40.5)
2008	2,921 (19.8)	222 (28.1)	169 (27.0)	79 (33.3)
2009	2,935 (19.9)	152 (19.2)	111 (17.7)	37 (15.6)
2010/2011[a]	6,037 (40.8)	178 (22.5)	145 (23.1)	25 (10.5)
Age at diagnosis (in years)				
66–70	5,804 (39.3)	318 (40.2)	246 (39.2)	84 (35.4)
71–75	4,937 (33.4)	251 (31.7)	196 (31.3)	67 (28.3)
76–80	4,025 (27.3)	222 (28.1)	185 (29.5)	86 (36.3)
Race/ethnicity				
Non-Hispanic white	11,899 (81.0)	608 (77.2)	475 (76.0)	175 (73.8)
African American	1,120 (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)	—[a]
American Indian/Native American	49 (0.3)	—[a]	—[a]	—[a]
Unknown	82	—[a]	—[a]	—[a]
Marital status				
Married	6,895 (46.7)	358 (45.3)	288 (45.9)	91 (38.4)
Widowed	4,043 (27.4)	216 (27.3)	172 (27.4)	84 (35.4)
Single/unmarried	1,368 (9.3)	70 (8.8)	55 (8.8)	24 (10.1)
Other	2,460 (16.7)	147 (18.6)	112 (17.9)	38 (16.0)
Tumor characteristics of the first breast cancer				
Stage at diagnosis				
I	9,410 (63.7)	294 (37.2)	203 (32.4)	54 (22.8)
II	5,356 (36.3)	497 (62.8)	424 (67.6)	183 (77.2)
ER/PR status				
ER^+/PR^+	10,413 (70.5)	394 (49.8)	303 (48.3)	75 (31.6)
ER^-/PR^-	1,908 (12.9)	239 (30.2)	201 (32.1)	109 (46.0)
ER^+/PR^-	1,707 (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[b]				
No	2,550 (17.3)	151 (19.1)	97 (15.5)	46 (19.4)
Yes	12,216 (82.7)	640 (80.9)	530 (84.5)	191 (80.6)
Receipt of chemotherapy				
No	11,512 (78.0)	477 (60.3)	357 (56.9)	138 (58.2)
Yes	3,254 (22.0)	314 (39.7)	270 (43.1)	99 (41.8)
Ever use of hormone treatment since diagnosis (only among ER+ cases)				
No	1,819 (15.0)	105 (20.3)	62 (15.6)	24 (22.2)
Yes	10,301 (85.0)	411 (79.7)	336 (84.4)	84 (77.8)
Other comorbidities at diagnosis				
Diabetes				
No	10,222 (69.2)	534 (67.5)	423 (67.5)	147 (62.0)
Yes	4,544 (30.8)	257 (32.5)	204 (32.5)	90 (38.0)
Hypertension				
No	3,399 (23.0)	159 (20.1)	122 (19.5)	44 (18.6)
Yes	11,367 (77.0)	632 (79.9)	505 (80.5)	193 (81.4)

[a]Cannot be displayed or collapsed due to restrictions regarding the publication of small cells in the data use agreement.
[b]A complete first course of treatment was defined as receiving either a total mastectomy or breast-conserving surgery with radiation.

Published OnlineFirst September 21, 2017; DOI: 10.1158/0008-5472.CAN-17-0687

HMO were in general comparable with women included in the study with respect to demographic and breast cancer characteristics (see Supplementary Table S1). Cancer patients with unknown month of diagnosis were excluded. Among a total of 16,397 breast cancer cases identified, women were excluded if they 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 incident breast cancer diagnosis; or did not have at least 12 months of continuous enrollment in Part A/B/D after their initial breast cancer diagnosis (unless they died during the first 12 months; $n = 548$). This left a final cohort of 14,766 women.

