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ORIGINAL PAPER

Diabetes, obesity, and subsequent risk of postmenopausal breast cancer among white and black women in the Southern Community Cohort Study

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Abstract

Purpose Meta-analyses have reported a small but positive association between diabetes and postmenopausal breast cancer risk, with summary relative risks of approximately 1.15. We analyzed data from the Southern Community Cohort Study (SCCS) following an underserved population with high diabetes prevalence to prospectively examine whether diabetes was associated with subsequent postmenopausal breast cancer risk and whether obesity modified this effect.

Methods Women with incident breast cancer were identified through linkage with state cancer registries and the National Death Index (213 white, 418 black cases). Person-years were calculated from date of entry into the SCCS until the earliest of date of breast cancer diagnosis, date of death, or date of last follow-up (8,277 white, 16,458 black noncases). Data on diabetes diagnosis were obtained through baseline and follow-up surveys. Cox regression was applied to examine the association between diabetes and postmenopausal breast cancer risk.

Results After adjustment for confounding, there was no association between self-reported diabetes and postmenopausal breast cancer risk among white (hazard ratio [HR] 1.02, 95% confidence interval [CI] 0.75–1.40) or black (HR 1.00, 95% CI 0.81–1.22) women. Nor was there evidence that obesity modified the effect of diabetes on postmenopausal breast cancer in women of either race.

Conclusions We found no evidence of the hypothesized increased risk of breast cancer among women with diabetes. The breast cancer risks among those with diabetes in this population suggest that the association between these two illnesses is complex.

Keywords Postmenopausal breast cancer · Diabetes · Obesity · Prospective cohort study

Introduction

Diabetes has been identified as a weak risk factor for breast cancer among postmenopausal women, independent of obesity [1]. In agreement with earlier meta-analyses [1–4], the largest meta-analysis of the association between diabetes and postmenopausal breast cancer risk among predominantly white women reported a summary relative risk (SRR) of 1.15 [95% confidence interval (CI) 1.07–1.24] prior to adjustment for body mass index (BMI, kg/m^2) [5]. Although not restricted to postmenopausal women (SRR 1.33, 95% CI 1.18–1.51), adjustment for BMI attenuated (SRR 1.16, 95% CI 1.08–1.24), but did not remove, the association [5]. More recently, the Multiethnic Cohort (MEC) which consists of an ethnically diverse population reported a hazard ratio (HR) of 1.16 for the diabetes and postmenopausal breast

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cancer risk association that was reduced to 1.09 and was no longer significant after adjustment for BMI at cohort entry [6]. Within the MEC, after stratifying by BMI, diabetes-associated breast cancer risk was of borderline significance among obese women only (HR 1.12, 95% CI 1.00–1.26) and there was no evidence of effect modification ($p = 0.31$) [6]. To date, only two prospective cohort studies have examined the diabetes and breast cancer risk association among black women [6, 7]. The MEC reported a HR of 1.14 (95% CI 0.99–1.33) after adjustment for BMI at cohort entry, but was not restricted to postmenopausal breast cancer [6]. Nor was the Black Women's Health Study (BWHS) restricted to postmenopusal breast cancer; after adjustment for BMI at cohort entry and at age 18, BWHS reported a HR of 1.18 (95% CI 1.00–1.40) [7].

Proposed biological mechanisms for the positive association between diabetes and postmenopausal breast cancer risk have included a direct effect of diabetes on increased breast cancer growth by altering levels of insulin, insulin-like growth factors, and endogenous sex hormones [1], residual confounding by obesity [8], or an indirect effect due to differences in mammography use among women who have diabetes compared with women who do not have diabetes [9]. In a previous analysis of the SCCS, we found that neither white nor black postmenopausal women with diabetes were more likely to have had a mammogram within the past year than women without diabetes [10]. The diabetes and postmenopausal breast cancer risk association has been complicated by the use of diabetes drugs such as metformin which pre-clinical studies show inhibit breast carcinogenesis [11]. However, a recent meta-analysis reported a significant reduction in risk of all-cause mortality, but not breast cancer incidence, associated with metformin use [12]. In an attempt to clarify and disentangle the associations between diabetes, obesity, and postmenopausal breast cancer risk in a racially diverse population, we conducted a prospective cohort study in the Southern Community Cohort Study (SCCS) to examine whether diabetes was associated with subsequent breast cancer and whether obesity modified this effect among postmenopausal white and black women.

