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Research Article

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Relationship between Diabetes and Diabetes Medications and Risk of Different Molecular Subtypes of Breast Cancer

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Abstract

Background: Type II diabetes and certain diabetes treatments have been observed to impact breast cancer risk. However, their associations with different breast cancer molecular subtype defined by estrogen receptor (ER)/progesterone receptor (PR)/HER2 status are unclear.

Methods: We conducted a retrospective multi-center population-based case–case study consisting of 4,557 breast cancer cases to evaluate the impact of type II diabetes and diabetes medications on the risk of different breast cancer molecular subtypes [$ER^+/HER2^-$, $ER^+/HER2^+$, triple negative ($ER^-/PR^-/HER2^-$), and HER2 overexpressing (H2E, $ER^-/PR^-/HER2^+$)]. Using $ER^+/HER2^-$ cases as the reference group, we estimated ORs and corresponding 95% confidence intervals (CI) for each subtype using polytomous logistic regression.

Results: Compared with those without a diabetes history, women with type II diabetes had a 38% (95% CI, 1.01–1.89) increased odds of triple-negative breast cancer (TNBC). Current and longer term recent metformin use (13–24 months of treatment within the 24-month period prior to breast cancer diagnosis) was associated with elevated odds of TNBC (OR = 1.54; 95% CI, 1.07–2.22 and OR = 1.80; 95% CI, 1.13–2.85, respectively).

Conclusions: The odds of having a triple-negative rather than $ER^+/HER2^-$ breast cancer is greater for women with type II diabetes, and particularly for those who were users of metformin. This finding is supported by some preclinical data suggesting that diabetes may be more strongly associated with risk of triple-negative disease.

Impact: Our study provides novel evidence regarding potential differential effects of type II diabetes and metformin use on risk of different molecular subtypes of breast cancer.

Introduction

Breast cancer is the most common cancer diagnosed among women worldwide (1). It is a molecularly heterogeneous disease that can be broadly categorized according to the expression of estrogen receptor (ER), progesterone receptor (PR), and HER2 (2, 3). ER-positive (ER^+) disease represents approximately two thirds of all breast cancers and has a better prognosis compared with the ER-negative (ER^-) subtypes (4, 5) that include both HER2-overexpressing (H2E, $ER^-/HER2^+$) and triple-negative ($ER^-/PR^-/HER2^-$) tumors (2, 6–8). Given this heterogeneity, growing evidence suggests that there is etiologic variability across breast cancer subtypes and there is interest in identifying risk factors specific to the more aggressive H2E and triple-negative phenotypes.

A history of type II diabetes has been associated with a 20% to 27% elevated risk of breast cancer in multiple meta-analyses (9–11). This is thought to be due to the direct impact hyperinsulinemia and hyperglycemia (12, 13) can have on breast epithelial tissue proliferation and their indirect effects on increasing circulating concentrations of estrogen, testosterone, and insulin-like growth factors (IGF; refs. 14, 15). Diabetes treatments such as metformin and insulin have also been implicated in breast cancer risk (16, 17). Metformin, a biguanide oral antidiabetic drug, has been shown in some (18–20) but not all (21–25) studies to reduce breast cancer risk by 17% to 56%. Both *in vivo* and *in vitro* studies have suggested that metformin can potentially lower the risk of breast cancer via hyperinsulinemia reversion, cancer cell growth inhibition, and downregulation of HER2 expression (26–29). Alternatively, patients with diabetes treated with insulin have been observed to have a modestly elevated risk of breast cancer, likely due to its interplay with IGFs on stimulating the proliferation of breast epithelial cells (19, 30–33). However, prior studies have not evaluated how diabetes or diabetes medications impact risk of different breast cancer subtypes. To further understand the impact of type II diabetes and diabetes medications on the risk of breast cancer we conducted a retrospective multi-center population-based case–case study of the major breast cancer subtypes.

