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ORIGINAL ARTICLE

A prospective study of type 2 diabetes, metformin use, and risk of breast cancer

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Background: Type 2 diabetes (T2D) has been associated with increased breast cancer risk, but commonly prescribed antidiabetic medications such as metformin may reduce risk. Few studies have investigated T2D and medications together in relation to breast cancer.

Patients and methods: Data came from 44 541 Sister Study participants aged 35 to 74 years at enrollment (2003-2009) who satisfied eligibility criteria, followed through 15 September 2017. Information on time-varying, self-reported, physician-diagnosed, prevalent and incident T2D, use of antidiabetic medications, and covariates was obtained from baseline and follow-up questionnaires. Incident breast cancers were confirmed with medical records. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated.

Results: During follow-up (median, 8.6 years), 2678 breast cancers were diagnosed at least 1 year after enrollment. There were 3227 women (7.2%) with prevalent and 2389 (5.3%) with incident T2D, among whom 61% ($n = 3386$) were ever treated with metformin. There was no overall association between T2D and breast cancer risk (HR 0.99; 95% CI, 0.87-1.13). However, T2D was associated with increased risk of triple-negative breast cancer (HR 1.40; 95% CI, 0.90-2.16). Compared with not having T2D, T2D with metformin use was not associated with overall breast cancer risk (HR 0.98; 95% CI, 0.83-1.15), but it was associated with decreased risk of estrogen receptor (ER)-positive breast cancer (HR 0.86; 95% CI 0.70-1.05) and increased risk of ER-negative (HR 1.25; 95% CI, 0.84-1.88) and triple-negative breast cancer (HR 1.74; 95% CI, 1.06-2.83). The inverse association with ER-positive cancer was stronger for longer duration (≥10 year) metformin use (HR 0.62; 95% CI, 0.38-1.01; P for trend = 0.09). Results were supported by sensitivity analyses.

Conclusion: Our findings suggest that associations between T2D and breast cancer may differ by hormone receptor status and that associations between T2D and ER-positive breast cancer may be reduced by long-term metformin use.

Key words: type 2 diabetes, metformin, antidiabetic medication, breast cancer, estrogen receptor, triple-negative

INTRODUCTION

Meta-analyses of studies before 2012 reported a 20% increased risk of breast cancer in women with type 2 diabetes (T2D).[1,2] Possible mechanisms include activating insulin or insulin-like growth factor receptors in breast epithelial tissue, or modifications of levels of sex hormones through insulin resistance and hyperinsulinemia.[3] Considering these mechanisms, drugs to treat T2D may alter breast cancer risk. Metformin, currently the preferred first-line T2D treatment, was first used in the 1950s, but it did not become widely used in the USA until 1995.[4] Metformin may help reduce breast cancer risk by improving insulin sensitivity and correcting hyperinsulinemia through reduction of circulating insulin and insulin-like growth factor concentrations.[5] Metformin may also constrain breast cancer growth through activation of adenosine monophosphate activated protein kinase (AMPK) and subsequent inhibition of the mammalian target of rapamycin (mTOR) signaling pathway.[6,7] In contrast, insulin might increase breast cancer risk.[8]

Epidemiologic evidence on the association between metformin and breast cancer risk is inconclusive.[9,10]

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Previous studies have been criticized for including only participants with T2D and for not considering prevalent versus incident T2D or duration of medication use.[11] In addition to having time-related biases,[12] many studies were not specific to breast cancer as an outcome and thus reproductive risk factors or time-varying menopausal status during follow-up were not well considered.[10] Furthermore, potential differential associations by breast cancer subtype have not been fully addressed,[9,10] although etiological and clinical characteristics of breast cancer differ by hormone receptor status.[13,14] Finally, the now widespread use of metformin for T2D treatment may have changed the relationship between T2D and breast cancer.

Therefore, we examined the association between T2D, use of metformin, and breast cancer risk, overall and by hormone receptor status, using data from the prospective Sister Study cohort.

METHODS

Study population

A total of 50 884 women from across the USA and Puerto Rico enrolled in the Sister Study between 2003 and 2009.[15] Eligible participants were 35-74 years old and had no previous diagnosis of breast cancer, but are sisters or half-sisters of women diagnosed with breast cancer. Details of the study design, data collection, and outcome measurements are described elsewhere.[15,16] At enrollment, participants completed in-person examinations (including anthropometric measurements and collection of biological samples), telephone interviews, and written questionnaires on demographic, medical, lifestyle, and reproductive factors. Participants complete annual health updates and comprehensive follow-up questionnaires every 3 years. Response rates have been around 90% or better throughout follow-up.[15] The Sister Study is overseen by the National Institutes of Health Institutional Review Board. All participants provided written informed consent.