Materials and methods

Detailed methods of the SCCS [13, 14] appear elsewhere. Briefly, the SCCS population included 15,463 white women and 32,457 black women aged 40–79 at enrollment who completed a baseline interview in 12 southeastern states between 2002 and 2009. Women were primarily low-income with the majority (86%) enrolled in-person at participating Community Health Centers (CHC) and the remaining women sampled from the general population. Computer-assisted in-person interviews were conducted for CHC enrollees, while general population participants completed mailed questionnaires. Women who had undergone treatment for cancer during the past year were excluded. Subsequent to enrollment, 1,181 white and black women who were diagnosed with incident invasive breast cancer postmenopausally were identified through linkage with state cancer registries in the study enrollment states and the National Death Index. Breast cancers were defined by International Classification of Disease for Oncology Codes (ICD-O-3) C50.0–C50.6 and C50.8–C50.9. An algorithm was used to define menopausal status for women who reported at baseline they were premenopausal or had unknown menopausal status, and follow-up questionnaires were used to clarify age and menopausal status at breast cancer diagnosis. Among the sub-cohort of 12,439 white women and 29,096 black women who had not been diagnosed with another cancer, follow-up surveys were completed from 2007 to 2011 (74.2% of whites and 67.7% of blacks), and from 2012 to 2015 (59.5% of whites and 51.9% of blacks). Person-years were calculated from the date of entry into the SCCS until the earliest of date of breast cancer diagnosis, date of death, or date of last follow-up. Cases and noncases who completed the baseline survey only ($n = 10{,}581$) were premenopausal or unknown menopausal status by the end of follow-up ($n = 3{,}922$), had unknown BMI ($n = 631$), unknown diabetes status ($n = 1{,}642$), and diabetes diagnosed subsequent to breast cancer or diabetes diagnosed within 1 year prior to a breast cancer diagnosis ($n = 50$) were excluded, resulting in 631 cases and 24,735 noncases for analysis. Of these, the distribution of surveys completed was baseline and first follow-up (3.5% of cases, 6.4% of noncases), baseline and second follow-up (30.9% of cases, 25.5% of noncases), and all three surveys (65.6% of cases, 68.4% of noncases). In this prospective cohort study, baseline and follow-up surveys collected information on suspected breast cancer risk factors including self-reported history of diagnosed diabetes, current metformin use, and BMI at cohort entry.

Institutional Review Boards of Vanderbilt University Medical Center and Meharry Medical College approved this study's protocol. With the exception of tumor estrogen receptor (ER) status available from cancer registries, all variables in the present analysis are based on self-report. Women were considered to have diabetes if they reported during their baseline or follow-up surveys having been told by their doctor they had diabetes or high blood sugar. A validation sub-study conducted within the SCCS found that 96% of self-reported diabetes could be confirmed through medical records or elevated HbA1c measurements [14]. Information on time since diabetes diagnosis (< 10 years, and ≥ 10 years) based on age at first diabetes diagnosis, and current use of metformin was used to further categorize diabetes.

We stratified by race a priori, since a recent analysis of the SCCS showed that obesity accounted for more incident

diabetes among white than among black participants [15], suggesting the biological pathways linking diabetes, obesity, and breast cancer may differ by race. We assessed effect modification by BMI (<30 kg/m^2 vs. ≥ 30 kg/m^2) for comparison with the MEC's examination of effect modification by BMI of the diabetes and breast cancer risk association [6]. Potential confounders of the diabetes and postmenopausal breast cancer risk associations included age, total annual household income, educational level, marital status, family history of breast cancer, health insurance coverage, recruitment source, age at menarche, history of benign breast disease, parity, age at first live birth, use of over the counter nonsteroidal anti-inflammatory drugs (OTC NSAIDs), hypertension, high cholesterol, years since last mammogram, smoking, alcohol intake, age at menopause, use of hormone replacement therapy (HRT), use of oral contraceptives, hysterectomy, BMI, BMI at age 21, moderate and vigorous physical activity in metabolic equivalent (MET) hours per week (quartiles among noncases), and energy intake in calories per day (quartiles among noncases).

