HHS Public Access

Author manuscript

Cancer Res. Author manuscript; available in PMC 2018 November 15.

Published in final edited form as:

Cancer Res. 2017 November 15; 77(22): 6462–6469. doi:10.1158/0008-5472.CAN-17-1903.

Type 2 Diabetes and Incidence of Estrogen Receptor Negative Breast Cancer in African American Women

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Abstract

White women with type 2 diabetes (T2D) have an estimated 20% increased risk of developing breast cancer. Little is known about associations by breast cancer subtype or among African American (AA) women, who are disproportionately affected by T2D and estrogen receptor negative (ER−) breast cancer. We assessed the relation of T2D to incidence of ER− and ER+ breast cancer in data from the Black Women's Health Study, a prospective cohort of AA women enrolled in 1995 and followed biennially. During 847,934 person-years of follow-up, there were 1,851 incident invasive breast cancers, including 914 ER+ and 468 ER− cases. Multivariable Cox proportional hazards models were used to compute hazard ratios (HR) for breast cancer incidence associated with T2D relative to no T2D, controlling for body mass index (BMI) and other potential confounders. The HR for T2D relative to no T2D was 1.18 (95% confidence interval (CI) 1.00–1.40) for overall breast cancer incidence, with the increase accounted for by ER− cancer: HRs were 1.02 (95% CI 0.80–1.31) for ER+ and 1.43 (95% CI 1.03–2.00) for ER− cancer. The HR for T2D and ER− breast cancer was highest among non-obese women (1.92, 95% CI 1.22–3.04). The findings suggest that AA women with T2D are at increased risk of developing ER− breast cancer, and that poor metabolic health may be more important than obesity for this subtype. Given the high prevalence of T2D in AA women, the observed association could, in part, explain racial disparities in incidence of ER− breast cancer.

Keywords

breast cancer; diabetes; estrogen receptor negative; disparities

INTRODUCTION

Diabetes mellitus has been hypothesized to play a role in the development of breast cancer. Postulated mechanisms include effects of hyperinsulinemia on sex-steroid availability (1,2) and insulin-like growth factor 1 (IGF-1) production (3,4). Hormone-independent

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Conflict of interest statement:
The authors declare no potential conflicts of interest.

mechanisms, including chronic inflammation with high levels of pro-inflammatory cytokines, infiltration of adipose depots with pro-inflammatory macrophages, and associated oxidative stress, have also been proposed (5). Epidemiologic evidence to date, while not completely consistent, suggests that women with type 2 diabetes (T2D) have an approximately 20% increased risk of breast cancer (6–10). Uncertainty remains as to whether the weak associations observed for T2D are partly or entirely explained by high body mass index (BMI), given that a high proportion of women with T2D are overweight or obese. Some prior studies have shown no change in the relative risk estimate for T2D with control for BMI (6), whereas in others, control for BMI moved estimates closer to the null (11). The prevalence of obesity is exceptionally high in African American women; in 2013–2014 data from the nationally representative National Health and Nutrition Examination Survey (NHANES), the age-adjusted prevalence of obesity (BMI ≥ 30 kg/m^2) was 57.2% in non-Hispanic black women as compared with 38.7% in non-Hispanic white women, 46.9% in Hispanic women, and 12.4% in non-Hispanic Asian women (12). Therefore, an analysis of T2D and breast cancer risk must carefully consider potential confounding from BMI.

There have been two reports on the relation of T2D to breast cancer risk specifically in African American (AA) women (11,13). The first, an early analysis of Black Women's Health Study (BWHS) data, found no association (13). The second, in the Multiethnic Cohort, reported a hazard ratio (HR) of 1.14 (95% CI 0.99–1.33) among AA women (11). The prevalence of T2D is twice as high in AA women as in white women (14), making it critical to determine whether T2D is associated with increased risk of breast cancer in this population. Further, the etiology of ER− breast cancer, which disproportionately affects AA women, differs in some respects from the etiology of ER+ cancer (15–17). Only a few studies have reported results on T2D and breast cancer by ER subtype and none has provided such data specifically in AA women (6,11). Here we extend previous research in the BWHS by conducting separate analyses for ER+ and ER− breast cancer in 18 years of follow-up.