Exposure assessment

Use of metformin, a sulfonylurea, insulin, or other diabetes medications (meglitinides, glitazones, acarbose, exenatide, liraglutide, miglitol, pramlintide acetate, saxagliptin, sitagliptin, and tolbutamide) after breast cancer diagnosis were our exposures of interest. Medicare Part D data during 2007 to 2012 were obtained, including information on medications dispensed, dispensing dates, and days of supply dispensed. Women were defined as users of a given medication at the day a medication in the class of interest was first dispensed after breast cancer diagnosis and would remain in the user category throughout the follow-up.

Table 2. Select patient and disease characteristics by baseline diabetes status and ever use of metformin[a]

	Baseline diabetes status		Among women with diabetes	
	No ($n = 10,222$) *n* **(%)**	**Yes ($n = 4,544$)** *n* **(%)**	**Nonusers ($n = 2,287$)** *n* **(%)**	**Users of metformin ($n = 2,257$)** *n* **(%)**
Year of diagnosis				
2007	2,126 (20.8)	747 (16.4)	307 (13.4)	440 (19.5)
2008	2,097 (20.5)	824 (18.1)	381 (16.7)	443 (19.6)
2009	2,007 (19.6)	928 (20.4)	499 (21.8)	429 (19.0)
2010	1,993 (19.5)	951 (20.9)	488 (21.3)	463 (20.5)
2011	1,999 (19.6)	1,094 (24.1)	612 (26.8)	482 (21.4)
Age at diagnosis				
66–70	4,214 (41.2)	1,590 (35.0)	721 (31.5)	869 (38.5)
71–75	3,329 (32.6)	1,608 (35.4)	794 (34.7)	814 (36.1)
76–80	2,679 (26.2)	1,346 (29.6)	772 (33.8)	574 (25.4)
Stage at diagnosis				
I	6,729 (65.8)	2,681 (59.0)	1,335 (58.4)	1,346 (59.6)
II	3,493 (34.2)	1,863 (41.0)	952 (41.6)	911 (40.4)
Tumor grade				
1	2,995 (29.3)	1,148 (25.3)	589 (25.8)	559 (24.8)
2	4,563 (44.6)	1,976 (43.5)	959 (41.9)	1,017 (45.1)
3	2,222 (21.7)	1,179 (25.9)	607 (26.5)	572 (25.3)
4	55 (0.5)	23 (0.5)	10 (0.4)	13 (0.6)
Others/unknown	387 (3.8)	218 (4.8)	122 (5.3)	96 (4.3)
Tumor size (in mm)				
1–10	3,521 (34.4)	1,302 (28.7)	618 (27.0)	684 (30.3)
11–25	5,058 (49.5)	2,326 (51.2)	1,180 (51.6)	1,146 (50.8)
26–50	1,309 (12.8)	759 (16.7)	406 (17.8)	353 (15.6)
>50	154 (1.5)	75 (1.7)	36 (1.6)	39 (1.7)
Others/unknown	180 (1.8)	82 (1.8)	47 (2.1)	35 (1.6)
Positive lymph nodes				
All negative	8,009 (78.4)	3,356 (73.9)	1,674 (73.2)	1,682 (74.5)
1–3	1,636 (16.0)	869 (19.1)	435 (19.0)	434 (19.2)
≥4	38 (0.4)	16 (0.4)	6 (0.3)	10 (0.4)
Others/unknown	539 (5.3)	303 (6.7)	172 (7.5)	131 (5.8)
ER/PR status				
ER^+/PR^+	7,208 (70.5)	3,205 (70.5)	1,632 (71.4)	1,573 (69.7)
ER^-/PR^-	1,318 (12.9)	590 (13.0)	285 (12.5)	305 (13.5)
ER^+/PR^-	1,208 (11.8)	499 (11.0)	243 (10.6)	256 (11.3)
ER^-/PR^+	70 (0.7)	33 (0.7)	20 (0.9)	13 (0.6)
Unknown	418 (4.1)	217 (4.8)	107 (4.7)	110 (4.9)
Receipt of radiation treatment				
No	4,298 (42.0)	2,265 (49.8)	1,179 (51.6)	1,086 (48.1)
Yes	5,686 (55.6)	2,187 (48.1)	1,062 (46.4)	1,125 (49.8)
Unknown	238 (2.3)	92 (2.0)	46 (2.0)	46 (2.0)
Receipt of surgery treatment				
Lumpectomy	7,033 (68.8)	2,882 (63.4)	1,445 (63.2)	1,437 (63.7)
Mastectomy	3,189 (31.2)	1,662 (36.6)	842 (36.8)	820 (36.3)
Receipt of chemotherapy				
No	7,967 (77.9)	3,545 (78.0)	1,830 (80.0)	1,715 (76.0)
Yes	2,255 (22.1)	999 (22.0)	457 (20.0)	542 (24.0)
Ever use of hormone treatment since diagnosis (only among ER^+ cases)				
No	1,276 (15.2)	543 (14.7)	299 (15.95)	244 (13.34)
Yes	7,140 (84.8)	3,161 (85.3)	1,576 (84.05)	1,585 (86.66)

