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ORIGINAL RESEARCH

Association between prior use of anti-diabetic medication and breast cancer stage at diagnosis

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ABSTRACT

Background: Knowledge regarding antidiabetic medication (ADM) use prior to breast cancer (BC) diagnosis remains limited. The objectives were to (1) evaluate if the prior use of ADM was associated with BC stage at diagnosis and (2) identify and compare patient characteristics among BC patients using different ADMs.

Research design and methods: Newly diagnosed female BC patients exposed to any medication during one year prior to cancer diagnosis were identified in 2008–2013 Linked Surveillance, Epidemiology, and End Results (SEER)-Medicare database. Stage at diagnosis, categorized as early and advanced, was the primary outcome. Chi-square tests were used to compare characteristics and logistic regression models were applied to examine the effect while controlling for patient's characteristics.

Results: A total of 1,719 female BC patients used ADM while 6,084 patients were non-ADM users. Although a higher proportion of ADM users (20.36%) were diagnosed with advanced stage compared to the non-ADM users (14.46%), the difference was not statistically significant after adjusting for the patients' characteristics. Besides, insulin users were more likely to be diagnosed with advanced stage (adjusted odds ratio 1.69; 95% CI 1.15, 2.48) compared to metformin users.

Conclusions: The association between ADM use and BC diagnostic characteristics varied based on different treatments.

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KEYWORDS
Breast cancer; diabetes; stage at diagnosis; medicare beneficiaries

1. Introduction

Cancers and diabetes are two prevalent conditions among older adults and contribute to high medical expenditures in healthcare systems. Although 5-year relative survival rates for women diagnosed with breast cancer have reached approximately 91% in 2007–2013 [1], breast cancer remains the second most common cause of cancer-specific mortality among women in the United States, with estimated 40,610 deaths in 2017 [2]. Among all cancer types, breast cancer accounts for the highest expenditure, estimated at 16.5 USD billion in 2010 [3]. As for diabetes, the Centers for Disease Control and Prevention (CDC) reported that more than 122million adults in the United States are now living with diabetes or prediabetes, including an estimated 1.5 million new cases diagnosed in 2018 [4]. According to the American Diabetes Association (ADA), diabetes accounts for a rising medical expenditure of 245 USD billion in 2012, a 41% increase from previous estimates [5].

The presence of diabetes has been associated with an increased risk of breast cancer and possibly worse cancer survival outcomes. A meta-analysis based on 97 prospective cohort studies among more than 8 million individuals found that diabetes was moderately associated with death from breast cancer [6]. All-cause mortality for breast cancer patients with preexisting diabetes was approximately 50% higher compared to those without [7]. Besides, women with preexisting diabetes might be more susceptible to advanced-staged breast cancers [8]. However, a literature review suggested this breast cancer and diabetes relationship be referred to as just correlation, and concluded that the link between use of diabetes drugs and cancer development based on real-world data is still limited and inconclusive [9]. Specifically, a large population-based study did not show any effect of metformin use on the stage or type of tumors in patients with both breast cancer and diabetes [10]. Besides, in a cross-sectional study, no associations were found between women with diabetes, treated with or without insulin, and breast cancer subtypes [11]. However, in another retrospective case-case design, diabetes medication may have impact on the breast cancer subtypes [12]. These two above study results were largely affected by their limitations in study design. Effect of other antidiabetic medications, such as insulin and sulfonylurea, on the breast cancer stage at diagnosis has not been assessed. Because increasing the relative proportion of early staged breast cancers could reduce cancer mortality [13]. Understanding the relationships between different

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antidiabetic medications and breast cancer diagnosis with a strong study design can inform initiatives to increase early stage diagnoses.

In addition, because disparities in female breast cancer stage upon diagnosis are well-documented in the literature [14], it is imperative to study whether the use of antidiabetic medication varied among women with different sociodemographic characteristics prior to their breast cancer diagnosis and also whether these patterns are associated with breast cancer diagnostic characteristics. Because randomized controlled trials often ignore the inclusion of diversified patient population [15], addressing disparities in research studies is more difficult. Observational studies investigating different antidiabetic medication patterns and their influences on breast cancer diagnostic characteristics are critical to ensure the optimum care of women with breast cancer and diabetes. Therefore, this study aimed to (1) evaluate if different antidiabetic medication use was associated with the stage at breast cancer diagnosis and (2) identify and compare patient characteristics among female patients who used different antidiabetic medications prior to their breast cancer diagnosis.