MATERIALS AND METHODS

Study population

The BWHS was established in 1995 when 59,000 African American women aged 21–69 years from across the U.S. completed mailed health questionnaires. Participants are followed by biennial questionnaires (18). Follow-up is complete through 2013 for 87% of person-time since 1995. The Institutional Review Board of Boston University approved the protocol and reviews the study annually. The study is carried out in accord with the U.S. Common Rule. Study participants give informed consent by completing questionnaires; each questionnaire is accompanied by a cover letter that details the elements of informed consent.

At baseline, participants were asked about weight (current and at age 18), height, waist circumference, hip circumference, number of births, timing of each full-term birth, lactation, age at menarche, oral contraceptive use, menopausal status, age at menopause, supplemental female hormone use, breast cancer in first degree relatives, vigorous physical activity, alcohol consumption, cigarette smoking, years of education, diagnosis of T2D, medications used for diabetes, as well as other factors. Follow-up questionnaires ascertained occurrences of incident breast cancer and updated information on T2D, weight, and other variables.

Breast cancer cases

Each BWHS questionnaire asks about new diagnoses of breast cancer and year of diagnosis. Pathology data is obtained from hospital medical records and the state cancer registries in 24 states in which 95% of participants live. Records have been obtained for approximately 95% of women who reported incident breast cancers, of which 99% were confirmed. Disconfirmed "cases" have been excluded. In the early years of the study, 1995–2000, testing for ER and progesterone receptors (PR) was not universal, leading to missing data on ER and PR status for some participants. We have found that cases with data on receptor status were similar to cases with unknown receptor status with regard to the prevalence of known breast cancer risk factors (19). We used pathology data to classify breast cancers according to SEER stage at time of diagnosis.

Assessment of T2D and covariates

On baseline and follow-up questionnaires, participants were asked if they had ever been diagnosed with diabetes, the age at first diagnosis, and use of injections or pills for diabetes. In a validation study, 217 of 229 (95%) self-reports of diabetes were confirmed by the participants' physicians (20). Given the high accuracy of self-report, we accepted self-report to classify participants as having T2D.

Under-diagnosis of T2D is common in the general population, including among African American women; in the most recent data from NHANES (1999–2002), the prevalence of undiagnosed diabetes among non-Hispanic Black women was estimated to be 4.1% (14). We estimated prevalence of undiagnosed diabetes in the BWHS using blood samples collected from approximately 25% of BWHS participants in 2013 through 2016. Blood specimens were collected, processed, and tested by Quest Diagnostics (Madison, NJ www.QuestDiagnostics.com), an accredited national clinical laboratory, according to the standards set by the Clinical Laboratory Improvement Amendments of 1988 (21). Among the 10,249 participants who had never reported a diagnosis of T2D, 6.1% had HgA1c levels ≥6.5%, a level commonly considered to indicate T2D. Therefore, it is likely that no more than 6% of participants had undiagnosed T2D.

For the present analyses, participants were classified as users of T2D medication if they reported use on any of their three most recent BWHS questionnaires and as nonusers if they did not report use of medications for treatment of T2D on any of those questionnaires. Type of medication was classified as "metformin" if they reported metformin use on any of the three questionnaires regardless of whether they also used another T2D medication during that time.

BMI was calculated as weight (kg) divided by height squared (m^2). Weight was updated by questionnaire every two years, allowing calculation of BMI for each two-year period. Self-reported waist and hip measures from the 1995 questionnaire were used to estimate waist-hip ratio.

Women were classified as premenopausal if they reported that they were still menstruating or had had a hysterectomy with retention of one or both ovaries and were still under the age of 44 (bottom decile of age at natural menopause in the BWHS). They were classified as postmenopausal if they reported a natural menopause (periods stopped at least a year ago), a bilateral oophorectomy, menopause due to radiation or medication, or if they had had a hysterectomy with retention of one or both ovaries and were age 56 or older (top decile of age at natural menopause in the BWHS).

Statistical analysis

Women who had been diagnosed with cancer before enrollment in 1995 (N=1,187) were excluded from the analysis. Women diagnosed with T2D before enrollment in 1995 (N=2,778) were also excluded; they may over-represent those who are not susceptible to a possible adverse effect of T2D because they would have been included in the analysis only if they did not develop breast cancer in the years between T2D diagnosis and enrollment.