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Materials and Methods

Study population

We conducted a population-based case–case study comparing different molecular subtypes of breast cancer defined by joint ER/PR/HER2 status. Details of this study have been published previously (34, 35). Cases were based on the patients with newly diagnosed invasive breast cancer with 20 to 69 years of age between June 1, 2004 and June 30, 2015 in the Seattle, Washington greater metropolitan area (King, Pierce, and Snohomish counties) and between June 1, 2004 and June 30, 2012 in the Albuquerque, New Mexico (Bernalillo, Sandoval, Santa Fe, Socorro, Torrance, and Valencia counties) greater metropolitan area. Only cases with complete tumor marker information were eligible for the study. We targeted all patients categorized as triple-negative ($ER^-/PR^-/HER2^-$) and H2E ($ER^-/PR^-/HER2^+$) molecular subtype for enrollment. In addition, we enrolled a random sample of ER^+ breast cancer cases that were frequency matched to the distribution of age at diagnosis, year of diagnosis, and study site of the triple-negative and H2E cases combined. A total of 4,557 breast cases were enrolled. A total of 217 cases with missing diabetes history data were excluded so the final analytic study population consisted of 4,340 breast cancer cases, including 1,992 $ER^+/HER2^-$, 324 $ER^+/HER2^+$, 1,446 triple negative, and 578 H2E cases. This study was approved by the Institutional Review Boards at the Fred Hutchinson Cancer Research Center (Seattle, Washington) and the University of New Mexico (Albuquerque, New Mexico).

Data collection

Demographic, epidemiologic, and clinical variables were collected through medical records reviews (for both sites) and/or structured telephone interviews (for the Seattle site only). Information on stage, grade, and ER/PR/HER2 status were collected from pathology, surgery, and laboratory reports, and were affirmed through the population-based Surveillance Epidemiology and End Results cancer registries serving the Seattle-Puget Sound and the state of New Mexico. For invasive breast cancer cases diagnosed during the study period in these regions, only a small proportion of patients had missing ER/PR/HER2 data (not exceeding 3% for any of the markers). Having known data for all three markers was an eligibility criterion for enrollment into this study and thus these data were complete for all 4,557 breast cancer cases enrolled. Misclassification of disease subtype, if any, is likely to be nondifferential and not related to diabetes diagnosis and medication use. Data on diabetes history and use of common diabetes medications (recency and duration) were ascertained from both medical records and patient self-reports. Medical records' data were manually abstracted from both electronic medical records and paper charts, which included records from primary care providers, oncologists, and hospital records. Data from medical records were prioritized, and the self-reported data were only used for patients with missing medical record data ($n = 598$). Among the individuals with both medical record and interview data available, we evaluated the concordance between these two sources for our two primary exposures of interest: history of type II diabetes and metformin use. We found strong agreement between these two sources for both exposures (type II diabetes: 96.2% agreement; Cohen $\kappa = 0.75$ and metformin use: 98.4% agreement; Cohen $\kappa = 0.77$). Women were categorized as having a history of type II diabetes if this diagnosis was made prior to their breast cancer diagnosis. Patients with a history of type I diabetes ($n = 17$) or gestational diabetes ($n = 52$), but without a history of type II diabetes were categorized as unexposed. History of diabetes medication use was restricted to the 2-year period prior to breast cancer diagnosis due to the availability of medical records. Recency of diabetes medication use was defined as never use, current use (use within the 6-month period prior to breast cancer diagnosis), and former use (last use >6 months prior to breast cancer diagnosis). Duration of use within the 24-month period prior to breast cancer diagnosis was categorized as none, 1 to 12 months of use, and 13 to 24 months of use. In addition, data on a wide range of established breast cancer risk factors were also collected, including menopausal status, first-degree family history, and use of oral contraceptives and menopausal hormone therapy. A random 10% of completed medical record abstracts were exchanged and reviewed between study sites to insure consistency in abstracting approach, methodology, and coding.