2. Methods

2.1. Data sources

This longitudinal, retrospective study used the Surveillance, Epidemiology and End Results (SEER)-Medicare database from 2007 to 2013, a linked database between two large population-based databases that provide detailed information about Medicare beneficiaries with cancer claims from the population-based cancer registry. The SEER-Medicare database is a unique data resource that makes it possible to conduct longitudinal research as well as derive incidence- and prevalence-based estimates of cancer-related outcomes stratified by disease site, disease stage, treatment approach, age, and gender. Detailed information on the SEER-Medicare database is published elsewhere [16]. This study was reviewed and approved by the University Institutional Review Board.

2.2. Study population

We identified eligible patients as those who were female, had newly diagnosed breast cancer between 2008 and 2013, and were continuously enrolled in Medicare Parts A, B, and D for 12 months before their cancer diagnosis. Newly diagnosed breast cancer was identified from SEER data, and the first breast cancer records for each patient were included. Patients enrolled in managed care were excluded. Breast cancer patients who had unknown diagnosis stages or did not use any medications within 1 year before cancer diagnosis were excluded from the analysis.

2.3. Exposure

Text string search was used to identify the antidiabetic medication users among female breast cancer patients during 1 year before their breast cancer diagnosis. Using the variable named 'GNN' (Generic Drug Name), records of antidiabetic medications (Table 1) were identified from the Medicare Part D event file. Patients who used at least one additional antidiabetic medication along with metformin were considered as 'Combination Drug Users' based on the American Diabetes Association (ADA) dual and triple therapy recommendation [17]. Both of the breast cancer diagnosis date and prescription date were available in the database. Breast cancer patients who did not use any antidiabetic medication during 1 year before their breast cancer diagnosis were considered as non-users of antidiabetic medications. Antidiabetic medication use was considered as the main predictor variable. Monotherapy users were defined as patients who only used a specific antidiabetic medication such as metformin, insulin, or sulfonylurea throughout the one-year time frame.

Table 1. List of antidiabetic drugs used in this study.

Antidiabetic Medication Group	Drug Name
Alpha Glucosidase Inhibitors	Acarbose
	Miglitol
Biguanide	Metformin
Bile acid sequestrants	Colesevelam
Dipeptyl peptidase-4 (DPP4)	Alogliptin
	Linagliptin
	Saxagliptin
	Sitagliptin
Dopamine receptor agonist	Bromocriptine Mesylate
Meglitinides	Nateglinide
	Repaglinide
Sodium glucose co-transporter 2 (SGLT2)	Canagliflozin
	Dapagliflozin
	Empagliflozin
Sulfonylureas	Glimepiride
	Glipizide
	Glyburide
	Chlorpromide
Thiazolidinedione	Pioglitazone
	Rosiglitazone
Amylin Mimetic	Pramlintide
Glucagon-like peptide-1 (GLP1)	Albiglutide
	Dulaglutide
	Exenatide
	Liraglutide
	Lixisenatide
Insulins	Aspart
	Detemir
	Glargine
	Glulisine
	Human regular
	Human NPH
	Degludec
	Lispro

2.4. Outcomes

The primary outcome of this study was the breast cancer stage at diagnosis. The National Breast Cancer Foundation defined stage 3 and stage 4 breast cancer as cancer that extended beyond the immediate region of the tumor and spread to other areas, respectively [18]. Based on that, stages 0-II were coded as 'early stage breast cancer', and stages III–IV were coded as 'advanced stage breast cancer'.

2.5. Covariates

Demographic information included age (considered as both categorical and continuous in separate models), race (White,

Black, Asian, Hispanic, and others), marital status (married, single, widowed, divorced, and separated), and geographical region. The variable 'geographic region' was categorized in two different ways: geographical location (i.e. Northeast, Midwest, South and West regions) and metropolitan status (Metro and Non-metro), predefined by SEER-Medicare. Comorbidities were summarized by Charlson Comorbidity Index (CCI) for each patient [19]. Lastly, the adapted Diabetes Complications Severity Index (aDCSI) was used to evaluate diabetes severity in each patient; this method has been previously validated in claims data [20]. The aDCSI included seven categories of complications, each of them scored as either 0 (no complication), 1 (non-severe complication), or 2 (severe complication) and overall ranged from 0 to 13. The aDCSI was adjusted in multivariable models to account for the diabetes severity [21].