Identification of T2D

Women with T2D were defined as those who reported being told by a physician or other health care provider that they had non-pregnancy-related T2D or were taking glucose-lowering medications currently (at enrollment) or in the past 12 months. Blood glucose was not measured. Baseline hemoglobin A1C (A1C) levels were measured for 1912 participants for another study in the cohort and used here to estimate the proportion of women with undiagnosed T2D. Among women without diagnosed T2D at enrollment who did or did not report developing T2D during follow-up, 7.7% and 1.0% had elevated A1C (A1C $\geq$ 6.5%), respectively. Thus, the prevalence of undiagnosed T2D among participants appears low compared with the general population.[17]

For the analysis of T2D and breast cancer risk, women with likely type 1 diabetes (T1D) (n = 124) or secondary diabetes (n = 75) were excluded. Women were considered to have T1D if they (i) reported T1D, (ii) were aged <20 years at diabetes diagnosis, or (iii) aged 20-34 years at diagnosis and began taking insulin <12 months after diagnosis.[18,19] Women with diabetes were considered to have 'secondary diabetes' if they were also diagnosed with drug-induced diabetes, hemochromatosis, hepatitis, liver cirrhosis, hyperthyroidism, polycystic ovary syndrome, or gestational diabetes within the 12 months before T2D diagnosis.[20]

Information on use of metformin or use of other classes of antidiabetic medications was obtained from baseline and follow-up questionnaires.[21] At baseline, women were asked to report the age at first use, the number of days per week, times per day on days they took it, and total years or months of use. Each reported antidiabetic medication was coded by product and class using the Slone Drug Dictionary.[22] Products with more than one active ingredient were assigned multiple class codes. Information on incident T2D and use of antidiabetic medications was ascertained in follow-up questionnaires.

Assessment of breast cancer

Breast cancer diagnoses and characteristics were self-reported but verified using medical records for >80% of cases. There was high agreement between self-reported breast cancer and medical records (positive predictive value >99% overall) and confirmation rates were not systematically different by demographic factors such as race/ethnicity or age.[16,23] Therefore, we used self-reported information when medical records were not obtained. Follow-up was through 15 September 2017 (data release 7.1, median 8.6 years of follow-up). We defined cancer subtypes according to estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor-2 (HER2) status. Tumors testing negative for all three markers were classified as triple-negative breast cancer (TNBC).

Statistical analysis

In addition to exclusions described above, we excluded women with a history of any cancer except nonmelanoma skin cancer (n = 2771), breast cancer with unknown timing or uncertain diagnosis (n = 6), or missing date of diabetes diagnosis (n = 488). To reduce bias related to undetected breast cancer present at baseline, we excluded person-time within the first 12 months of follow-up. This excluded 310 incident cases and 265 other women with short follow-up. After further excluding women with missing covariate data, a total of 44 541 women remained. Person-time was calculated from the age 1 year after enrollment until the age of breast cancer diagnosis or until death, last follow-up, or when they dropped out of the study, whichever occurred first. For subtype-specific analyses, if a participant was diagnosed with one type of breast cancer, they were censored for all other types of breast cancer at the time of diagnosis.

Multivariable Cox proportional hazard models were used to estimate hazard ratios (HRs) and 95% confidence

intervals (CIs) for breast cancer incidence with age as the primary time scale. T2D and use of antidiabetic medications were modeled as time-varying during follow up. Ages at diabetes diagnosis and initiation of diabetes medication use were updated at the reported age of each event. In this way, women with prevalent T2D contributed T2D person-time from the date of enrollment. For incident T2D, women contributed T2D person-time from the time of T2D diagnosis until censored. Women contributed person-time as non-diabetic subjects during the time before their T2D diagnosis.[12]

Potential confounders were identified *a priori* based on a review of the literature and presumed causal relationships among the covariates.[24] Potential confounders included: race/ethnicity (non-Hispanic white, non-Hispanic black, or other), educational attainment (high school degree or less, some college, college degree or higher), height (continuous), body mass index (BMI) at 30-39 years old ($<$18.5, 18.5 to $<$25, 25 to $<$30, 30 to $<$35, 35 to $<$40, or $\geq$40 kg/m^2), physical activity (quintiles of metabolic equivalent h/week), recent mammogram screening ($<$1 year, 1-2 years, $>$2 years), age at menarche $\leq$11 years old, number of relatives diagnosed with breast cancer (1, $\geq$2), and birth cohort (born before 1945, between 1945 and 1954, between 1955 and 1964, or 1965 or later). The following time-varying covariates were also included: BMI, menopausal status (binary), interaction term between BMI and menopausal status, alcohol consumption (never drinker, former drinker, current drinker $<$1 drink/day, current drinker 1-1.9 drinks/day, current drinker $\geq$2 drinks/day), smoking status ($\geq$20, $<$20, and $\geq$10 pack-years, $<$10 and $>$0 pack-years, never smoker), use of any hormonal birth control (never, ever), hormone therapy (none, estrogen only, both estrogen and progesterone), age at first childbirth (nulliparous, $<$21, 21 to $<$25, 25 to $<$29, or $\geq$29 years), age at menopause ($<$40, 40-49, 50-55, $\geq$55 years), lifetime duration of breastfeeding (weeks, none and tertiles among women with any breastfeeding), and parity (0, 1, 2, $\geq$3 births). Menopause was updated at the reported age at onset. All other time-varying covariates were updated based on follow-up reports with exposure changes assumed to have taken place at the beginning of each detailed follow-up questionnaire cycle. If missing at a given cycle of follow-up, covariate values were carried forward from the previous cycle. Potential effect modification was evaluated with likelihood ratio tests for time-varying menopausal status, race/ethnicity, income, diet quality, time-varying BMI ($<$30 and $\geq$18.5, $\geq$30), degree of family history of breast cancer, and time since last mammogram ($<$1 year, $\geq$1 years).