Each participant contributed person-time from baseline in 1995 until diagnosis of breast cancer, death, loss to follow-up, or end of follow-up in 2014, whichever came first. Exposure data for each participant were taken from two questionnaire cycles before the end of her follow-up. Thus, for a woman with breast cancer, data on T2D represented her status at least two but less than four years before diagnosis of the cancer. We used Cox proportional hazards regression, stratified by age and questionnaire cycle, to calculate hazard ratios (HR) and 95% confidence intervals (CIs), with adjustment for BMI (continuous), BMI at age 18 (<20, 20–24, ≥25 kg/m^2), number of births (0, 1 or 2, ≥3), age at first birth (<25, ≥25), age at menarche (<11, 11, 12–13, ≥14), first degree family history of breast cancer (yes, no), oral contraceptive use (never, <5 years duration, ≥5 years duration), and use of estrogen with progesterone postmenopausal hormones (never, <5 years duration, ≥5 years duration). Covariates were updated throughout follow-up. For analyses of ER-specific cancer, women were censored at the time of diagnosis of any other breast cancer. We conducted analyses stratified on BMI and waist-hip ratio in order to disentangle obesity and T2D. We also stratified on menopausal status because BMI has been shown to have different associations for pre- and postmenopausal breast cancer (22,23). We used interaction terms and Wald statistics to test for multiplicative interaction, and we performed a contrast test to assess heterogeneity of associations across ER subtypes (24).

RESULTS

The prevalence of T2D in the overall BWHS cohort in 2015 was 19.0%. Among 54,337 women in the analytic cohort, 6,694 were diagnosed with T2D after enrollment in 1995. During 870,358 person-years of follow-up, there were 1,851 incident invasive breast cancers, including 914 ER+ and 485 ER− cancers. As shown in Table 1, women with T2D were older, had a higher recent BMI and BMI at age 18, fewer years of education, earlier age at menarche, and less frequent vigorous physical activity than non-diabetic women. Frequency of mammographic screening was high, with 81% of both diabetics and non-diabetics aged 40–69 years having had a recent mammogram.

In age-adjusted analyses, the HR for T2D relative to no T2D in relation to breast cancer risk was 1.12 (95% CI 0.95–1.32) (Table 2). In multivariable analyses, HRs were 1.18 (95% CI 1.00–1.40) for all T2D and 1.20 (95% CI 1.00–1.43) for T2D diagnosed at least five years previously. Our models included both recent BMI and BMI at age 18 in order to account for possible independent effects. The correlation coefficient for the two BMI variables was 0.51, and statistical models performed well with inclusion of both terms. The fully adjusted model with no BMI terms yielded a HR of 1.16 for T2D and breast cancer; the HR was increased very slightly to 1.18 or 1.19 with inclusion of recent BMI alone, BMI at age 18 alone, or both BMI terms. Results were essentially the same when we repeated the analyses with additional control for waist-hip ratio (<75, 75–85, ≥85) as a measure of central obesity (data not shown).

A positive association with T2D was observed for ER− breast cancer but not for ER+ cancer: multivariable HRs were 1.43 (95% CI 1.03–2.00) for ER− breast cancer and 1.02 (95% CI 0.80–1.31) for ER+ cancer (Table 2). A contrast test to assess heterogeneity of associations by ER status gave a p-heterogeneity of 0.11. All other analytic runs were carried out separately for ER+ and ER− breast cancer.

The positive association of T2D with incidence of ER− breast cancer was evident at all stages, with HRs of 1.47 (95% CI 0.87–2.48) for stage 1, 1.35 (95% CI 0.76–2.38) for stage 2, and 2.34 (95% CI 1.15–4.76) for cancer diagnosed at stages 3 or 4 (data not shown).

For ER+ breast cancer, HRs were close to 1.0 regardless of whether or not T2D was treated with medication (Table 3). However, the HR for T2D with metformin was 0.92, whereas the HR was 1.49 (95% CI 0.96–2.32) for T2D treated with medications other than metformin. For ER− breast cancer, HRs were 2.03 (95% CI 1.13–3.62) for T2D not treated with medication and 1.30 (95% CI 0.88–1.92) for treatment with diabetes medications. Results for ER− breast cancer did not differ by type of medication used. An examination of HgA1c levels among the subset of diabetic women who provided a blood sample (n=2,025) indicated that their T2D was not well-controlled: only 38% of the women had HgA1c levels below 6.5% and 40% had levels ≥7.0%. HgA1c levels were highest in women who reported use of diabetes medications, with only 32% below 6.5% and 47% ≥7.0%.