[a]Women with two diabetes diagnosis codes [International Statistical Classification of Disease (ICD)-9 code, 250.x] within 180 days of their initial cancer diagnosis were identified as having baseline diabetes. Use of metformin was defined as ever use of the medication study's follow-up period.

Published OnlineFirst September 21, 2017; DOI: 10.1158/0008-5472.CAN-17-0687

Outcome assessment

Second breast cancer events (SBCE), 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. We used a high-specificity algorithm to identify SBCE (sensitivity = 89%, specificity = 99% in the original validation study) and recurrence (sensitivity = 69%, specificity = 99%), as prioritizing specificity is desired to reduce bias in studies using algorithms to identify outcomes (17). The algorithm uses procedure codes, diagnoses codes, frequency, and timing of these events to identify SBCEs and recurrence and have been validated against medical records abstraction in different settings (list of codes has been published elsewhere; refs. 18, 19). Breast cancer death was determined using SEER data, which included primary cause of death abstracted from death certificates. Date of death was obtained using Medicare data, and the agreement of vital status between SEER and Medicare data were >99.0% for the study cohort. To enhance the likelihood that the procedures and diagnoses captured in the algorithm were truly related to breast cancer secondary events rather than the first course treatment for the initial cancer, the assessment of all outcomes started 180 days after the breast cancer diagnosis (our exclusion criteria ensured that all women in the cohort survived at least 180 days after cancer diagnosis). Because of availability of the data based on the most recent SEER-Medicare linkage at the time of analyses, the last day of follow-up was December 31, 2012, for SBCEs and recurrence, and December 31, 2011, for breast cancer death.

Statistical analyses

Time-varying cause-specific Cox proportional hazards models were used to estimate HRs and 95% confidence intervals (CI) for the associations between postcancer use of diabetes treatments (yes vs. no) 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 after cancer diagnosis. In addition to evaluating ever use after cancer diagnosis, we also examined 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 as: 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 (stoppers were dropped due to small numbers). Separate time-varying Cox models were constructed to compare risks across these categories of women.

All 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, receipt of chemotherapy, use of adjuvant hormone therapy, baseline diabetes, and baseline hypertension (as grouped in Table 1). As only stage I and II cases were included, a complete first course of treatment was defined as receiving either a total mastectomy or breast-conserving surgery with radiation. Primary treatments less than this were considered an incomplete first course of treatment. Receipt of chemotherapy was defined by any related claims within 180 days of the breast cancer diagnosis. Use of adjuvant hormonal therapy was defined as having any dispensings for tamoxifen, raloxifene, toremifene, anastrozole, letrozole, exemestane, leuprolide, or goserelin after cancer diagnosis and was modeled as a time-varying covariate. A woman with two diagnoses codes of diabetes [International Statistical Classification of Disease (ICD)-9 code, 250.x] or hypertension (ICD-9 code, 401.x) within 180 days of the initial cancer diagnosis was identified as having the respective condition at baseline (data before cancer diagnosis were used to supplement the identification of these two conditions). Other potential confounders assessed were race/ethnicity and marital status, but neither materially changed the risk estimates and thus were not included in the final models. We assessed potential effect modification by ER status and stage of women's first breast cancer using Wald tests while adjusting for all other covariates, but none of the interaction terms was statistically significant at $P < 0.05$.