The proportional hazards assumption was checked utilizing Martingale residuals. A case-case analysis was done to explore etiological heterogeneity in the association between T2D, metformin use, and breast cancer by ER status with spline adjustment for age at diagnosis.[25] We conducted several sensitivity analyses in the evaluation of association between metformin use and breast cancer: (i) analysis based on incident T2D after excluding prevalent T2D (i.e. with exclusion of women who were diabetic at enrollment),[26] (ii) further categorizing the exposure based on duration of T2D (no T2D, $<$5, 5 to $<$10, 10 to $<$15, or $\geq$15 years for all T2D; no T2D, $<$2, 2 to $<$4, or $\geq$4 years for incident T2D); (iii) considering exposed participants to be those with T2D who were ever prescribed any antidiabetic medications to minimize confounding by indication; and (iv) those with T2D who received metformin monotherapy (i.e. not using combination therapy or starting on one medication and progressing to another); and (v) excluding insulin ever users among women with T2D to narrow the range of T2D severity; (vi) excluding cases missing data on PR and HER2 from breast cancer subtype analyses; (vii) limiting to invasive breast cancer as the outcome, censoring women with ductal carcinoma *in situ* (DCIS) at their age of diagnosis; and (viii) analyzing data using inverse probability weighting to account for possible bias from attrition due to selective loss to follow-up (n = 3888 lost to follow-up before 2017). We also calculated E-values to evaluate how much confounding would be required to explain away an estimate.[27]

The P values provided are two-sided, with the level of significance at 0.05. All statistical analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

There were 3227 women (7.2%) with prevalent and 2389 women (5.3%) with incident T2D. Baseline characteristics by T2D status are shown in Table 1. Among women with T2D, 61% (n = 3386) were ever treated with metformin monotherapy or combination therapy (74% among prevalent versus 42% among incident T2D); among women with prevalent or incident T2D who were ever treated with antidiabetic medications, ~86% took metformin. Women with T2D were older, had a higher enrollment-measured BMI and self-reported BMI at 30-39 years, less physical activity, lower diet quality, and shorter lifetime duration of breastfeeding than nondiabetic women. They were also more likely to be from racial/ethnic minorities, less educated, and to have lower income and earlier age at menarche.

During median follow-up of 8.6 years with 373 665 person-years, we identified 2678 incident primary breast cancer cases (invasive and DCIS). Associations between T2D and breast cancer are shown in Table 2. There was no overall association between T2D and breast cancer risk (HR 0.99; 95% CI, 0.87-1.13). However, T2D was associated with increased risk of TNBC (HR 1.40; 95% CI, 0.90-2.16). Although there was no statistically significant difference in the association by ER status in a case-case analysis, long-duration T2D ($\geq$15 years) was inversely associated with ER+ breast cancer (HR 0.61; 95% CI, 0.37-1.03).

In comparison with not having T2D, having T2D and using metformin was not associated with breast cancer risk (HR 0.98; 95% CI, 0.83-1.15) (Table 3). Having T2DM and using metformin was inversely associated with ER+ breast cancer

Table 1. General characteristics at baseline by type 2 diabetes status, The Sister Study