2.6. Statistical analysis

Patient baseline characteristics were all categorized. Hence, proportions were used to report patient baseline characteristics across cohorts including demographics, comorbidities, and tumor characteristics. Chi-square tests were used to compare the baseline characteristics between antidiabetic medication user and non-user cohorts. Separate multivariable logistic regression models were used to examine: (1) association between any antidiabetic medication use (yes = 1, no = 0) and breast cancer stage at diagnosis, adjusting for age, race, geographic location, metropolitan status, comorbidity index, marital status, and year of breast cancer diagnosis; (2) association between non-metformin antidiabetic medication use and breast cancer stage at diagnosis compared to metformin among the antidiabetic medication users, adjusting for diabetes severity (aDCSI) and all the covariates above; and (3) whether different monotherapy users had similar likelihood of being diagnosed with advanced-stage breast cancer compared to their non-monotherapy user counterparts among the antidiabetic medication users and adjusted for diabetes severity only. Early staged breast cancer diagnosis was considered as the reference group in all logistic regression models. Chi-square tests were further used to compare the baseline characteristics between each monotherapy medication users and all other monotherapy non-user counterparts, respectively. Significance level was set at 0.05 for all statistical analyses, which were performed using SAS 9.4 (SAS Institute, Cary, NC).

3. Results

3.1. Results for baseline characteristics

Of 49,151 fee-for-service female patients with breast cancer diagnosed between 2008 and 2013, only 1,719 patients used antidiabetic medications during the one year before their breast cancer diagnosis, and 6,084 patients were identified as non-antidiabetic medication users in that same period. The remaining patients who did not use any medications during 1 year before their breast cancer diagnosis were excluded. The baseline characteristics of the sample (n = 7,803) are presented in Table 2. Compared to non-antidiabetic users, antidiabetic users were significantly different in age, race, region, marital status, stage at diagnosis, grade, and comorbidities. They were less likely to be white, married, reside in the west, and diagnosed with early breast cancer stages (all $P < 0.01$).

3.2. Multivariable logistic regression for overall cohort

Figure 1 addresses the first multivariable regression model to examine the association between any antidiabetic medication use and breast cancer stage at diagnosis. Overall, compared to non-antidiabetic user counterparts, antidiabetic users had similar odds of being diagnosed with advanced-stage breast cancer (adjusted odds ratio (aOR) 0.97; 95% CI 0.83, 1.14). As one got older, the odds of being diagnosed with advanced staged breast cancer became higher (aOR 1.14; 95% CI 1.06, 1.23). Blacks had higher odds (aOR 1.28; 95% CI 1.06, 1.55) of being diagnosed with advanced-stage breast cancer compared to whites, regardless of whether they used antidiabetic medication or not. Patients who resided in non-metropolitan areas had higher odds (aOR 1.31; 95% CI 1.11, 1.55) of being diagnosed with advanced-stage breast cancer compared to those who resided in metropolitan areas. Single, separated/divorced, or widowed patients had higher odds (aOR 1.70; 95% CI 1.37, 2.10; aOR 1.32; 95% CI 1.07, 1.63; and aOR 1.43; 95% CI 1.21, 1.70, respectively) of being diagnosed with advanced-stage breast cancer compared to married counterparts. A one-unit increase of comorbidity count increased the odds of being diagnosed with advanced-stage breast cancer by 1.16 (aOR 1.16; 95% CI 1.13, 1.19).

3.3. Multivariable logistic regression for antidiabetic medication users

Figure 2 shows the second regression model. Compared to metformin users, patients who used insulin had higher odds of being diagnosed with advanced-stage breast cancer (aOR 1.69; 95% CI 1.15, 2.48). Patients categorized into 'other' antidiabetic medication groups had higher odds (aOR 1.55; 95% CI 1.06, 2.26) of being diagnosed with advanced-stage breast cancer compared to metformin users, but all other antidiabetic medication categories were insignificant. Diabetes severity score (aDCSI) was not a significant predictor in this model.

3.4. Multivariable logistic regression for monotherapy users

Results on disproportionality analysis for monotherapy users are presented in Figure 3. Metformin monotherapy users had lower odds (OR: 0.66; 95% CI 0.45, 0.96) of being diagnosed with advanced-stage breast cancer compared to all other antidiabetic medication users. For insulin monotherapy users, sulfonylurea monotherapy users, and combination drug users, no statistically significant difference was found when compared to their respective counterparts. The diabetes severity index did not have any significant effect on the breast cancer stage at diagnosis in this model.

Table 2. Baseline characteristics of antidiabetic users and non-antidiabetic users among patients before their breast cancer diagnosis.