Statistical analysis

We used polytomous logistic regression to estimate ORs and corresponding 95% confidence intervals (CI) to assess associations between type II diabetes and diabetes medications and risks of different molecular subtypes of breast cancer. Patients with $ER^+/HER2^-$ breast cancer served as the reference case group in all analyses. All regression models were adjusted for study site and year of breast cancer diagnosis as matching variables, as well as race/ethnicity, body mass index (BMI, modelled as a continuous variable), and age at breast cancer diagnosis given their associations with both diabetes and breast cancer. Stratified analyses were conducted by study sites (Seattle or New Mexico), age at cancer diagnosis (<55 or 55–69 years old), and BMI at cancer diagnosis (<30 or $\geq$30 kg/m^2). For diabetes medications, we first assessed them in the whole-study population, and then in an analysis restricted to women with diabetes to address potential confounding by indication. We also performed two sensitivity analyses, one restricted to diabetes information ascertained from medical records (excluding the 598 patients without medical record data) and the other excluded patients with a history of either type I or only gestational diabetes ($n = 69$) from the unexposed group. Neither the magnitudes nor directions of our risk estimates changed appreciably in either analysis (data not shown). All analyses were conducted using SAS 9.4 (SAS Institute).

Results

Compared with other breast cancer subtypes, patients with $ER^+/HER2^-$ disease were somewhat more likely to be non-Hispanic white and current users of menopausal hormone therapy (Table 1). Patients in the $ER^+/HER2^+$ group were somewhat younger at breast cancer diagnosis and less likely to be current or former users of menopausal hormone therapy. Triple-negative and $ER^+/HER2^-$ patients more frequently had a first-degree family history of breast cancer. H2E cases were more likely to be diagnosed at an older age, and less likely to be nulliparous and to be users of hormonal contraceptives.

Compared with $ER^+/HER2^-$ cases, women diagnosed with type II diabetes had a 38% increased odds of triple-negative breast cancer (TNBC, 95% CI, 1.01–1.89) compared with those without a history of diabetes (Table 2). The odds of H2E breast cancer was also observed to be elevated among type II diabetics (OR = 1.38; 95% CI, 0.93–2.06), but this estimate was within the limits of

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Table 1. Distribution of demographic variables and breast cancer risk factors by breast cancer subtype in the study population ($n = 4,340$)

Demographic variables	ER$^+$/HER2$^-$ ($n = 1,992$) *N* (%)	ER$^+$/HER2$^+$ ($n = 324$) *N* (%)	Triple negative ($n = 1,446$) *N* (%)	H2E ($n = 578$) *N* (%)
Study site				
Seattle	1,846 (92.7)	291 (89.8)	1,224 (84.6)	465 (80.3)
New Mexico	146 (7.3)	33 (10.2)	222 (15.4)	114 (19.7)
BMI				
<25	797 (40.1)	147 (45.7)	474 (33.0)	219 (38.0)
25–30	544 (27.4)	86 (26.7)	425 (29.6)	187 (32.4)
≥30	645 (32.5)	89 (27.6)	537 (37.4)	171 (29.6)
Missing	6	2	10	1
Race/ethnicity				
Non-Hispanic white	1,628 (81.7)	248 (76.5)	1,119 (77.4)	450 (77.9)
Hispanic white	111 (5.6)	27 (8.3)	117 (8.1)	53 (9.2)
African American	69 (3.5)	15 (4.6)	121 (8.4)	25 (4.3)
Asian/Pacific Islander	150 (7.5)	26 (8.0)	61 (4.2)	40 (6.9)
Native American	34 (1.7)	8 (2.5)	28 (1.9)	10 (1.7)
Age at breast cancer diagnosis				
<40	268 (13.4)	74 (22.8)	206 (14.2)	70 (12.1)
40–49	555 (27.9)	119 (36.7)	409 (28.3)	133 (23.0)
50–59	639 (32.1)	88 (27.2)	457 (31.6)	220 (38.1)
60–69	530 (26.6)	43 (13.3)	374 (25.9)	155 (26.8)
Year of breast cancer diagnosis				
2004–2006	571 (28.7)	75 (23.2)	401 (27.7)	147 (25.4)
2007–2008	420 (21.1)	78 (24.1)	316 (21.9)	120 (20.8)
2009–2010	341 (17.1)	70 (21.6)	269 (18.6)	107 (18.5)
2011–2012	341 (17.1)	50 (15.4)	240 (16.6)	106 (18.3)
2013–2015	319 (16.0)	51 (15.7)	220 (15.2)	98 (17.0)
First-degree family history of breast cancer				
Yes	436 (22.5)	56 (17.7)	326 (23.1)	108 (19.2)
No	1,502 (77.5)	261 (82.3)	1,087 (76.9)	455 (80.8)
Missing	54	7	33	15
Menopausal status				
Premenopausal	962 (49.1)	200 (63.9)	647 (45.7)	248 (43.7)
Postmenopausal	999 (50.9)	113 (36.1)	769 (54.3)	320 (56.3)
Missing	31	11	30	10
Number of full-term pregnancy				
0	485 (24.4)	78 (24.2)	316 (20.5)	116 (20.1)
1	326 (16.4)	66 (20.5)	268 (17.4)	98 (17.0)
2	748 (37.6)	104 (32.3)	594 (38.5)	212 (36.8)
≥3	426 (21.5)	74 (23.0)	363 (23.6)	150 (26.1)
Missing	7	2	5	2
Smoking status				
Never	1,137 (57.2)	185 (57.5)	799 (55.4)	330 (57.2)
Current	309 (15.6)	54 (16.7)	252 (17.5)	102 (17.7)
Former	541 (27.2)	83 (25.8)	391 (27.1)	145 (25.1)
Missing	5	2	4	1
Menopausal hormone use at cancer diagnosis				
Never	1,646 (83.8)	291 (91.5)	1,178 (84.3)	476 (85.6)
Former	108 (5.5)	9 (2.8)	98 (7.0)	41 (7.4)
Current estrogen	97 (4.9)	12 (3.8)	89 (6.4)	29 (5.2)
Current estrogen + progestin	111 (5.7)	6 (1.9)	32 (2.3)	10 (1.8)
Missing	28	6	49	22
History of hormonal contraceptive use at cancer diagnosis				
Never	1,612 (81.9)	251 (79.9)	1,150 (81.5)	492 (87.4)
Former	150 (7.6)	31 (9.9)	153 (10.8)	39 (6.9)
Current within 6 months	207 (10.5)	34 (10.8)	108 (7.7)	32 (5.7)
Missing	23	8	35	15