Characteristic	Without type 2 diabetes (n = 38 960)	With type 2 diabetes	
		Prevalent diabetes (n = 3204)	Incident diabetes (n = 2377)
Mean (SD)			
Age at baseline, years	55.1 (8.9)	58.2 (8.2)	56.2 (8.4)
Height at baseline, cm	164.4 (6.4)	163.3 (6.6)	163.7 (6.4)
Measured BMI at baseline, kg/m^2	27.0 (5.7)	33.7 (7.2)	32.1 (6.6)
Self-reported BMI at 30-39 years old, kg/m^2	22.9 (3.6)	26.1 (5.6)	24.9 (4.7)
Total MET-hours of physical activity/week	51.8 (31.5)	42.7 (29.1)	44.9 (28.2)
Healthy eating index-2015[a]	72.2 (9.5)	70.4 (9.4)	69.8 (9.9)
Age at first birth, years[b]	25.0 (5.3)	23.0 (4.9)	23.5 (4.9)
Lifetime duration of breastfeeding, weeks[c]	66.2 (71.4)	56.3 (67.3)	59.3 (70.2)
Age at menopause, years[d]	49.4 (6.1)	48.8 (7.3)	48.8 (7.0)
Proportion (%)			
Race/ethnicity			
Non-Hispanic white	86	69	75
Non-Hispanic black	8	18	15
Other[e]	7	13	10
Educational attainment			
High school degree or less	14	22	18
Some college	33	39	38
College degree or higher	53	39	44
Income			
<$49 999	22	39	31
$50 000-$99 999	40	38	42
$100 000+	35	20	23
Missing	4	3	4
Alcohol consumption			
Never	3	6	5
Former	13	27	21
Current drinker, <1 drink/day	68	62	67
Current drinker, 1-1.9 drink/day	9	3	5
Current drinker, ≥2 drink/day	5	2	2
Smoking status			
Never	57	52	57
<10 and >0 pack-years	22	19	19
<20 and ≥10 pack-years	9	10	9
≥20 pack-years	11	19	16
Recent mammogram screening			
<1 year	82	79	80
1-2 years	15	17	16
>2 years	4	4	5
Number of first-degree relatives diagnosed with breast cancer (≥2)	25	25	25
Age at menarche ≤11 years	19	28	25
Parity			
0	18	17	17
1	14	15	15
2	37	32	37
≥3	30	36	31
Ever use of hormonal birth control	86	83	85
Use of hormone therapy			
None	59	51	53
Estrogen only	18	28	25
Progesterone or combination therapy	23	21	22
Postmenopausal	63	78	69
Ever use of metformin[f]	N/A	74	42
Ever use of antidiabetic medications[f]	N/A	86	49
Use of metformin only[g]	N/A	30	68
Use of metformin with other medications[g]	N/A	56	17
Use of other medications only[g,h]	N/A	14	14

Data are presented as mean ± standard deviation, or percentage.
BMI, body mass index; MET, metabolic equivalent; SD, standard deviation.
[a] Among women with plausible energy intake (≥500 and ≤5000 kcal/day) (n = 43 193).
[b] Among parous women (n = 36 413).
[c] Among women who ever breastfed (n = 25 469).
[d] Among postmenopausal women (n = 28 799).
[e] Hispanic and non-Hispanic other race.
[f] Included use at both baseline and follow-up.
[g] Among women who ever took antidiabetic medications.
[h] Sulfonylureas, thiazolidinediones, dipeptidyl peptidase-4 inhibitors, insulin, and others.

Table 2. Association between type 2 diabetes and breast cancer, The Sister Study

	Total breast cancer			ER+ breast cancer		ER− breast cancer		TNBC	
	No. of cases	Age-adjusted HR (95% CI)[a]	Multivariable-adjusted HR (95% CI)[b]	No. of cases	Multivariable-adjusted HR (95% CI)[b]	No. of cases	Multivariable-adjusted HR (95% CI)[b]	No. of cases	Multivariable-adjusted HR (95% CI)[b]
Presence of T2D									
No	2401	1 (reference)	1 (reference)	1800	1 (reference)	303	1 (reference)	155	1 (reference)
Yes	277	1.02 (0.90-1.16)	0.99 (0.87-1.13)	184	0.92 (0.78-1.07)	36	1.07 (0.75-1.53)	25	1.40 (0.90-2.16)
Time since T2D diagnosis (years)									
No T2D	2401	1 (reference)	1 (reference)	1800	1 (reference)	303	1 (reference)	155	1 (reference)
<5	129	1.07 (0.90-1.28)	1.03 (0.86-1.23)	90	0.98 (0.79-1.22)	19	1.21 (0.76-1.93)	12	1.46 (0.81-2.63)
5 to <10	81	1.03 (0.83-1.29)	1.00 (0.80-1.25)	53	0.91 (0.69-1.21)	9	0.95 (0.49-1.84)	8	1.55 (0.76-3.16)
10 to <15	40	1.07 (0.78-1.46)	1.03 (0.75-1.41)	26	0.96 (0.65-1.43)	8	0.94 (0.47-1.90)	5	1.09 (0.44-2.69)
≥15	27	0.78 (0.53-1.13)	0.76 (0.52-1.12)	15	0.61 (0.37-1.03)				
P trend		0.74	0.45		0.10		0.99		0.26