A set of sensitivity analyses were conducted to further explore these associations. To evaluate potential confounding by indication, we restricted analyses to women with diabetes who had used at least one of the antidiabetic agents (n = 3,189) after 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

Table 3. Risk of adverse breast cancer outcomes by diabetes treatment among women diagnosed with stage I/II breast cancer, 2007–2011

Ever use after breast cancer diagnosis	All women N = 14,766 n (%)[a]	SBCE n = 791 n (%)[a]	SBCE n = 791 HR[b] (95% CI)	Recurrence n = 627 n (%)[a]	Recurrence n = 627 HR[b] (95% CI)	Breast cancer death n = 237 n (%)[a]	Breast cancer death n = 237 HR[b] (95% CI)
Metformin							
No	12,208 (82.7)	661 (83.6)	Reference	524 (83.6)	Reference	205 (86.5)	Reference
Yes	2,558 (17.3)	130 (16.4)	0.72 (0.57–0.92)	103 (16.4)	0.69 (0.53–0.90)	32 (13.5)	0.51 (0.33–0.78)
Sulfonylureas							
No	13,065 (88.5)	678 (85.7)	Reference	535 (85.3)	Reference	191 (80.6)	Reference
Yes	1,701 (11.5)	113 (14.3)	1.04 (0.81–1.33)	92 (14.7)	1.07 (0.81–1.40)	46 (19.4)	1.49 (1.00–2.23)
Insulin							
No	13,667 (92.6)	703 (88.9)	Reference	552 (88.0)	Reference	199 (84.0)	Reference
Yes	1,099 (7.4)	88 (11.1)	1.17 (0.88–1.56)	75 (12.0)	1.28 (0.94–1.75)	38 (16.0)	2.58 (1.72–3.90)
Other diabetes treatment							
No	13,533 (91.6)	713 (90.1)	Reference	570 (90.9)	Reference	215 (90.7)	Reference
Yes	1,233 (8.4)	78 (9.9)	0.80 (0.60–1.07)	57 (9.1)	0.72 (0.51–1.00)	22 (9.3)	0.75 (0.46–1.21)

[a]Ever use was defined as having at least one prescription of a given drug after diagnosis for the purpose of presenting number of users, but 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, and diabetes.

Published OnlineFirst September 21, 2017; DOI: 10.1158/0008-5472.CAN-17-0687

for the same set of covariates as in the primary analyses except for diabetes status. We also created a cohort of women who were only using one of the diabetes treatments (i.e., monotherapy users) for at least some time and compared use of other treatments against metformin. These subsets of women were created in a time-varying fashion such that a diabetic woman would enter the pharmacologically treated subcohort when she first filled a prescription of any diabetes treatments examined in the study and would then be censored at her first filled prescription of insulin for the analyses among treated diabetic patients excluding insulin users. Similarly, for analyses assessing the possible influence of monotherapy, the follow-up of women would be censored at the date they started another diabetes treatment.