chance. No significant interactions were detected by study site, BMI, or age at cancer diagnosis (Supplementary Table S1).

Compared with ER$^+$/HER2$^-$ cases, diabetic patients currently taking diabetes had an increased odds of triple-negative disease (OR = 1.41; 95% CI, 1.03–1.95), relative to nondiabetic women (Table 3). Furthermore, current and longer term recent use of metformin were associated with elevated odds of TNBC (OR = 1.54; 95% CI, 1.07–2.22 and OR = 1.80; 95% CI, 1.13–2.85, respectively). Increasing duration of metformin use within the 24-month period prior to breast cancer diagnosis was associated with an increased odds of triple-negative disease ($P_{trend} = 0.01$). These positive associations remained unchanged in analyses restricted to patients with a history of type II diabetes in an effort to account for potential confounding by indication (Table 3).

Discussion

In this analysis we assessed the relationships between type II diabetes and diabetes medications and risk of different molecular subtypes of breast cancer. A history of diabetes, use of diabetes medications, and use of metformin specifically were positively associated with risk of TNBC with some suggestion that they were also positively associated with H2E breast cancer. Type II diabetes is widely accepted as an established risk factor for breast cancer overall (9), but data on specific subtypes is limited. Our results with respect to triple-negative disease are consistent with a handful of small published case–control and cross-sectional studies that have reported that diabetes is associated with risk of TNBC (16, 17, 36). Bronsveld and colleagues reported that diabetes is associated with a nonsignificant 121% higher risk triple-negative disease among premenopausal women cases and a 30% higher risk among postmenopausal women in a cross-sectional study using Danish Breast Cancer Cooperative Group data (17). In a case–control study with 557 patients with breast cancer and 592 controls, Crispo and colleagues reported a 51% increased risk of TNBC in a diabetic population, which was not statistically significant (36). Finally, García-Esquinas, and colleagues conducted a case–control study of postmenopausal women that included 916 breast cancer cases and 1,094 population-based controls (16). It found that diabetes was associated with a 2.25-fold increased risk of TNBC. These three studies were limited by the inclusion of few triple-negative cases (n = 50–91 triple-negative cases across these studies). However, there are also two studies that have found no association between type II diabetes and TNBC. One was the Carolina Breast Cancer Study, which included 225 triple-negative patients (37), and the other was a Mexican case–case study that included 469 triple-negative patients of whom 46 were diabetic (38). Thus, while there is some inconsistency in the literature, ours is the largest of the existing studies and is consistent with three of the five studies.