95% CI, 95% confidence interval; ER, estrogen receptor; HR, hazard ratio; T2D, type 2 diabetes; TNBC, triple-negative breast cancer.
[a] Adjusted for age (age as the primary time scale).
[b] Adjusted for race/ethnicity (non-Hispanic white, non-Hispanic black, or other), educational attainment (high school degree or less, some college, college degree or higher), height, body mass index (BMI) at 30-39 years old (<18.5, 18.5 to <25, 25 to <30, 30 to <35, 35 to <40, or ≥40 kg/m^2), physical activity (metabolic equivalent hours/week), recent mammogram screening (<1, 1-2, >2 years), age at menarche ≤11 years old, number of relatives diagnosed with breast cancer (1, ≥2), and birth cohort (born before 1945, between 1945 and 1954, between 1955 and 1964, or 1965 or later), as well as time varying covariates including BMI, menopausal status (binary), interaction term between BMI and menopausal status, age at menopause (<40, 40-49, 50-55, ≥55 years), alcohol consumption (never drinker, former drinker, current drinker <1 drink/day, current drinker 1-1.9 drinks/day, current drinker ≥2 drinks/day), smoking status (≥20 pack-years, <20 and ≥10 pack-years, <10 and >0 pack-years, never smoker), use of any hormonal birth control (never, ever), hormone therapy (none, estrogen only, both estrogen and progesterone), age at first childbirth (nulliparous, <21, 21 to <25, 25 to <29, or ≥29 years), lifetime duration of breastfeeding (weeks, none and tertiles among women with any breastfeeding), and parity (0, 1, 2, ≥3 births).

(HR, 0.86; 95% CI, 0.70-1.05), especially with long-term use (≥10 years) (HR, 0.62; 95% CI, 0.38-1.01; *P* for trend = 0.09). By contrast, risk was increased for ER− breast cancer (HR, 1.25; 95% CI, 0.84-1.88) and TNBC (HR, 1.74; 95% CI, 1.06-2.83). There was no notable difference in the association by ER status ($P > 0.10$), whereas a significant difference in the association for TNBC versus ER+ breast cancer was found (odds ratio, 2.14; 95% CI, 1.24-3.68, $P = 0.006$) in a case-case analysis. Results for metformin and ER+ breast cancer were similar in analyses limited to incident T2D, i.e. with exclusion of women who were diabetic at enrollment. In analyses of incident T2D, having T2D and being treated with medications other than metformin was associated with increased risk of breast cancer overall (HR 2.04; 95% CI, 1.17-3.57) and ER+ breast cancer (HR 2.62; 95% CI, 1.46-4.70) in comparison with not

Table 3. Association between metformin use and breast cancer, The Sister Study

	Total breast cancer			ER+ breast cancer		ER− breast cancer		TNBC	
	No. of cases	Age-adjusted HR (95% CI)[a]	Multivariable-adjusted HR (95% CI)[b]	No. of cases	Multivariable-adjusted HR (95% CI)[b]	No. of cases	Multivariable-adjusted HR (95% CI)[b]	No. of cases	Multivariable-adjusted HR (95% CI)[b]
Antidiabetic medication use									
No T2D	2401	1 (reference)	1 (reference)	1800	1 (reference)	303	1 (reference)	155	1 (reference)
No medication	70	1.07 (0.84-1.35)	1.02 (0.81-1.30)	46	0.93 (0.70-1.25)	6	0.74 (0.33-1.66)	3	NA
Other medication[c]	30	0.96 (0.67-1.38)	0.95 (0.66-1.37)	27	1.20 (0.82-1.76)	3	NA	2	NA
Metformin	177	1.02 (0.87-1.19)	0.98 (0.83-1.15)	111	0.86 (0.70-1.05)	27	1.25 (0.84-1.88)	20	1.74 (1.06-2.83)
Duration of metformin use (years)									
No T2D	2401	1 (reference)	1 (reference)	1800	1 (reference)	303	1 (reference)	155	1 (reference)
No metformin use	100	1.03 (0.85-1.26)	1.00 (0.82-1.23)	73	1.01 (0.80-1.28)	9	0.75 (0.39-1.47)	5	0.80 (0.33-1.93)
<2	33	0.94 (0.67-1.33)	0.91 (0.64-1.29)	26	0.96 (0.65-1.42)	14	1.35 (0.78-2.32)	10	1.83 (0.95-3.50)
2 to <5	43	0.99 (0.73-1.34)	0.95 (0.70-1.29)	27	0.82 (0.56-1.21)				
5 to <10	70	1.19 (0.94-1.51)	1.14 (0.90-1.46)	42	0.96 (0.70-1.32)	13	1.16 (0.66-2.05)	10	1.65 (0.85-3.21)
≥10	31	0.85 (0.60-1.21)	0.81 (0.57-1.16)	16	0.62 (0.38-1.01)				
P trend		0.79	0.81		0.09		0.44		0.05

