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A Prospective Study of Type 2 diabetes, metformin use, and risk of breast cancer

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Abstract

Background: Type 2 diabetes (T2D) has been associated with increased breast cancer risk, but commonly prescribed anti-diabetic 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 September 15, 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 (HR) and 95% confidence intervals (CIs) were estimated.

Results: During follow-up (median, 8.6 years), 2,678 breast cancers were diagnosed at least 1 year after enrollment. There were 3,227 women (7.2%) with prevalent and 2,389 (5.3%) with incident T2D, among whom 61% (n=3,386) 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 to 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

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DISCLOSURE

All authors declare no conflict of interest.

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.

Keywords

type 2 diabetes; metformin; anti-diabetic 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 US 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] 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 US and Puerto Rico enrolled in the Sister Study between 2003 and 2009.[15] Eligible participants were 35 to 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 NIH 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 1,912 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≥6.5%), respectively. Thus, the prevalence of undiagnosed T2D among participants appears low compared to the general population.[17]

For the analysis of T2D and breast cancer risk, women with likely type 1 diabetes (n=124) or secondary diabetes (n=75) were excluded. Women were considered to have type 1 diabetes if they (1) reported type 1 diabetes, or (2) were <20 years at diabetes diagnosis, or (3) ages 20 to 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 anti-diabetic 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 more than 80% of cases. There was high agreement between self-reported breast cancer and medical records (positive predictive value over 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 September 15, 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 non-melanoma skin cancer (n=2,771), 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 one 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 and 95% confidence intervals 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 prior to 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 ≥40 kg/m^2), physical activity (quintiles of metabolic equivalent hours/week), recent mammogram screening (<1y, 1 to 2y, >2y), age at menarche ≤11 years old, number of relatives diagnosed with breast cancer (1, ≥2), and birth cohort (born in <1945, 1945 to <1955, 1955 to <1965 or ≥1965). 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 ≥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 years, 21 to <25 years, 25 to <29 years, or ≥29 years), age at menopause (<40, 40-49, 50-55, ≥55 years), lifetime duration (weeks) of breastfeeding (none and tertiles among women with any breastfeeding), and parity (0, 1, 2, ≥3 births). Menopause was updated at the reported age of each event. All other time-varying covariates were updated based on follow-up reports with exposure

changes assumed to taken place at the beginning of each detailed follow-up questionnaire cycle. If missing at a given period 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 ≥18.5, ≥30), degree of family history of breast cancer, and a history of mammogram (<1y, ≥1y).

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: (1) analysis based on incident T2D after excluding prevalent T2D (i.e. with exclusion of women who were diabetic at enrollment),[26] (2) further categorizing the exposure based on duration of T2D (no T2D, <5 years, 5 to <10 years, 10 to <15 years, or ≥15 years for the all T2D; no T2D, <2 years, 2 to <4 years, or ≥4 years for the incident T2D); (3) considering exposed participants to be those with T2D who were ever prescribed any antidiabetic medications to minimize confounding by indication; and (4) those with T2D who received metformin monotherapy (i.e. not using combination therapy or starting on one medication and progressing to another); and (5) excluding insulin ever users among women with T2D to narrow the range of T2D severity; (6) excluding cases missing data on PR and HER2 from breast cancer subtype analyses; (7) limiting to invasive breast cancer as the outcome, censoring women with ductal carcinoma *in-situ* (DCIS) at their age of diagnosis; and (8) analyzing data using inverse probability weighting to account for possible bias from attrition due to selective loss-to follow-up (n=3,888 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, USA).

RESULTS

There were 3,227 women (7.2%) with prevalent and 2,389 (5.3%) with incident T2D. Baseline characteristics by T2D status are shown in Table 1. Among women with T2D, 61% (n=3,386) were ever treated with metformin monotherapy or combination therapy (74% among prevalent vs. 42% among incident T2D; among women with prevalenet or incidentT2D 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 2,678 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 (≥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 (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 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 having T2D, although there were small numbers of cases (Supplemental Table 1).

The associations between metformin use and breast cancer were not appreciably changed after adjusting for duration of diabetes (Supplemental Table 2). Inverse associations between metformin use and ER+ breast cancer were strengthened in analyses considering exposed participants to be those with T2D who were ever prescribed any antidiabetic medications (Supplemental Table 3). The results were not materially changed in analyses with exposure defined as metformin alone (48% among metformin users)(Supplemental Table 4) or after excluding insulin users (23% among those ever treated with antidiabetic medications) (Supplemental Table 5).

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 (Supplemental Table 6). The results were not materially altered when we used inverse probability weighting to address attrition and non-response (Supplemental Table 7). 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 risk. 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 estrogen receptors.[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 nondiabetics (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 for 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 subtpe-speceific 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 U.S. reported a

positive association between recent (13-24 months before diagnosis) metformin use and TNBC (OR, 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 biological evidence has supported anti-cancer effects of metformin on ER− breast cancer and TNBC.[42, 43]

We observed a positive association between breast cancer risk and incident T2D with non-metformin anti-diabetic 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. those with untreated diabetes considered not to have 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 between 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 for T2D, those using other anti-diabetic 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]

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 a 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 over 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 HR 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 to

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. On the other hand, 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 assess 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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HIGHLIGHTS

- Breast cancer risk associated with diabetes and antidiabetic medication use was studied prospectively in the Sister Study.
- Time varying information on self-reported diagnoses of Type 2 diabetes (T2D) and medication use was available for 44,541 women.
- Compared to no T2D, T2D with metformin use was associated with lower risk of estrogen receptor (ER)-positive breast cancer.
- By contrast, T2D with metformin use was associated with higher risk of ER-negative and triple-negative breast cancer.
- Associations between T2D and breast cancer may be altered by metformin use and differ by hormone receptor status.