	Diabetes medication use during one-year period before the breast cancer diagnosis (n, %)		
Characteristics	Yes	No	P Value[±]
Observations	1719 (22.03)	6084 (77.97)	
Age			<0.01
<55	45 (2.62)	193 (3.17)	
55–64	153 (8.90)	328 (5.39)	
65–74	657 (38.22)	2238 (36.79)	
75–84	643 (37.41)	2172 (35.70)	
>85	221 (12.86)	1153 (18.95)	
Race			<0.01
White	1212 (70.51)	5197 (85.42)	
Black	324 (18.85)	534 (8.78)	
Asian	68 (3.96)	144 (2.37)	
Hispanic	50 (2.91)	92 (1.51)	
Others	65 (3.78)	117 (1.92)	
Region			<0.01
Northeast	131 (7.62)	338 (5.56)	
Midwest	178 (10.35)	520 (8.55)	
South	666 (38.74)	2240 (36.82)	
West	744 (43.28)	2986 (49.08)	
Metropolitan Status			0.26
Metropolitan Counties	1409 (81.97)	5058 (83.14)	
Non-Metropolitan Counties	310 (18.03)	1026 (16.86)	
Marital Status			<0.01
Single	212 (12.33)	719 (11.82)	
Married	466 (27.11)	2186 (35.93)	
Separated/Divorced	224 (15.36)	766 (12.59)	
Widowed	687 (39.97)	2099 (34.50)	
Unmarried/Unregistered/Unknown	90 (5.24)	314 (5.16)	
Stage			<0.01
0	287 (16.70)	1229 (20.20)	
I	575 (33.45)	2529 (41.57)	
II	507 (29.49)	1446 (23.77)	
III	186 (10.82)	463 (7.61)	
IV	164 (9.54)	417 (6.85)	
Stage			<0.01
Early	1369 (79.64)	5204 (85.54)	
Advanced	350 (20.36)	880 (14.46)	
Grade			<0.01
1	296 (17.22)	1334 (21.93)	
2	654 (38.05)	2345 (38.54)	
3	530 (30.83)	1685 (27.70)	
4	20 (1.16)	72 (1.18)	
5	219 (12.74)	648 (10.65)	
ER Status			0.44
Positive	1274 (74.11)	4430 (72.81)	
Negative	306 (17.80)	1166 (19.17)	
Borderline and Unknown	139 (8.09)	488 (8.02)	
PR Status			0.65
Positive	1094 (63.64)	3798 (62.43)	
Negative	471 (27.40)	1727 (28.39)	
Borderline and Unknown	154 (8.96)	559 (9.19)	
Cancer Site			0.31
Nipple & Axillary tail of breast	24 (1.40)	82 (1.35)	
Central portion of breast	130 (7.56)	382 (6.28)	
Upper-inner quadrant of breast (UIQ)	186 (10.82)	647 (10.63)	
Lower-inner quadrant of breast (LIQ)	109 (6.34)	367 (6.03)	
Upper-outer quadrant of breast (UOQ)	519 (30.19)	1970 (32.38)	
Lower-outer quadrant of breast (LOQ)	109 (6.34)	396 (6.51)	
Overlapping lesion of breast	360 (20.94)	1333 (21.91)	
Breast, NOS (excludes Skin of breast)	282 (16.40)	907 (14.91)	
Comorbidity			<0.01
0–1	128 (7.45)	2382 (39.15)	
2–3	276 (16.06)	1689 (27.76)	
4–5	395 (22.98)	982 (16.14)	
6–7	329 (19.14)	511 (8.40)	
8+	591 (34.38)	520 (8.55)	
Total Number of Antidiabetic Medication			
1	1162 (67.60)	N/A	
2	430 (25.01)	N/A	
3	109 (6.34)	N/A	
4	18 (1.05)	N/A	

(*Continued*)

Table 2. (Continued).

Characteristics	Diabetes medication use during one-year period before the breast cancer diagnosis (n, %) Yes	No	P Value±
Year			0.74
2008	243 (14.14)	825 (13.56)	
2009	250 (14.54)	832 (13.68)	
2010	242 (14.08)	873 (14.35)	
2011	291 (16.93)	1021 (16.78)	
2012	317 (18.44)	1104 (18.15)	
2013	376 (21.87)	1429 (23.49)	

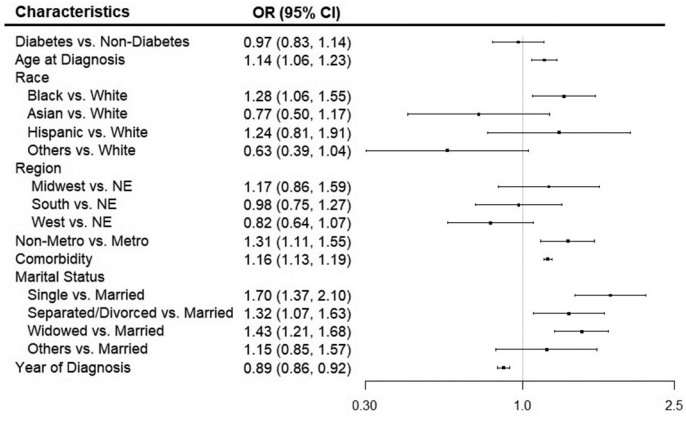

Figure 1. Association between overall antidiabetic medication use and breast cancer stage at diagnosis for overall female breast cancer cohort.