95% CI, 95% confidence interval; ER, estrogen receptor; HR, hazard ratio; T2D, type 2 diabetes; TNBC, triple-negative breast cancer.
[a] Adjusted for age (age as the primary time scale).
[b] Adjusted for race/ethnicity (non-Hispanic white, non-Hispanic black, or other), educational attainment (high school degree or less, some college, college degree or higher), height, body mass index (BMI) at 30-39 years old (<18.5, 18.5 to <25, 25 to <30, 30 to <35, 35 to <40, or ≥40 kg/m^2), physical activity (metabolic equivalent hours/week), recent mammogram screening (<1, 1-2, >2 years), age at menarche ≤11 years old, number of relatives diagnosed with breast cancer (1, ≥2), and birth cohort (born before 1945, between 1945 and 1954, between 1955 and 1964, or 1965 or later), as well as time varying covariates including BMI, menopausal status (binary), interaction term between BMI and menopausal status, age at menopause (<40, 40-49, 50-55, ≥55 year), alcohol consumption (never drinker, former drinker, current drinker <1 drink/day, current drinker 1-1.9 drinks/day, current drinker ≥2 drinks/day), smoking status (≥20, <20 and ≥10 pack-years, <10 and >0 pack-years, never smoker), use of any hormonal birth control (never, ever), hormone therapy (none, estrogen only, both estrogen and progesterone), age at first childbirth (nulliparous, <21, 21 to <25, 25 to <29, or ≥29 years), lifetime duration of breastfeeding (weeks, none and tertiles among women with any breastfeeding), and parity (0, 1, 2, ≥3 births).
[c] Sulfonylureas, thiazolidinediones, dipeptidyl peptidase-4 inhibitors, insulin, and others.

Table 4. Hazard ratios and 95% CIs for the association between type 2 diabetes, metformin use and total breast cancer stratified by selected factors, The Sister Study

	Cases/person-years	Presence of T2D		T2D and metformin use, versus no T2D	
		All T2D	*P* interaction	All T2D	*P* interaction
Time varying menopausal status					
Premenopausal	464/68 733	0.80 (0.48-1.35)	0.43	0.92 (0.50-1.68)	0.60
Postmenopausal	2214/304 932	1.00 (0.87-1.14)		0.98 (0.83-1.16)	
Race/ethnicity					
Non-Hispanic white	2314/319 621	0.93 (0.80-1.08)	0.05	0.94 (0.78-1.13)	0.36
Non-Hispanic black	189/29 030	0.99 (0.69-1.42)		1.06 (0.70-1.61)	
Other	175/25 014	1.50 (1.02-2.19)		1.20 (0.73-1.99)	
Income, $					
<49 999	615/86 247	0.96 (0.76-1.21)	0.66	0.97 (0.73-1.29)	0.62
50 000-99 999	1019/149 212	1.00 (0.81-1.22)		0.95 (0.74-1.23)	
≥100 000	926/12 635	1.04 (0.80-1.35)		1.07 (0.79-1.47)	
Healthy eating index-2015					
<Median	1311/180 607	1.02 (0.86-1.21)	0.09	0.99 (0.80-1.21)	0.28
≥Median	1301/182 837	0.95 (0.77-1.18)		0.98 (0.76-1.28)	
Time-varying BMI, kg/m^2					
Non-obese (<30 and ≥18.5)	1857/266 796	0.97 (0.79-1.19)	0.90	1.07 (0.83-1.37)	0.40
Obese (≥30)	797/102 219	1.02 (0.86-1.21)		0.95 (0.77-1.17)	
Stronger family history[a]					
No	1766/280 119	1.03 (0.88-1.21)	0.41	1.06 (0.87-1.29)	0.20
Yes	912/93 545	0.92 (0.73-1.15)		0.84 (0.63-1.12)	
Recent mammogram screening, years					
<1	2255/305 675	0.97 (0.84-1.12)	0.38	0.96 (0.80-1.14)	0.43
≥1	423/67 989	1.06 (0.78-1.43)		1.08 (0.75-1.57)	

BMI, body mass index; T2D, type 2 diabetes.

Adjusted for race/ethnicity (non-Hispanic white, non-Hispanic black, or other), educational attainment (high school degree or less, some college, college degree or higher), height, BMI at 30-39 years old (<18.5, 18.5 to <25, 25 to <30, 30 to <35, 35 to <40, or ≥40 kg/m^2), physical activity (metabolic equivalent hours/week), recent mammogram screening (<1, 1-2, >2 years), age at menarche ≤11 years old, number of relatives diagnosed with breast cancer (1, ≥2), and birth cohort (born before 1945, between 1945 and 1954, between 1955 and 1964, or 1965 or later), as well as time varying covariates including BMI, menopausal status (binary), interaction term between BMI and menopausal status, age at menopause (<40, 40-49, 50-55, ≥55 years), alcohol consumption (never drinker, former drinker, current drinker <1 drink/day, current drinker 1-1.9 drinks/day, current drinker ≥2 drinks/day), smoking status (≥20, <20 and ≥10, <10 and >0 pack-years, never smoker), use of any hormonal birth control (never, ever), hormone therapy (none, estrogen only, both estrogen and progesterone), age at first childbirth (nulliparous, <21, 21 to <25, 25 to <29, or ≥29 years), lifetime duration of breastfeeding (weeks, none and tertiles among women with any breastfeeding), and parity (0, 1, 2, ≥3 births) except each stratified variable.