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 (these events were not mutually exclusive; Table 1). Compared with the overall cohort, women who had one of these outcomes had substantially higher proportions of ER^-/PR^- tumors (30%–46% among women with events compared with 12.9% overall) and stage II diseases (63%–77% among women with events compared with 36.3% overall). Women with these outcomes were also somewhat less likely to be non-Hispanic white and to be on adjuvant hormonal therapy if they had ER^+ breast cancers. They were somewhat more likely to be older, to have received chemotherapy, and to have diabetes and hypertension at cancer diagnosis. Comparisons of select patient and disease characteristics by baseline diabetes status and post-cancer metformin use are presented in Table 2. Women with diabetes at baseline were more likely to have tumors that were stage II, node positive, and of higher grade and larger size. However, among women with diabetes, these characteristics were similar between women who ever used metformin after cancer diagnosis versus those who did not.

In multivariate adjusted analyses, metformin users had 28%, 31%, and 49% lower risks of a SBCE (95% CI, 0.57–0.92), breast cancer recurrence (95% CI, 0.53–0.90), or breast cancer death (95% CI, 0.33–0.78) compared with nonusers of metformin (Table 3). Use of a sulfonylurea or insulin was associated with 1.49 (95% CI, 1.00–2.23) and 2.58-fold (95% CI, 1.72–3.90)

Table 4. Risk of adverse breast cancer outcomes among treated diabetic women, 2007–2011[a]

Ever use after breast cancer diagnosis	All n[b]	SBCE n[b]	SBCE HR[c] (95% CI)	Recurrence n[b]	Recurrence HR[c] (95% CI)	Breast cancer death n[b]	Breast cancer death HR[c] (95% CI)
Among all treated diabetic women (n = 3,189)							
Metformin							
No	932 (29.2)	71 (38.8)	Reference	58 (40.3)	Reference	40 (58.0)	Reference
Yes	2,257 (70.8)	112 (61.2)	0.62 (0.46–0.83)	86 (59.7)	0.58 (0.41–0.81)	29 (42.0)	0.34 (0.21–0.55)
Sulfonylureas							
No	1,585 (49.7)	82 (44.8)	Reference	62 (43.1)	Reference	28 (40.6)	Reference
Yes	1,604 (50.3)	101 (55.2)	1.04 (0.78–1.40)	82 (56.9)	1.11 (0.80–1.55)	41 (59.4)	1.34 (0.82–2.17)
Insulin							
No	2,138 (67.0)	106 (57.9)	Reference	78 (54.2)	Reference	34 (49.3)	Reference
Yes	1,051 (33.0)	77 (42.1)	1.15 (0.84–1.57)	66 (45.8)	1.27 (0.90–1.80)	35 (50.7)	2.42 (1.50–3.91)
Other diabetes treatments							
No	2,025 (63.5)	112 (61.2)	Reference	92 (63.9)	Reference	47 (68.1)	Reference
Yes	1,164 (36.5)	71 (38.8)	0.77 (0.56–1.06)	52 (36.1)	0.68 (0.47–0.97)	22 (31.9)	0.73 (0.44–1.23)
Among all treated diabetic women excluding insulin users (n = 2,138)							
Metformin							
No	418 (19.6)	29 (27.4)	Reference	23 (29.5)	Reference	15 (44.1)	Reference
Yes	1,720 (80.4)	77 (72.6)	0.58 (0.39–0.88)	55 (70.5)	0.53 (0.33–0.87)	19 (55.9)	0.37 (0.18–0.73)
Sulfonylurea							
No	1,038 (48.6)	44 (41.5)	Reference	33 (42.3)	Reference	12 (35.3)	Reference
Yes	1,100 (51.4)	62 (58.5)	1.15 (0.78–1.69)	45 (57.7)	1.12 (0.71–1.76)	22 (64.7)	1.76 (0.86–3.60)
Other diabetes treatments							
No	1,397 (65.3)	62 (58.5)	Reference	48 (61.5)	Reference	—[d]	Reference
Yes	741 (34.7)	44 (41.5)	0.82 (0.54–1.25)	30 (38.5)	0.67 (0.40–1.10)	—[d]	0.85 (0.41–1.78)
Among all treated diabetic women who were only using one diabetes treatment (n = 1,803)							
Metformin	930 (51.6)	31 (34.8)	Reference	25 (35.2)	Reference		
Sulfonylureas	368 (20.4)	24 (27.0)	1.99 (1.14–3.46)	21 (29.6)	2.12 (1.16–3.89)		
Insulin	337 (18.7)	25 (28.1)	2.34 (1.35–4.06)	19 (26.8)	2.25 (1.21–4.21)		
Other diabetes treatments	168 (9.3)	—[d]	1.84 (0.86–3.94)	—[d]	1.49 (0.60–3.70)		