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=3,204)		Incident diabetes (n=2,377)	
Mean (SD)						
Age at baseline, y	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/ wk	51.8	(31.5)	42.7	(29.1)	44.9	(28.2)
Healthy Eating Index-2015 *	72.2	(9.5)	70.4	(9.4)	69.8	(9.9)
Age at first birth, y †	25.0	(5.3)	23.0	(4.9)	23.5	(4.9)
Lifetime duration of breastfeeding, wk ‡	66.2	(71.4)	56.3	(67.3)	59.3	(70.2)
Age at menopause, y §	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 ‖	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						

Characteristic	Without type 2 diabetes (n=38,960)	With type 2 diabetes	
		Prevalent diabetes (n=3,204)	Incident diabetes (n=2,377)
<1 y	82	79	80
1 - 2 y	15	17	16
> 2 y	4	4	5
Number of first-degree relatives diagnosed with breast cancer (≥2)	25	25	25
Age at menarche ≤ 11 y	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[¶]	N/A	74	42
Ever use of antidiabetic medications[¶]	N/A	86	49
Use of metformin only [**]	N/A	30	68
Use of metformin with other medications [**]	N/A	56	17
Use of other medications only [**, ††]	N/A	14	14

Abbreviations: BMI, body mass index; MET, metabolic equivalent.

Data are presented as mean ± standard deviation, or percentage.

[*] Among women with plausible energy intake (≥500 and ≤5000 kcal/d) (n=43,193)

[†] Among parous women (n=36,413)

[‡] Among women who ever breastfed (n=25,469)

[§] Among postmenopausal women (n=28,799)

[//] Hispanic and non-Hispanic other race

[¶] Included use at both baseline and follow-up.

[**] Among women who ever took antidiabetic medications.

[††] Sulfonylureas, thiazolidinediones, DPP-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) *	Multivariable-adjusted HR (95% CI) †	No. of cases	Multivariable-adjusted HR (95% CI) †	No. of cases	Multivariable-adjusted HR (95% CI) †	No. of cases	Multivariable-adjusted HR (95% CI) †
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 (y)	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 -<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 -<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

Abbreviations: T2D, type 2 diabetes; ER, estrogen receptor; HR, hazard ratio; 95% CI, 95% confidence interval; +, positive; −, negative; TNBC, triple-negative breast cancer.

*Adjusted for age (age as the primary time scale)

†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 y, 1 to 2y, >2y), age at menarche ≤11 years old, number of relatives diagnosed with breast cancer (1, ≥2), and birth cohort (born in <1945, 1945 to <1955, 1955 to <1965 or ≥1965), as well as time varying covariates including BMI, menopausal status (binary), interaction term between BMI and menopausal status, age at menopause, 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 years, 21 to <25 years, 25 to <29 years, or ≥29 years), lifetime duration of breastfeeding (weeks, none and tertiles among women with any breastfeeding), and parity (0, 1, 2, ≥3 births).

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) *	Multivariable-adjusted HR (95% CI) †	No. of cases	Multivariable-adjusted HR (95% CI) †	No. of cases	Multivariable-adjusted HR (95% CI) †	No. of cases	Multivariable-adjusted HR (95% CI) †
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‡	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 (y)	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

Abbreviations: T2D, type 2 diabetes; ER, estrogen receptor; HR, hazard ratio; 95% CI, 95% confidence interval; +, positive; −, negative; TNBC, triple-negative breast cancer.

*Adjusted for age (age as the primary time scale)

†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 y, 1 to 2y, >2y), age at menarche ≤11 years old, number of relatives diagnosed with breast cancer (1, ≥2), and birth cohort (born in <1945, 1945 to <1955, 1955 to <1965 or ≥1965), as well as time varying covariates including BMI, menopausal status (binary), interaction term between BMI and menopausal status, age at menopause, 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 years, 21 to <25 years, 25 to <29 years, or ≥29 years), lifetime duration of breastfeeding (weeks, none and tertiles among women with any breastfeeding), and parity (0, 1, 2, ≥3 births).

‡Sulfonylureas, thiazolidinediones, DPP-4 inhibitors, insulin, and others.

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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

			Presence of T2D		T2D and Metformin use, versus no T2D	
		Cases / person-years	All T2D	P interaction	All T2D	P interaction
Time varying menopausal status	Pre-menopausal	464 / 68,733	0.80 (0.48-1.35)	0.43	0.92 (0.50-1.68)	0.60
	Post-menopausal	2,214 / 304,932	1.00 (0.87-1.14)		0.98 (0.83-1.16)	
Race/ethnicity	Non-Hispanic White	2,314 / 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	1,019 / 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	1,311 / 180,607	1.02 (0.86-1.21)	0.09	0.99 (0.80-1.21)	0.28
	≥ median	1,301 / 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)	1,857 / 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 *	No	1,766 / 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	<1y	2,255 / 305,675	0.97 (0.84-1.12)	0.38	0.96 (0.80-1.14)	0.43
	≥ 1y	423 / 67,989	1.06 (0.78-1.43)		1.08 (0.75-1.57)	

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

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 y, 1 to 2y, >2y), age at menarche ≤11 years old, number of relatives diagnosed with breast cancer (1, ≥2), and birth cohort (born in <1945, 1945 to <1955, 1955 to <1965 or ≥1965), as well as time varying covariates including BMI, menopausal status (binary), interaction term between BMI and menopausal status, age at menopause, 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 years, 21 to <25 years, 25 to <29 years, 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.

*No. of first-degree relatives diagnosed with breast cancer ≥2

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