Table 4 presents results on both T2D and BMI within strata of menopausal status. Associations of T2D with ER+ cancer were close to the null in both pre- and postmenopausal women (p-interaction 0.95). T2D was associated with ER− breast cancer among premenopausal women (HR 2.39, 95% CI 1.30–4.39), but not among postmenopausal women (p-interaction 0.13). Higher BMI was associated with increased risk of ER+ breast cancer in postmenopausal women but not premenopausal women (p-interaction 0.02), whereas there was no association of BMI with risk of ER− breast cancer in either group.

To disentangle associations of obesity and T2D with breast cancer risk, we repeated the T2D analyses within strata of BMI (<30, ≥30 kg/m^2) and waist-hip ratio (<0.85, ≥0.85) (Table 5). T2D was not associated with increased risk of ER+ breast cancer in any subgroup of BMI or waist-hip ratio. For ER− breast cancer, however, T2D was associated with increased risk among women with BMI <30 (HR 1.92, 95% CI 1.22–3.04) but not among women with BMI ≥30 (p-interaction 0.05). A positive association of T2D with risk of ER− breast cancer was also observed among women with waist-hip ratio <0.85 (HR 1.55 (95% CI 0.99–2.45)), whereas the comparable estimate was smaller, 1.26, and not statistically significant among women with waist-hip ratio ≥0.85 (p-interaction 0.40).

DISCUSSION

The present analysis, from a large cohort of AA women, suggests that women with T2D have a 40% increased risk of developing ER− breast cancer. The association was observed primarily among women who were not obese. T2D was not associated with incidence of ER + breast cancer.

Meta-analyses of T2D and risk of overall breast cancer have shown an approximately 20% increased risk associated with T2D (7,8). Two large individual studies have been published since the most recent meta-analysis (9,11). The first, which linked electronic medical records from a health maintenance organization in Israel with registry data, reported that the HR for incident T2D diagnosed 2–11 years before the end of follow-up was 1.29 (1.22–1.36) in postmenopausal women, whereas the comparable HR in pre-menopausal women was 1.02 (9). The other, based on data from the Multiethnic Cohort Study (MEC), reported an HR of 1.08 (95% CI 1.00–1.16) across all ethnic groups (11). In MEC, analyses stratified by race/ethnicity, the only statistically significant association was in Latina women; the HR in AA women was 1.14 (95% CI 0.99–1.33).

Two previous studies have reported results separately by ER subtype (6,11). Both reported similar associations with ER+ and ER− breast cancer, with no evidence of a stronger association with ER− cancer. The MEC did not provide ER-specific results by race/ethnicity (11). Three case-only cross-sectional studies reported on breast tumor characteristics according to T2D status (25–27) and all three reported a higher proportion of ER− relative to ER+ tumors among diabetics as compared with nondiabetics among premenopausal women. In the present study, associations with ER− cancer were stronger among premenopausal women. Most previous case-control and cohort studies have not had adequate power to assess associations among premenopausal women because T2D, until recently, has occurred primarily among postmenopausal women or women close to menopause. For example, in a report from the Nurses' Health Study based on 5,189 incident cases of breast cancer, only 14 incident breast cancer cases occurred among premenopausal women with T2D (6). Among AA women, T2D occurs at younger ages and more frequently (14); nevertheless, in the present analysis, there were only 24 premenopausal cases with T2D and the higher HRs observed in premenopausal vs. postmenopausal women may be a chance finding

Metformin, an oral biguanide that increases insulin sensitivity and improves glycemic control, was introduced in the early 1990s and is now the most widely used oral medication for T2D (28,29). In Women's Health Initiative clinical trial data, there was no association of T2D with incidence of invasive breast cancer overall (30). However, relative to nondiabetics, there was an increased incidence (HR 1.16, 95% CI 0.93–1.45) for women taking medications other than metformin and a reduced incidence (HR 0.75, 95% CI 0.57–0.99) in women taking metformin. That pattern was observed for both ER+/PR+ breast cancer and ER−/PR− breast cancer, with a stronger association for ER−/PR− breast cancer: HR 1.78, 95% CI 1.05–3.03, for non-users of metformin. Our findings are somewhat consistent. Relative to non-diabetics, diabetics who used medications other than metformin had a 40% increased risk of both ER+ and ER− breast cancer, whereas HRs for those who used metformin were lower: 0.92 for ER+ and 1.26 for ER− breast cancer. In addition, diabetics who reported no diabetes medication use had a two-fold risk of ER− breast cancer. However, the BWHS findings regarding medication use were based on small numbers of cases and the only statistically significant association was a two-fold risk of ER− cancer for T2D without medication use. The stronger association observed for T2D not treated with medication appears to lend support to the hypothesis that uncontrolled disease influences breast cancer development through metabolic pathways. On the other hand, diabetic women who are not being treated with medications tend to have less severe disease. Indeed, among the approximately 2,000 diabetic women in the BWHS who gave a recent blood sample, those who had never taken diabetes medications had lower levels of HgA1c than did those who reported using diabetes medications.