[a]Subsets of women were created in a time-varying fashion such that women entered the cohort when they first filled a prescription of diabetes treatment. For analyses among women only using one treatment, the users of each diabetes treatment were also defined in a similar time-varying fashion and would be censored when they started a second diabetes treatment.

[b]Ever use was defined as having at least one prescription of a given drug after diagnosis for the purpose of presenting number of users, but the Cox models defined ever use as time-varying such that at risk time before one becomes a user contributes to the nonuser category. Counts of monotherapy users were women exclusively used one medication for at least some time (those who later used another medication were included in the counts but censored in the Cox model).

[c]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.

[d]Cannot be displayed due to restrictions regarding the publication of small cells in the data use agreement.

Published OnlineFirst September 21, 2017; DOI: 10.1158/0008-5472.CAN-17-0687

higher risks of breast cancer death, respectively, but not with SBCE or recurrence risk. Couse of multiple diabetes treatment was common among women with diabetes. A total of 1,107 women (49% of all metformin users) filled a prescription for both metformin and sulfonylurea, and 537 (23.8% of all metformin users) filled a prescription for both metformin and insulin during study follow-up (see Supplementary Table S2). In sensitivity analyses where we adjusted for concurrent use of other types of diabetes treatments as time-varying covariates, no meaningful changes in risk estimates were observed. Results regarding breast cancer death were similar when we restricted to 140 cases who had an SBCE prior to death.

Similar patterns in these associations were observed in analyses aimed to reduce confounding by indication that were restricted to women with diabetes receiving any type of antidiabetic medication (Table 4). Use of metformin after breast cancer was associated with 38%, 42%, and 66% lower risks of an SBCE (95% CI, 0.46–0.83), recurrence (95% CI, 0.41–0.81), and breast cancer death (95% CI, 0.21–0.55), respectively, whereas use of insulin was associated with a 2.42-fold (95% CI, 1.50–3.91) higher risk of breast cancer death. Same patterns for metformin use were observed again when further excluding insulin users. In analyses restricted to 1,803 women who were on only one treatment for at least some time during study period, use of sulfonylureas or insulin therapy was associated with 1.99- to 2.34-fold higher risks of all adverse breast cancer outcomes compared with use of metformin.

In another sensitivity analysis in which we compared 930 metformin monotherapy users to 1,355 untreated diabetic women, there was some suggestion that use of metformin was associated with lower risks of all outcomes (SBCE: HR, 0.71; 95% CI, 0.46–1.10; recurrence: HR, 0.72; 95% CI, 0.44–1.17; breast cancer death: HR, 0.80; 95% CI, 0.34–1.88), but due to the reduced sample size, all of these estimates were not statistically significant.

In analyses stratified by time of treatment initiation among the 11,494 women with at least one year of Medicare enrollment prior to breast cancer diagnosis, those who used metformin before their cancer diagnosis and continued using it afterwards had 23%, 34%, and 59% lower risks of an SBCE (95% CI, 0.55–1.06), recurrence (95% CI, 0.45–0.96), and breast cancer death (95% CI, 0.22–0.74), respectively, compared with women who never used metformin (Table 5). There was some suggestion that risks were also lower among women who started using metformin after breast cancer, but these estimates were not statistically significant. We observed 3.08-fold higher risks of breast cancer death for women who started using sulfonylurea after breast cancer, but not among those who had been on sulfonylurea before cancer diagnosis. Similarly, new users of insulin therapy had 1.97- to 3.37-fold higher risks of all adverse outcomes compared with women who never used insulin. Continuous users of insulin also had a 2.14-fold higher risk (95% CI, 1.14–4.00) of breast cancer death compared with never users of insulin.