OR: Odds Ratio; CI: Confidence Interval; NE: Northeast.

3.5. Factors associated with monotherapy antidiabetic medication users

Factors associated with monotherapy antidiabetic medication use are presented in Table 3. Metformin and insulin monotherapy users were significantly different in race, age at diagnosis, comorbidity index, stage at diagnosis, and diabetes severity score (aDCSI) compared to their non-user counterparts (all P < 0.01). Metformin monotherapy users were also significantly different in grade (P = 0.03) compared to metformin monotherapy non-users, while insulin monotherapy users were significantly different in geographic region (P = 0.01) compared to their insulin monotherapy non-user counterparts. Sulfonylurea monotherapy users were significantly different in age at diagnosis (P < 0.01), and combination drug users were significantly different in comorbidity index score (P = 0.04) compared to their respective counterparts. Overall, most metformin monotherapy users were white, aged 65–74, resided in West, married, diagnosed as early stage breast cancer, and had diabetes severity scores between 0 and 2 compared to the metformin monotherapy non-users. In contrast, insulin monotherapy users consisted of a higher proportion of Black patients and had more advanced stage breast cancer compared to their insulin monotherapy non-user counterparts. Most of the sulfonylurea monotherapy users were aged 75–84 years old and resided in the South compared to the sulfonylurea monotherapy non-users.

4. Discussion

This large population-based cohort study identified factors associated with different antidiabetic medication use 1 year

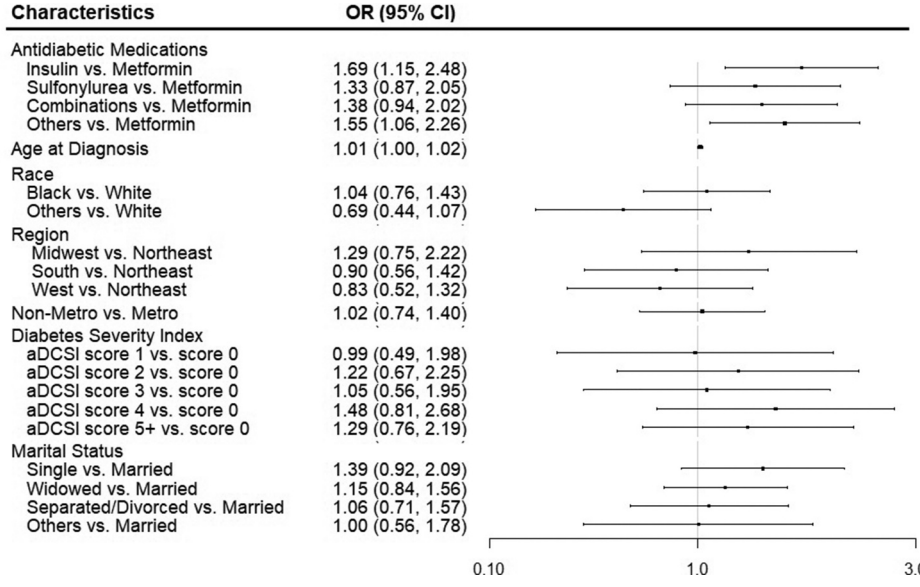

Figure 2. Association between different antidiabetic medication use and breast cancer stage at diagnosis for antidiabetic medication cohort.

OR: Odds Ratio; CI: Confidence Interval.

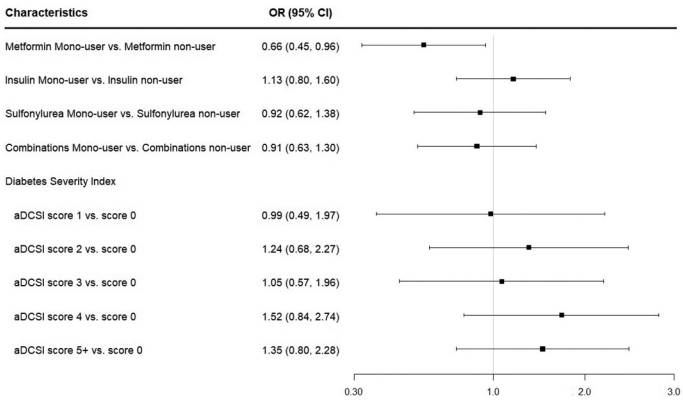

Figure 3. Association between antidiabetic medication mono or combination therapy user and breast cancer stage at diagnosis.