The biological mechanisms underlying the potential association between diabetes and diabetes medications and risk of TNBC risk are understudied. A primary hypothesized pathway linking diabetes to breast cancer risk overall is the potentially oncogenic effects of elevated insulin and IGF levels as they can promote breast cancer proliferation (39). The expression of IGF receptors has been found to be relatively higher in TNBC cells compared with ER-responsive cells (40), which suggests that this mechanism may be have a more pronounced impact on the development of triple-negative disease. Another possible mechanism relates to elevated cytokine production by adipose tissue that promotes insulin resistance. Evidence suggests that accumulation of cytokines in the breast adipose microenvironment may affect the cell cycle of breast epithelial cells, including increasing cell proliferation and deferring cell death, which are both associated with

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Table 2. Association between breast cancer subtype and type II diabetes diagnosed prior to cancer[a]

History of type II diabetes	$ER^+/HER2^-$ *N* (%)	$ER^+/HER2^+$ *N* (%)	Adjusted OR (95% CI)	Triple negative *N* (%)	Adjusted OR (95% CI)	H2E *N* (%)	Adjusted OR (95% CI)
No	1,863 (93.5)	313 (96.6)	1.00 (ref)	1,322 (91.4)	1.00 (ref)	532 (92.0)	1.00 (ref)
Yes	129 (6.5)	11 (3.4)	0.77 (0.40–1.48)	124 (8.6)	1.38 (1.01-1.89)[b]	46 (8.0)	1.38 (0.93–2.06)

[a]All models were adjusted for study site, year of breast cancer diagnosis, BMI, age of breast cancer diagnosis, and race/ethnicity.
[b]$P < 0.05$.

carcinogenic process (41). Some cytokines, including IL6 and IL8, have been shown to be impact growth and resistance to apoptosis for triple-negative but not ER^+ breast cancer cells (42).

We also observed the suggestion of a positive association between H2E disease and type II diabetes, but these results were not statistically significant due to the smaller number of H2E patients included. The consistency of results obtained for H2E and triple-negative subtypes suggests a potentially stronger effect of diabetes in elevating the risk of ER^- breast cancers. Previous large prospective studies have provided conflicting results on the association between type II diabetes and risk of breast cancer by ER status. In the Black Women's Health Study cohort, Palmer, and colleagues reported a positive association between type II diabetes and risk of ER^- disease (HR, 1.43; 95% CI, 1.03–2.00), but found no association with ER^+ disease (HR, 1.02; 95% CI, 0.80–1.31; ref. 43). In the Southern Community Cohort Study, Gross, and colleagues reported similar results observing and increased risk of ER^- disease among those with a history of type II diabetes (HR, 1.45; 95% CI, 1.01–2.08; ref. 44). However, in the Nurses' Health Study (45) and the Multiethnic Cohort Study (46), the opposite associations were observed as they found that a history of diabetes was positively associated with risk of ER^+, but not ER^-, disease. Future investigations are thus needed to further clarify the impact of diabetes on breast cancer risk by molecular subtype.

We observed that the relative odds of TNBC was higher among diabetic women actively treated with a diabetes medication at the time of their cancer diagnosis or who had used a diabetes medication for a long duration prior to cancer diagnosis, compared with nondiabetic women and diabetic women not being treated with a diabetes medication. This suggests that diabetes medications may increase TNBC risk. Alternatively, it may be that more severe diabetes requiring medical treatment may be associated with TNBC risk. As our data only included history of type II diabetes and medication use up to 2 years prior to breast cancer diagnosis, we are unable to disentangle these two possibilities.