[a] Number of first-degree relatives diagnosed with breast cancer ≥2.

having T2D, although there were small numbers of cases (Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2020.12.008).

The associations between metformin use and breast cancer were not appreciably changed after adjusting for duration of diabetes (Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2020.12.008). Inverse associations between metformin use and ER+ breast cancer were strengthened in analyses limiting exposed participants to be those with T2D who were ever prescribed any antidiabetic medications (Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2020.12.008). The results were not materially changed in analyses with exposure defined as metformin alone (48% among metformin users) (Supplementary Table S4, available at https://doi.org/10.1016/j.annonc.2020.12.008) or after excluding insulin users (23% among those ever treated with antidiabetic medications) (Supplementary Table S5, available at https://doi.org/10.1016/j.annonc.2020.12.008).

Stratified results for T2D and metformin use are shown for time-varying menopausal status, race/ethnicity, income, diet quality, obesity, degree of family history, and mammogram history (Table 4). The most notable difference was finding increased risk among women with race/ethnicities other than non-Hispanic white or black (*P* interaction = 0.05).

In a sensitivity analysis for the association between T2D, metformin use, and breast cancer subtypes among women with complete data for ER, PR, and HER2, the strength of associations tended to increase for ER− breast cancer and to decrease for ER+ breast cancer, though overall conclusions were unchanged (Supplementary Table S6, available at https://doi.org/10.1016/j.annonc.2020.12.008). The results were not materially altered when we used inverse probability weighting to address attrition and non-response (Supplementary Table S7, available at https://doi.org/10.1016/j.annonc.2020.12.008). The results also were not materially changed in analyses that were limited to invasive breast cancer (data not shown) by treating diagnoses of DCIS as censoring events. We obtained E-values of 1.6, 1.81, and 2.87 for the association of metformin use with ER+ breast cancer, ER− breast cancer, and TNBC, respectively.

CONCLUSIONS

In this nationwide prospective cohort, we did not observe an association between T2D and overall breast cancer risk. However, there was some evidence that having T2D is

associated with an increased risk of TNBC. In contrast, long-duration T2D (≥15 years) was associated with decreased risk of ER+ breast cancer. This may be explained in part by the observed inverse association between long-term metformin use for T2D and the more common ER+ breast cancer. It is possible that long-term use of metformin has reduced any risk of breast cancer associated with T2D.[28] While this may be true for ER+ breast cancer, T2D with metformin use was in fact positively associated with ER− breast cancer and TNBC, as was incident T2D treated with other medications. This suggests that ER+ and ER− breast cancer involve different mechanisms. Alternatively, metformin may influence the molecular evolution of a developing tumor, somehow preventing expression of ERs.[29]

Although previous meta-analyses reported positive associations between T2D and breast cancer risk,[1,2] several cohort studies have reported null findings.[30-32] Prior positive associations could be explained, in part, by detection bias to the extent that there may be increased cancer screening after T2D diagnosis.[30,33] In the Sister Study, prevalent cases of T2D were slightly less likely, however, to have had a mammogram in the preceding year compared with women without diabetes (79% versus 82%, respectively). In addition, as suggested by our finding that women with T2D treated by medications other than metformin had increased risk for ER+ breast cancer, prior null findings might be partially explained by the fact that metformin, as currently the most common treatment of T2D, may offset the adverse effects of T2D on breast cancer risk.

In our study, positive associations between T2D and breast cancer risk tended to be strongest for TNBC. Prior studies that have reported ER-specific results have had somewhat conflicting results. The Black Women's Health Study reported increased risk of ER− breast cancer (HR 1.43; 95% CI, 1.03-2.00), but no association with ER+ breast cancer.[26] In contrast, the Nurses' Health Study found increased risk for both ER+ breast cancer (HR 1.22; 95% CI, 1.01-1.47) and ER− cancer (HR 1.13; 95% CI, 0.79-1.62).[34] While some studies reported null findings,[35,36] others also observed positive associations between T2D and TNBC overall[37] or in postmenopausal breast cancer.[38,39]

In our study, the combination of T2D and metformin use was associated with a suggestive decreased risk of ER+ breast cancer and increased risks of ER− breast cancer and TNBC. These associations also remained after considering exposed participants to be those with T2D who received metformin monotherapy or excluding insulin ever users. Previous epidemiological studies on metformin use and breast cancer risk have had mixed results.[26,31,40] In a study based on administrative health care records for elderly diabetic women from a Canadian cohort, there was no evidence of association between metformin use and either overall or subtype-specific breast cancer.[40] In the Black Women's Health Study, there was a suggestive inverse association with ER+ breast cancer and a positive association with ER− breast cancer.[26] In contrast, in the Women's Health Initiative cohort, inverse associations were found for both ER+/PR+ (HR 0.64; 95% CI, 0.45-0.92) and ER−/PR− breast cancer (HR 0.68; 95% CI, 0.29-1.59).[31] A case-case study in the USA reported a positive association between recent (13-24 months before diagnosis) metformin use and TNBC (odds ratio, 1.80; 95% CI, 1.13-2.85),[37] which is consistent with our results. Our finding that metformin use in T2D may be associated with decreased risk of ER+ breast cancer is consistent with biological mechanisms.[5-7,41]