OR: Odds Ratio; CI: Confidence Interval.

prior to the breast cancer diagnosis and examined the effect of those antidiabetic medication use on the breast cancer stage at diagnosis. Almost one-third of those antidiabetic medication users had taken more than one type of antidiabetic medication. Although more antidiabetic users had advanced breast cancer compared to the non-antidiabetic user counterparts, overall, the odds of having advanced-stage breast cancer were similar for groups after controlling for patient characteristics. However, when specific antidiabetic medications were considered, insulin users were more likely to be in the advanced stage group compared to metformin users. Also, different patient and disease characteristics were found to be associated with different antidiabetic medication use among those breast cancer patients such as race, age, region, comorbidity index, and diabetes severity index, etc. Notably, diabetes severity was not a significant predictor in any of those multivariable models.

Blacks had a higher likelihood of being diagnosed with advanced-stage breast cancer compared to whites. Another study using the SEER data from 1995 to 2005 also reported similar findings [22]. However, among the antidiabetic medication cohort, such association was not observed. Multivariable model among the antidiabetic medication cohort was adjusted for diabetes severity with aDCSI and maybe the reason for these varied results. This study also observed higher odds of getting advanced-stage breast cancer among the non-metro population, which could be explained by similar findings from a systematic review [23]. Challenges experienced by the rural residents included difficult access to cancer screening services and greater travel distances to receive primary treatment compared to urban residents. Previous studies showed that patients living in the South experience a higher percentage of advanced-stage breast cancer compared to other regions [23,24]. In contrast, higher likelihood for the Midwest region was observed in this study and such linkage could be attributed to more rural women living in this region compared to the South [23]. Since the relationship between geographic regions and breast cancer is likely multifactorial [24], future research is necessary based on our findings about the complex relationship between these three domains: breast cancer, antidiabetic medication use, and geographic variation. Furthermore, findings regarding marital status are supported by recent evidence from SEER database analysis [25]. In addition, another SEER-Medicare study reported that married women had decreased mortality risk followed by a lower likelihood of getting advanced-stage breast cancer [26].

Our results suggest that patients who used insulin had a higher likelihood of getting advanced stage breast cancer compared to metformin users. This can be explained by the diabetes severity because metformin is the first line of treatment for type 2 diabetes while insulin is related to type 1 diabetes, which refers to more severe diabetes. A recent SEER-Medicare study concluded that diabetes severity was associated with the higher likelihood of having advanced-stage breast cancer diagnosis [27]. However, this study did not show any effect of diabetes severity on the breast cancer stage at diagnosis. One possible reason could be this study used adapted DCSI score, which was validated in claims data, but the previous study did not use this version.

To the best of our knowledge, this is the first study that examined the factors associated with metformin monotherapy, insulin monotherapy, sulfonylurea monotherapy, and antidiabetic combination drug users prior to their breast cancer diagnosis. Metformin, insulin, and sulfonylurea monotherapy users were significantly different in several demographic and tumor characteristics, which could be of interest to policymakers analyzing drug utilization. Racial disparities regarding the use of metformin monotherapy and insulin monotherapy could be a striking finding, but this may seem contradictory to a previous study that reported similar utilization across different racial groups of patients with diabetes [28]. This current study used breast cancer-specific cohort, which may be the reason for inconsistent results. Besides, metformin monotherapy users had less severity index scores while insulin monotherapy users and combination users had higher severity index scores. This study also found significantly higher proportions of early stage breast cancer among metformin monotherapy users. An inverse relationship was observed for insulin monotherapy users. Again, none of the regression models found any effect of diabetes severity index score on breast cancer stage at diagnosis. Therefore, the relationship between diabetes severity and breast cancer stage at diagnosis for each medication is subtle enough to warrant further analysis with a separate concentration on each medication.

In addition, this study examined the association between different antidiabetic monotherapy and breast cancer stage at diagnosis. In the antidiabetic monotherapy user vs. antidiabetic monotherapy non-user analysis, only metformin monotherapy users seemed to have a lower likelihood of getting advanced-stage breast cancer compared to any other antidiabetic medication users. Researchers have long debated whether metformin and breast cancer have some inverse relationship as the exact mechanism is still not clear [29]. Several possible mechanisms of anti-tumor activities of metformin have been described in a recent review [30]. However, it is still unknown why metformin works in some cases while not in others and controversy exists regarding the required

Table 3. Factors associated with different antidiabetic medication use among the breast cancer patients.