Discussion

This large population-based cohort study of older breast cancer patients adds to evidence from prior smaller 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 (20). An insulin-

Table 5. Risk of adverse breast cancer outcomes by diabetes treatment stratified by time of initiation

	All women	SBCE		Recurrence		Breast cancer death	
	n = 11,494	*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	9,277 (80.7)	438 (81.6)	Reference	338 (81.6)	Reference	110 (82.1)	Reference
Continuous user	1,463 (12.7)	62 (11.5)	0.77 (0.55–1.06)	44 (10.6)	0.66 (0.45–0.96)	15 (11.2)	0.41 (0.22–0.74)
Began use after cancer diagnosis	484 (4.2)	21 (3.9)	0.83 (0.49–1.41)	19 (4.6)	0.93 (0.54–1.62)	—[c]	0.61 (0.22–1.71)
Sulfonylurea							
Never users	10,010 (87.1)	457 (85.1)	Reference	351 (84.8)	Reference	100 (74.6)	Reference
Continuous user	976 (8.5)	50 (9.3)	1.03 (0.73–1.45)	38 (9.2)	0.99 (0.67–1.47)	18 (13.4)	1.18 (0.65–2.15)
Began use after cancer diagnosis	289 (2.5)	21 (3.9)	1.48 (0.88–2.50)	18 (4.3)	1.72 (0.99–2.96)	—[c]	3.08 (1.53–6.20)
Insulin							
Never users	10,625 (92.4)	473 (88.1)	Reference	359 (86.7)	Reference	106 (79.1)	Reference
Continuous user	519 (4.5)	26 (4.8)	1.08 (0.70–1.68)	22 (5.3)	1.22 (0.75–1.99)	14 (10.4)	2.14 (1.14–4.00)
Began use after cancer diagnosis	301 (2.6)	35 (6.5)	1.97 (1.25–3.13)	31 (7.5)	2.45 (1.52–3.96)	12 (9.0)	3.37 (1.73–6.58)
Other diabetes treatments							
Never users	10,296 (89.6)	473 (88.1)	Reference	366 (88.4)	Reference	115 (85.8)	Reference
Continuous user	643 (5.6)	34 (6.3)	0.99 (0.66–1.47)	24 (5.8)	0.82 (0.51–1.32)	12 (9.0)	0.90 (0.47–1.72)
Began use after cancer diagnosis	255 (2.2)	15 (2.8)	0.82 (0.41–1.60)	—[c]	0.78 (0.36–1.69)	—[c]	0.55 (0.17–1.79)

[a]Analyses were restricted to women enrolled in Medicare Part A/B/D at least 1 year prior to cancer diagnosis. 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. Numbers may not add up to the column total and 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]Cannot be displayed due to restrictions regarding the publication of small cells in the data use agreement.

Published OnlineFirst September 21, 2017; DOI: 10.1158/0008-5472.CAN-17-0687

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 nondiabetic breast cancer patients (21, 22). Metformin may also exert anticancer effects directly through interfering with cellular energy processes through the activation of AMPK, a cellular energy sensor (23). These proposed anticancer properties of metformin are supported by recent evidence from small-scale early-phase trials, in which reduced levels of tumor proliferation biomarkers were observed among nondiabetic women randomly assigned to receive metformin after breast cancer diagnosis (24–26).