With respect to metformin, biological studies suggest that metformin may be antioncogenic as it has been shown to block cell-cycle progression and selectively induce apoptosis in triple-negative and $HER2^+$ breast cancer cells (41, 47–50). In previous epidemiologic studies, data on the relationship between metformin use and breast cancer are mixed with few evaluating risk by breast cancer subtype (43, 51, 52). In the Women's Health Initiative (WHI) cohort, metformin use was associated with lower risks of hormone receptor–positive and $HER2^-$ breast cancers relative to nondiabetic women, but was not observed to

Table 3. Association between breast cancer subtype and diabetes medication factors in the whole population and type II diabetic population[a]

	$ER^+/HER2^-$ *N* (%)	$ER^+/HER2^+$ *N* (%)	OR (95% CI)	Triple negative *N* (%)	OR (95% CI)	H2E *N* (%)	OR (95% CI)
Whole study population							
Used a diabetes medication within the 6 months prior to breast cancer diagnosis							
Nondiabetic	1,842 (93.6)	310 (97.0)	1.00 (ref)	1,298 (91.6)	1.00 (ref)	524 (92.2)	1.00 (ref)
Diabetic, no medication use	39 (2.0)	5 (1.5)	1.02 (0.40–2.65)	21 (1.5)	0.73 (0.42–1.27)	6 (1.1)	0.54 (0.23–1.31)
Diabetic, used a diabetes medication	86 (4.4)	5 (1.5)	0.58 (0.24–1.36)	98 (6.9)	1.41 (1.03–1.95)[b]	38 (6.7)	1.43 (0.94–2.19)
Used metformin within the 6 months prior to breast cancer diagnosis							
Nondiabetic	1,848 (93.7)	310 (96.9)	1.00 (ref)	1,303 (91.6)	1.00 (ref)	526 (92.1)	1.00 (ref)
Diabetic, no metformin use	65 (3.3)	7 (2.2)	0.90 (0.40–2.01)	45 (3.2)	0.88 (0.59–1.32)	18 (3.2)	0.90 (0.52–1.57)
Diabetic, used metformin	60 (3.0)	3 (0.9)	0.41 (0.13–1.32)	74 (5.2)	1.54 (1.07–2.22)[b]	27 (4.7)	1.47 (0.90–2.40)
Months of metformin use within the 2 years prior to breast cancer diagnosis							
Nondiabetic	1,846 (93.6)	310 (96.6)	1.00 (ref)	1,303 (91.5)	1.00 (ref)	526 (92.1)	1.00 (ref)
Diabetic, no metformin use	62 (3.1)	6 (1.9)	0.81 (0.34–1.92)	42 (3.0)	0.86 (0.57–1.30)	18 (3.2)	0.94 (0.54–1.63)
Diabetic, 1–12 months of metformin use	30 (1.5)	3 (0.9)	0.78 (0.23–2.64)	30 (2.1)	1.22 (0.72–2.07)	10 (1.7)	1.09 (0.52–2.30)
Diabetic, 13–24 months of metformin use	34 (1.7)	2 (0.6)	0.48 (0.11–2.04)	49 (3.4)	1.80 (1.13–2.85)[b]	17 (3.0)	1.60 (0.87–2.96)
P_{trend}			0.37		0.01[b]		0.20
Patients with a history of type II diabetes							
Used a diabetes medication within the 6 months prior to breast cancer diagnosis							
No	39 (31.2)	5 (45.5)	1.00 (ref)	21 (17.6)	1.00 (ref)	6 (13.6)	1.00 (ref)
Yes	86 (68.8)	6 (54.5)	0.45 (0.12–1.74)	98 (82.4)	2.03 (1.06–3.87)[b]	38 (86.4)	3.34 (1.25–8.96)[b]
Used metformin within the 6 months prior to breast cancer diagnosis							
No	65 (52.0)	7 (70.0)	1.00 (ref)	45 (37.8)	1.00 (ref)	18 (40.0)	1.00 (ref)
Yes	60 (48.0)	3 (30.0)	0.46 (0.11–1.91)	74 (62.2)	1.81 (1.06–3.08)[b]	27 (60.0)	1.71 (0.83–3.52)
Months of metformin use within the 2 years prior to breast cancer diagnosis							
0	62 (49.2)	6 (54.5)	1.00 (ref)	42 (34.7)	1.00 (ref)	18 (40.0)	1.00 (ref)
1–12	30 (23.8)	3 (27.3)	1.04 (0.24–4.58)	30 (24.8)	1.43 (0.73–2.77)	10 (22.2)	1.17 (0.46–2.95)
13–24	34 (27.0)	2 (18.2)	0.54 (0.10–4.06)	49 (40.5)	2.20 (1.19–4.08)[b]	17 (37.8)	1.85 (0.82–4.21)
P_{trend}			0.52		0.01[b]		0.15

[a]All models were adjusted for study site, year of breast cancer diagnosis, BMI, age of breast cancer diagnosis, and race/ethnicity.
[b]$P < 0.05$.