Factors	Metformin n = 392 (22.80%)	All other non-user n = 1327 (77.20%)	P-value	Insulin n = 359 (20.88%)	All other non-user n = 1360 (79.12%)	P-value	Sulfonylurea n = 240 (13.96%)	All other non-user n = 1479 (86.04%)	P-value	Combination drugs n = 356 (20.71%)	All other non- users n = 1363 (79.29%)	P-value
Race												
White	296 (75.51)	916 (69.03)	*P = 0.01*	236 (65.74)	976 (71.76)	*P < 0.01*	173 (72.08)	1039 (70.25)	*P = 0.64*	258 (72.47)	954 (69.99)	*P = 0.31*
Black	54 (13.78)	270 (20.35)		93 (25.91)	231 (16.99)		40 (16.67)	284 (19.20)		68 (19.10)	256 (18.78)	
Others	42 (10.71)	141 (10.71)		30 (8.36)	153 (11.25)		27 (11.25)	156 (10.55)		30 (8.43)	153 (11.23)	
Age at Diagnosis												
<65	38 (9.69)	160 (12.06)	*P < 0.01*	52 (14.48)	146 (10.74)	*P < 0.01*	19 (7.92)	179 (12.10)	*P < 0.01*	44 (12.36)	154 (11.30)	*P = 0.13*
65–74	181 (46.17)	476 (35.87)		143 (39.83)	514 (37.79)		64 (26.67)	593 (40.09)		146 (41.01)	511 (37.49)	
75–84	139 (35.46)	504 (37.98)		110 (30.64)	533 (39.19)		105 (43.75)	538 (36.38)		133 (37.36)	510 (37.42)	
≥85	34 (8.67)	187 (14.09)		54 (15.04)	167 (12.28)		52 (21.67)	169 (11.43)		33 (9.27)	188 (13.79)	
Region												
Northeast	23 (5.87)	108 (8.14)	*P = 0.03*	39 (10.86)	92 (6.76)	*P = 0.01*	22 (9.17)	109 (7.37)	*P = 0.04*	23 (6.46)	108 (7.92)	*P = 0.69*
Midwest	39 (9.95)	139 (10.47)		46 (12.81)	132 (9.71)		25 (10.42)	153 (10.34)		34 (9.55)	144 (10.56)	
South	138 (34.69)	530 (39.94)		131 (36.49)	535 (39.34)		109 (45.42)	557 (37.66)		138 (38.76)	528 (38.74)	
West	194 (49.09)	550 (41.45)		143 (39.83)	601 (44.19)		84 (35.00)	660 (44.62)		161 (45.22)	583 (42.77)	
Region												
Metro	318 (81.12)	1091 (82.22)	*P = 0.62*	293 (81.62)	1116 (82.06)	*P = 0.84*	200 (83.33)	1209 (81.74)	*P = 0.55*	72 (20.22)	238 (17.46)	*P = 0.23*
Non-Metro	74 (18.88)	236 (17.78)		66 (18.38)	244 (17.94)		40 (16.67)	270 (18.26)		284 (79.78)	1125 (82.54)	
Marital Status												
Single	49 (12.50)	163 (12.28)	*P = 0.42*	54 (15.04)	158 (11.62)	*P = 0.09*	28 (11.67)	184 (12.44)	*P = 0.92*	40 (11.24)	172 (12.62)	*P = 0.78*
Married	116 (29.59)	350 (26.38)		85 (23.68)	381 (28.01)		64 (26.67)	402 (27.18)		97 (27.25)	369 (27.07)	
Others	227 (57.91)	814 (61.34)		220 (61.28)	821 (60.37)		148 (61.67)	893 (60.38)		219 (61.52)	822 (60.31)	
CCI[a]												
0–2	84 (21.43)	132 (9.95)	*P < 0.01*	15 (4.18)	201 (14.78)	*P < 0.01*	29 (12.08)	187 (12.64)	*P = 0.91*	46 (12.92)	170 (12.47)	*P < 0.01*
3–4	112 (28.57)	250 (18.84)		35 (9.75)	410 (24.04)		54 (22.50)	308 (20.82)		97 (27.25)	265 (19.44)	
5–6	93 (23.72)	297 (22.38)		73 (20.33)	181 (23.31)		56 (23.33)	334 (22.58)		84 (23.60)	306 (22.45)	
7+	103 (26.28)	648 (48.83)		236 (65.74)	170 (37.87)		101 (42.08)	650 (43.95)		129 (36.24)	622 (45.63)	
Stage												
Early	333 (84.95)	1036 (78.07)	*P < 0.01*	270 (75.21)	1099 (80.81)	*P = 0.02*	191 (79.58)	1178 (79.65)	*P = 0.98*	285 (80.06)	1084 (79.53)	*P = 0.83*
Advanced	59 (15.05)	291 (21.93)		89 (24.79)	261 (19.19)		49 (20.42)	301 (20.35)		71 (19.94)	279 (20.47)	
Grade												
Well differentiated	81 (20.66)	215 (16.20)	*P = 0.03*	57 (15.88)	239 (17.57)	*P = 0.82*	43 (17.92)	253 (17.11)	*P = 0.59*	58 (16.29)	238 (17.46)	*P = 0.56*
Moderately differentiated	155 (39.54)	499 (37.60)		135 (37.60)	519 (38.16)		91 (37.92)	563 (38.07)		127 (35.67)	527 (38.66)	
Poorly/ Undifferentiated	120 (30.61)	430 (32.40)		121 (33.70)	429 (31.54)		70 (29.17)	480 (32.45)		121 (33.99)	429 (31.47)	
Others	36 (9.18)	183 (13.79)		46 (12.81)	173 (12.72)		36 (15.00)	183 (12.37)		50 (14.04)	169 (12.40)	
aDCSI score[b]												
0–2	156 (39.80)	293 (22.08)	*P < 0.01*	33 (9.19)	416 (30.59)	*P < 0.01*	63 (26.25)	386 (26.10)	*P = 0.14*	114 (32.02)	335 (24.58)	*P < 0.01*
3–5	150 (38.27)	430 (32.40)		91 (25.35)	489 (35.96)		93 (38.75)	487 (32.93)		124 (34.83)	456 (33.46)	
6+	86 (21.94)	604 (45.52)		235 (65.46)	455 (33.46)		84 (35.00)	606 (40.97)		118 (33.15)	572 (41.97)	