However, it is unclear what mechanism explains increased risks of ER− breast cancer and TNBC among women with T2D who used metformin because some biological evidence has supported anticancer effects of metformin on ER− breast cancer and TNBC.[42,43] However, if the beneficial aspects of metformin are largely relevant for ER+ breast cancer, it is possible that it is the underlying diabetes that is associated with the increased risk for ER− breast cancer in the absence of any protection from metformin use.

We observed a positive association between breast cancer risk and incident T2D with non-metformin antidiabetic medication use, although the number of cases was small. Thus, the inverse association between metformin use and ER+ breast cancer risk was strengthened when exposure definition was limited to those with T2D who were ever prescribed antidiabetic medications (i.e. considering those with untreated diabetes as not having it). Insulin and its analogues and sulfonylureas may contribute to enhanced cancer risk through increasing circulating levels of insulin which can activate metabolic and mitogenic signaling,[44] whereas thiazolidinediones may act similarly to metformin, decreasing cancer risk by increasing insulin sensitivity.[45] However, prior studies reported no association of sulfonylureas and thiazolidinediones with breast cancer risk.[46,47] Dipeptidyl peptidase-4 inhibitors, which became widely used during the follow-up period of our participants,[48] stimulate insulin secretion indirectly, but have been associated with some decreased risk of breast cancer.[49] Considering that metformin is now a first-line treatment of T2D, those using other antidiabetic medications may have had more severe disease or been treated with insulin, which has been suggested to increase risk of breast cancer.[8] This finding may be aligned with our finding of no association between untreated T2D and ER+ breast cancer, but could be due to those women having less severe disease. This is consistent with results from a previous study.[50] Furthermore, those using other antidiabetic medications would have had an opportunity to experience any risks due to worsening glycemic control without the protection afforded by metformin.

In stratified analyses, there was a possible inverse association between T2D and premenopausal breast cancer, but no association with postmenopausal disease. This finding was consistent with a previous study,[34] and consistent with our prior observation that metabolic dysfunction with high BMI is associated with lower risk of breast cancer among premenopausal women.[51] We observed small positive associations between incident T2D and breast cancer risk among racial/ethnic minority women, findings also observed in a prior study.[50]

It is possible that women with T2D are screened more often for breast cancer because of more frequent contact with health care providers. However, since >80% of the participants reported a mammogram within a year of baseline, such detection bias was not likely to have been substantial. Indeed, slightly fewer women with prevalent diabetes reported having had a recent mammogram.

The estimated E-values for associations with unmeasured confounders that could account for the observed associations ranged from 1.6 to 2.87. These values are not especially large because our observed HRs are not large.[27] We adjusted for a wide range of known or potential confounders. Furthermore, the risk estimates for most risk factors for breast cancer are small.[52] For example, the reported association between BMI > 35 kg/m^2 compared with normal BMI (mean 21.75 kg/m^2) and breast cancer is around 1.26.[53] Thus, it seems unlikely that the effect of unmeasured confounders is strong enough to explain away the observed associations.

Strengths of this study include its prospective design, large sample size, and high rates of follow-up. Information on T2D, medication use, recent mammogram screening, and important confounders such as menopausal status, BMI, and lifestyle and reproductive factors was collected at baseline and updated during follow-up, enabling us to limit potential time-related biases. By contrast, T2D and medication use were self-reported and subject to misclassification. However, positive and negative predictive values for self-reported T2D are reportedly high (>90%),[54] and an evaluation of A1C levels in a sample of our population suggested that undetected T2D was rare. Nevertheless, we were unable to account for glucose control and T2D progression or improvement, which could affect breast cancer risk.[55] Finally, while we carried out analyses to evaluate the impact of disease duration and metformin use, it is difficult to disentangle the effects of diabetes from the effects of medication since so many women were prescribed metformin and used it for many years. In addition, we did not consider metformin dose in the association between use and duration of metformin and breast cancer risk, and treating it as a dichotomy might attenuate the associations.

In conclusion, our findings provide evidence that T2D and use of metformin may be associated with breast cancer differentially by hormone receptor status. Specifically, T2D with metformin use may be associated with decreased risk of ER+ breast cancer and increased risk of ER− breast cancer and TNBC. Our analysis is consistent with a potential protective effect of metformin and suggests that long-term use of metformin may reduce breast cancer risk associated with T2D.

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DISCLOSURE

The authors have declared no conflicts of interest.

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