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significantly change risks of other subtypes (although triple-negative disease was not assessed; ref. 51). Hou and colleagues conducted a breast cancer case-only analysis with 1,013 diabetic and 4,621 nondiabetic Chinese women. It found that metformin use was inversely associated with risk of $HER2^+$ breast cancer, but was not associated with risk of other types of breast cancer (52). In the study based on Black Women's Health Study cohort, no significant difference in risk of ER^+ or ER^- disease was found among nondiabetic women, metformin-treated diabetic women, and diabetic women treated by all other medications (43). However, none of these studies evaluated the impact of recency or duration of metformin on disease risk. The inconsistent results in the literature may partially be attributed to the prevalence of diabetes medication use in the study population. Also, the metformin data in WHI were self-reported and subject to potential misclassification bias. With a reliable data resource and extensively collected prescription variables, our study is the first population-based study to report an excessive risk of triple-negative disease compared with $ER^+/HER2^-$ subtype among metformin-treated diabetic women. However, this finding requires confirmation.

Our study has certain strengths and limitations. Our case–case design provided us with sufficient power to investigate how the associations between diabetes and diabetes medications vary across cancer subtypes with a particular emphasis on the triple-negative and H2E subtypes that represent 15% and 10% of all breast cancers, respectively. Specifically, prior studies evaluating these associations included only 65 to 469 triple-negative and 40 to 130 H2E cases, while our study was three times larger than the largest studies because we had 1,446 triple-negative and 578 H2E cases. However, the $ER^+/HER2^+$ and H2E group in our study still had a relatively small number of women with diabetes, which made it difficult to reach a conclusion about their associations with the exposures of interest. In our polytomous regression model, potential confounders including BMI and age at breast cancer diagnosis have been adjusted as continuous variables to minimize residual confounding. While recall bias is often a concern in retrospective studies, here we relied primarily on medical record data, which is not subject to this bias and our results did not change appreciably in analyses restricted to data only from medical records. With respect to limitations, the lack of a cancer-free control group necessitates the interpretation of our risk estimates as odds of developing certain subtypes relative to the reference subtype ($ER^+/HER2^-$). Given the existing literature supporting a positive relationship between diabetes and overall breast cancer risk, it may be reasonable to infer based on our data that the magnitude of this relationship is larger for risk of TNBC than it is for risk of ER^+ breast cancer. However, interpretation of our metformin data is less clear given existing studies demonstrating metformin's potential protective effects. Consequently, our results are consistent with various potential scenarios including metformin use being associated with a reduced risk of ER^+ disease but not being associated with risk of triple-negative disease, or alternatively that metformin use is not associated with ER^+ disease but does elevate risk of triple-negative disease. So while our results suggest that there is heterogeneity in these relationships across subtypes, further work characterizing them is needed. Our collection of medical record data on diabetes history and medication use was limited to the 2-years prior to breast cancer diagnosis, limiting our ability to evaluate the impact of longer term use of diabetes medications. Only a few diabetic women in our study were treated by medications other than metformin, which impaired our ability to quantify the association between breast cancer subtypes and other antidiabetic medications. Finally, our study population primarily consisted of non-Hispanic Whites. This impairs the generalizability of our study results to African-Americans, a population that is disproportionately impacted by TNBC (53).

In conclusion, our results provide epidemiologic evidence that type II diabetes and diabetes medications differentially impact risk across the major breast cancer molecular subtypes and potentially have the greatest impact on risk of triple-negative disease. If replicated, these results could aid in the identification of a population with a higher risk of TNBC.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: H. Chen, L.S. Cook, D.A. Hill, C.I. Li
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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): L.S. Cook, D.A. Hill, C.L. Wiggins, C.I. Li
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): H. Chen, L.S. Cook, M.-T.C. Tang, D.A. Hill, C.I. Li
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Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): M.-T.C. Tang, C.I. Li
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