CCI[a] = Baseline Charlson Comorbidity Index; aDCSI[b] = Adapted Diabetes Complications Severity Index.

dose of metformin to achieve a proper therapeutic response. Taking all of these into account, this study findings could be considered as another feather in the cap of the proponents of the theory that metformin may have positive effects on breast cancer diagnostic characteristics.

5. Limitation

This study has several limitations. First, we did not control for the factors that correlate with both diabetes and breast cancer, such as family history, body mass index (BMI), smoking, HbA1c level, diabetes duration, and alcohol use, etc. Among those, obesity is an important factor that has relationship with both diseases [31]. Second, misclassification is also possible in claims data-based algorithm such as algorithms for comorbidity scoring and diabetes severity scoring. However, this study used diabetes severity index which was previously validated in claims database [20]. Third, around 89% of the antidiabetic medication user cohort were older patients (≥65 years old); thus, findings may not be generalizable to younger females with breast cancer. Fourth, the number of prescriptions for each antidiabetic medication was not considered in this study. Therefore, it is possible that some patients only used an antidiabetic medication once in the whole one-year time frame. Fifth, because of the small sample size, this study had to exclude patients with other antidiabetics listed in the Table 1 such as thiazolidinediones, alpha-glucosidase inhibitors, dipeptidyl peptidase-4 (DPP4), and sodium-glucose co-transporter 2 (SGLT2) etc. Future research focusing on these antidiabetics with more recent data are required. Finally, small sample size for each of those monotherapy antidiabetic medication groups was another study limitation, which may lead the results toward the null. Thus, careful interpretation of these results should be practiced.

6. Conclusions

In summary, our findings reemphasized that breast cancer patients who previously used antidiabetic medications had similar odds of having advanced-stage breast cancer diagnosis. When considering diabetes severity, results also suggested that exposure to various antidiabetic medications may pose different risks in stage at breast cancer diagnosis. Future research investigating the causality between antidiabetic medication use and breast cancer diagnostic characteristics are warranted.

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Author contributions

Shahariar Mohammed Fahim: Acquisition, analysis, and interpretation of data; writing–initial draft; and writing–review and editing. Chiu-Hsieh Hsu: Analysis, and interpretation of data; and writing–review and editing. Fang-Ju Lin: Analysis, and interpretation of data; and writing–review and editing. Jingjing Qian: Study concept and design; acquisition, analysis, and interpretation of data; and writing–review and editing. Chiahung Chou: Study concept and design; acquisition, analysis, and interpretation of data; writing–initial draft; writing–review and editing; and study supervision.

Consent for publication

This study did not include any individual person's data in any form, therefore, consent for publication was not required.

Data availability

The data that support the findings of this study are available from Information Management Services, Inc. (IMS), the information technology contractor for National Cancer institute (NCI), but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Information Management Services, Inc. (IMS).

Ethics approval and consent to participate

This study was approved by the Auburn University Institutional Review Board. This study did not include any human participants. No informed consent was required since this study used secondary data.

Disclosure statement

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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