A concern in previous research on T2D and breast cancer risk is potential confounding by BMI given that high BMI is the major contributing cause of T2D and a risk factor for postmenopausal ER+ breast cancer. Even when BMI is included in regression models, there is a potential for residual confounding because of measurement error. In the present study, adjustment for BMI changed the estimates only slightly, and away from the null rather than closer to the null, suggesting that BMI was not a material confounder.

The present research was prompted, in part, by the emerging concept of “metabolically healthy obesity” (31,32). We hypothesized that T2D may lead to an increased risk of breast cancer, and especially to ER− breast cancer, independent of obesity, through mechanisms unrelated to steroid hormones (e.g., inflammation). Our results from analyses stratified on obesity and waist-hip ratio lend support to the hypothesis. T2D was associated with a 92% increased risk of ER− breast cancer among non-obese women and a 55% increased risk among women with waist-hip ratio <0.85. A study of Asian-American women found a similar pattern for all breast cancer: T2D was more strongly associated with breast cancer risk among women in the lowest BMI category and among women in the lowest waist-hip ratio category (33). A recent analysis of Women’s Health Initiative data classified women as to metabolic status using data on insulin resistance (i.e., HOMA-IR) or fasting insulin level and examined breast cancer risk according to cross-classification of metabolic health and normal vs. overweight status (32). Compared with women who were metabolically healthy and of normal weight, women classified as metabolically unhealthy were at increased risk of breast cancer regardless of their BMI; women who were overweight but apparently metabolically healthy were not at increased risk (32).

Multiple mechanisms have been proposed to explain associations of T2D with breast cancer risk (5,34). Perhaps of most relevance to the current findings of increased risk of ER− cancer, the dysregulated glucose metabolism experienced by diabetics can lead to a chronic pro-inflammatory condition with associated oxidative stress and promotion of tumor initiation and progression (35,36). In a chronic inflammatory state, there are typically high levels of pro-inflammatory cytokines (37), reductions in adiponectin (38), and infiltration of adipose depots with immune cells, notably pro-inflammatory macrophages (39). These adipose tissue macrophages secrete cytokines that promote insulin resistance in adipocytes (40) and are identifiable histologically as CD68+ 'crown-like' structures that encircle stressed or dead adipocytes (41,42). Evidence is accumulating that chemokines and cytokines of the breast adipose microenvironment, such as interleukin-6 (43), promote carcinogenic processes in epithelial cells (44), including increased cell proliferation (45) and survival (46), and epithelial-to-mesenchymal transition in early stage breast cancer cells (47,48).

Increased mammographic screening in diabetic women is an unlikely explanation for the present results as the positive association of T2D with risk of ER− breast cancer was evident regardless of stage at diagnosis. In addition, a high proportion of BWHS participants over the age of 40 reported regular screening.

Potential limitations include reliance on self-report rather than medical records for exposure status. However, misclassification of T2D status was likely to be small; a validation study of self-reported diabetes yielded a positive predictive value of over 95% and estimates from within the BWHS and U.S. population data indicate that only 4–6% of African American women who have not been diagnosed with T2D actually have HgA1c levels above the cut-point used to indicate T2D. Misclassification of T2D status would weaken associations between T2D and breast cancer risk, meaning that the observed associations with risk of ER − breast cancer may underestimate the true association. As further reassurance on the validity of T2D classification in the BWHS, we note that the BWHS has published numerous papers on risk factors for T2D that have identified associations consistent with the literature (49,50). A more important limitation is the lack of statistical power for robust analyses of medication use for T2D. Although our analyses included 6,694 women with T2D, our ability to make inferences about the intriguing results on use of metformin and other medications was limited by the relatively small numbers of users in each category.