Our study observed higher risks of adverse breast cancer outcomes associated with 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 (20), 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 (27, 28). Furthermore, a higher level of fasting insulin has been associated with a higher risk of breast cancer recurrence and death among early-stage breast cancer patients without preexisting diabetes (29). However, few prior studies have addressed a possible adverse influence of use of sulfonylureas or insulin on breast cancer outcomes, with only one observing a 2.2-fold higher risk of breast cancer death among insulin users (3), so the results we obtained regarding these drugs should be interpreted cautiously. Of note, both our study and the previous study (3) observed that insulin use increased risk of breast cancer death but not risks of an SBCE or recurrence.

Confounding by indication is a potential limitation of observational studies of medication use. Type II diabetes itself is an established risk factor for breast cancer progression, and we adjusted for diabetes status in our primary analysis. 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. Furthermore, 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 II 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 women with diabetes and were on diabetes treatment other than insulin, as use of insulin is an indicator of more severe or less well-controlled diabetes. Again though, quite similar associations were observed in this analysis. Another limitation of this claims/registry data–based study is the lack of data on several characteristics that correlate with both diabetes and breast cancer progression. Obesity is of particular importance, given its known positive associations with both diabetes and poor breast cancer outcomes (30, 31). 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. We adjusted for various covariates in our Cox models, but residual confounding is still possible. Although this study focused on 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 and only 5.8% of the entire cohort died of all causes during the study period, limiting its impact on the observed results. Misclassification of SBCE and recurrence is possible with the use of a claims data–based algorithm. As we used an algorithm prioritizing specificity to reduce bias, the algorithm may not be sensitive enough to identify all SBCEs/recurrence as only 140 of 237 breast cancer death cases had a SBCE/recurrence prior to death. A woman was defined as a user of a given medication at her first prescription date after cancer diagnosis, but most of them had more than one prescription of that medication with the average duration of cumulative use ranging from 22 to 26 months across the different diabetes medications studied. However, the follow-up time in our cohort is 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. Of note, in this elderly population, the majority of women (75%) who ever used metformin after breast cancer diagnosis had initiated metformin prior to their breast cancer diagnosis. Although a protective effect was seen among the women who initiated metformin use after their breast cancer diagnosis, its magnitude was smaller than that seen among women who started using metformin prior to their diagnosis, and it is unclear whether this is due to differences in duration of use or timing of initiation. Finally, the population characteristics of our study sample were impacted by several factors, including population characteristics in SEER catchment area (which is generally comparable with total U.S. population except for a slightly higher proportion of foreign-born individuals; ref. 32), requirement of enrollment to Medicare Part A/B without concurrent enrollment to HMO and Part D, possibly limiting the generalizability of our results to younger population and those who receive care in a HMO setting.

In summary, the results of this study suggest that among older women with breast cancer, use of metformin after diagnosis is associated with lower risks of SBCEs, 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 trials (e.g., a presurgical trial with 35 newly diagnosed breast cancer patients with tumor proliferation as the primary outcome; ref. 33) 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. 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, because metformin has been used for diabetes management for decades with a generally good safety

Published OnlineFirst September 21, 2017; DOI: 10.1158/0008-5472.CAN-17-0687

profile, it may prove to have utility in improving outcomes among breast cancer survivors without diabetes.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

The interpretation and reporting of these data are the sole responsibility of the authors.

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Acknowledgments

This study used the linked SEER-Medicare database. The authors acknowledge the efforts of the NCI, the Office of Research, Development and Information, CMS, Information Management Services (IMS), Inc., and the Surveillance, Epidemiology, and End Results (SEER) Program tumor registries in the creation of the SEER-Medicare database.

Grant Support

This work was supported by NCI grant N01-PC-2013-00012 (to C.I. Li).

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Received March 7, 2017; revised June 15, 2017; accepted September 14, 2017; published OnlineFirst September 21, 2017.

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Published OnlineFirst September 21, 2017; DOI: 10.1158/0008-5472.CAN-17-0687

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Published OnlineFirst September 21, 2017; DOI: 10.1158/0008-5472.CAN-17-0687

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Cancer Res 2017;77:6033-6041. Published OnlineFirst September 21, 2017.