In conclusion, findings from the present study suggest that AA women with T2D are at increased risk of developing ER− breast cancer and that poor metabolic health may be more important than BMI for ER− disease. Given that the prevalence of T2D is twice as high in non-Hispanic blacks as in non-Hispanic whites (14), the observed association, if confirmed, may explain in part why AA women have a disproportionately high incidence of ER− breast cancer compared to U.S. white women. Whether adequate treatment with metformin or other medications can ameliorate the increased risk associated with diabetes requires further research.

Acknowledgments

Financial support:

This research was funded by National Institutes of Health U01 CA182898, R01 CA058420, and UM1 CA164974. KAB was supported in part by the Dahod Breast Cancer Research Program at the Boston University School of Medicine. The sponsors were not involved in the study design, data collection, data analyses and interpretation, or manuscript writing and submission.

Pathology data were obtained from numerous state cancer registries (Arizona, California, Colorado, Connecticut, Delaware, District of Columbia, Florida, Georgia, Hawaii, Illinois, Indiana, Kentucky, Louisiana, Maryland, Massachusetts, Michigan, New Jersey, New York, North Carolina, Oklahoma, Pennsylvania, South Carolina, Tennessee, Texas, Virginia). The results reported do not necessarily represent their views or the views of the NIH.

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Table 1

Age-standardized characteristics of 54,337 participants of the Black Women's Health Study according to diabetes status

	No diabetes	Type 2 diabetes
Total person-years (n)	815,252	55,106
Mean age (years)	47.0 ± 11.2	56.1 ± 10.6
Mean body mass index (kg/m^2)	29.5 ± 6.8	34.9 ± 8.4
Mean body mass index at age 18 (kg/m^2)	21.3 ± 3.9	23.7 ± 5.5
Waist to hip ratio ≥ 0.85 (%)	29	51
≥ 16 years of education (%)	53	47
Age at menarche ≤ 11 (%)	11	18
Nulliparous (%)	27	28
First birth before age 25 (%)	73	74
Never lactation among parous women (%)	56	60
Premenopausal (%)	60	57
Use of oral contraceptives for ≥ 5 years (%)	37	35
Ever use estrogen with progesterone supplements (%)	10	10
First degree family history of breast cancer (%)	9	7
Vigorous activity, ≥ 3 hrs/wk (%)	20	13
Current drinker, ≥ 7 drinks/wk (%)	5	3
Current smoker (%)	13	13
Recent mammography among women age 40–69 (%)	81	81
Tumor characteristics among breast cancer cases		
Estrogen receptor status		
Estrogen receptor positive (n)	841	73
Estrogen receptor negative (n)	426	42
Unknown estrogen receptor status (n)	411	48
Stage at diagnosis		
Stage I (n)	638	62
Stage II (n)	509	36
Stage III (n)	141	15
Stage IV (n)	49	4
Unknown stage (n)	351	46

Table 2

Type 2 diabetes (T2D) in relation to incidence of invasive breast cancer

	Person years	Breast cancer cases	Age-adjusted HR (95% CI)	MV HR* (95% CI)
All breast cancer				
No diabetes	812,945	1,688	Reference	Reference
T2D	54,875	163	1.12 (0.95–1.32)	1.18 (1.00–1.40)
Time since T2D diagnosis				
< 5 years	6,649	18	1.03 (0.65–1.64)	1.07 (0.67–1.70)
≥ 5 years	48,225	145	1.13 (0.95–1.35)	1.20 (1.00–1.43)
ER+ breast cancer				
No diabetes	812,034	841	Reference	Reference
T2D	54,780	73	0.98 (0.77–1.25)	1.02 (0.80–1.31)
Time since T2D diagnosis				
< 5 years	6,639	8	0.86 (0.43–1.72)	0.88 (0.44–1.77)
≥ 5 years	48,141	65	1.00 (0.77–1.29)	1.05 (0.80–1.36)
ER− breast cancer				
No diabetes	811,623	426	Reference	Reference
T2D	54,759	42	1.33 (0.96–1.85)	1.43 (1.03–2.00)
Time since T2D diagnosis				
< 5 years	6,637	5	1.17 (0.48–2.84)	1.23 (0.51–2.98)
≥ 5 years	48,122	37	1.36 (0.96–1.92)	1.46 (1.03–2.08)

*Adjusted for age, body mass index (BMI), BMI at age 18, parity, age at first birth, age at menarche, duration of oral contraceptive use, duration of menopausal hormone use, and first degree family history of breast cancer.

HR, hazard ratio; CI, confidence interval; MV, multivariable; ER, estrogen receptor

Table 3

Use of medications for type 2 diabetes in relation to ER+ and ER− breast cancer incidence

	ER+ breast cancer		ER− breast cancer	
	Cases	**MV HR (95% CI)**	**Cases**	**MV HR (95% CI)**
No diabetes	841	Reference	426	Reference
T2D medication use *				
No	13	0.93 (0.54, 1.61)	12	2.03 (1.13–3.62)
Yes	58	1.07 (0.81, 1.40)	29	1.30 (0.88–1.92)
Type of medication *				
Metformin	37	0.92 (0.65–1.28)	21	1.26 (0.80–1.98)
All other types	21	1.49 (0.96–2.32)	8	1.41 (0.69–2.86)

* Medications reported in the three most recent follow-up questionnaires, covering period of approximately 6 years prior to breast cancer diagnosis (for cases) or end of follow-up (non-cases)

HRs adjusted for age, BMI, BMI at age 18, parity, age at first birth, age at menarche, duration of oral contraceptive use, duration of menopausal hormone use, and first degree family history of breast cancer.

Table 4

Body mass index (BMI) and type 2 diabetes (T2D) in relation to ER+ and ER− breast cancer incidence, stratified by menopausal status

	ER+ breast cancer		ER− breast cancer	
	Cases	**MV HR (95% CI)**	**Cases**	**MV HR (95% CI)**
Premenopausal				
Type 2 diabetes				
No	300	Reference	176	Reference
Yes	12	1.15 (0.64–2.08)	12	2.39 (1.30–4.39)
BMI (kg/m^2)				
< 25	92	Reference	53	Reference
25–29	103	1.00 (0.75–1.34)	66	1.12 (0.77–1.62)
30–34	58	0.96 (0.68–1.36)	41	1.13 (0.73–1.76)
≥ 35	59	1.20 (0.82–1.76)	27	0.81 (0.47–1.40)
Postmenopausal				
Type 2 diabetes				
No	441	Reference	188	Reference
Yes	56	0.99 (0.74–1.32)	26	1.27 (0.83–1.95)
BMI (kg/m^2)				
< 25	89	Reference	48	Reference
25–29	176	1.22 (0.95–1.59)	90	1.07 (0.75–1.53)
30–34	141	1.53 (1.16–2.02)	46	0.82 (0.54–1.24)
≥ 35	97	1.53 (1.12–2.09)	35	0.83 (0.52–1.34)

HRs adjusted for age, BMI at age 18, parity, age at first birth, age at menarche, duration of oral contraceptive use, duration of menopausal hormone use, first degree family history of breast cancer, and BMI for the T2D analysis or T2D for the BMI analysis

p-value for interaction of T2D and menopausal status: 0.95 for ER+ and 0.13 for ER− cancer

p-value for interaction of BMI and menopausal status: 0.02 for ER+ and 0.52 for ER− cancer

Table 5

Type 2 diabetes in relation to ER+ and ER− breast cancer incidence, within strata of body mass index (BMI) and waist-hip ratio (WHR)

	ER+ breast cancer		ER− breast cancer	
	Cases	**MV HR (95% CI)**	**Cases**	**MV HR (95% CI)**
BMI < 30kg/m^2				
No diabetes	494	Reference	264	Reference
Type 2 diabetes	21	0.86 (0.55–1.33)	22	1.92 (1.22–3.04)
BMI ≥ 30 kg/m^2				
No diabetes	342	Reference	161	Reference
Type 2 diabetes	51	1.07 (0.79–1.46)	19	1.05 (0.64–1.72)
WHR < 85				
No diabetes	532	Reference	274	Reference
Type 2 diabetes	38	1.13 (0.81–1.60)	22	1.55 (0.99–2.45)
WHR ≥ 85				
No diabetes	210	Reference	114	Reference
Type 2 diabetes	25	0.81 (0.53–1.24)	16	1.26 (0.72–2.18)

HRs adjusted for age, BMI at age 18, parity, age at first birth, age at menarche, duration of oral contraceptive use, duration of menopausal hormone use, and first degree family history of breast cancer.

p-value for interaction of type 2 diabetes with BMI: 0.20 for ER+ and 0.05 for ER−

p-value for interaction of type 2 diabetes with WHR: 0.22 for ER+ and 0.40 for ER−