Statistical analyses were performed with SAS version 9.4. Crude and age-adjusted incidence rates based on the United States 2000 standard population were calculated by race and diabetes status. We utilized Cox proportional hazards regression using age as the time scale to estimate the hazard ratio (HR) of breast cancer associated with diabetes while accounting for effect modification and controlling for potential confounding factors [16]. Diabetes was treated as a time-dependent variable with women contributing person-years without diabetes followed by person-years with diabetes if the diagnosis was reported during follow-up. Menopausal status was also time-dependent such that person-years after menopause only were included. An interaction term, the product of diabetes and race or BMI, was added to Cox regression models and likelihood ratio tests were performed to test for effect modification. We assessed differences between women with breast cancer and women without breast cancer for potential confounders using Chi-square tests. Variables were considered confounders if their addition to the model changed the crude HR by 10 percent or more. We stratified by race and adjusted for age, health insurance coverage, and high cholesterol; we further adjusted for BMI for comparability with other studies. In addition, we examined the association between self-reported diabetes and breast cancer risk by ER status.

Results

Table 1 presents those demographic and other characteristics that differed significantly between white postmenopausal breast cancer cases ($n=213$) and noncases ($n=8{,}277$) or black postmenopausal cases ($n=418$) and noncases ($n=16{,}458$). In comparison with noncases of both races, cases tended to be older, to have a family history of breast cancer, to have a history of benign breast disease, to have high cholesterol, and to have had a shorter time since their last mammogram. In addition, white cases were more likely to have hypertension, while black cases tended to be on Medicare/Medicaid only, to have never smoked, and to have higher BMI. The distribution of all other examined characteristics was similar between cases and noncases, regardless of race.

Table 2 presents the crude and age-adjusted incidence rates of breast cancer among white and black women with and without diabetes. Breast cancer incidence was lower among white women without diabetes than white women with diabetes, while the reverse was true among black women.

The prevalence of diabetes was lower among whites (31.1%) than among blacks (43.7%) (data not shown). The mean time since diabetes diagnosis (whites 7.3 years, blacks 7.6 years), age at first diagnosis (whites 50.2 years, blacks 49.3 years), and time between diabetes and breast cancer diagnosis (whites 12.3 years, blacks 13.9 years) were similar across racial groups. Among women with diabetes, whites (56.5%) were more likely than blacks (48.5%) to report current use of metformin. Those women who did not report current metformin use may have been controlling their diabetes through diet, another formulation, insulin, or a combination of therapies.

Table 3 presents age- and multivariate-adjusted HRs and 95% CIs for the association between diabetes measures and breast cancer risk among white and black postmenopausal women. After adjustment for age, health insurance coverage, high cholesterol, and BMI, there was no association between self-reported diabetes and postmenopausal breast cancer risk among white (hazard ratio [HR] 1.02, 95% confidence interval [CI] 0.75–1.40) or black (HR 1.00, 95% CI 0.81–1.22) women, nor were these effects modified by race (p for interaction $=0.88$). Among white women with diabetes, there was no association with time since diabetes diagnosis, but black women were at greater risk of breast cancer if their diabetes diagnosis was 10 or more years prior (HR 1.48, 95% CI 1.09–2.02). The associations between the current use of metformin and breast cancer were modified by race with white women at increased risk and black women at decreased risk (p for interaction $=0.003$).

In sensitivity analyses, our findings were comparable after (1) including premenopausal women (white HR 1.02, 95% CI 0.75–1.39; black HR 0.95, 95% CI 0.78–1.17), (2) excluding the 4.7% of women who reported they were diagnosed with diabetes prior to age 30 and were assumed to have type 1 diabetes (white HR 1.05, 95% CI 0.77–1.43; black HR 0.98, 95% CI 0.79–1.20), and (3) adjusting for BMI at age 21 in addition to BMI at cohort entry (white HR

Table 1 Comparison of white and black postmenopausal cases and noncases for demographic characteristics and breast cancer risk factors, Southern Community Cohort Study, 2002–2015

Whites	Cases ($n=213$)		Noncases ($n=8,277$)		
	n	%	*n*	%	*p* value
Age (years)					
40–44	7	3.3	1004	12.1	<0.0001
45–49	27	12.7	1662	20.1	
50–54	39	18.3	1736	21.0	
55–59	59	27.7	1570	19.0	
60–64	32	15.0	1178	14.2	
65–69	28	13.1	664	8.0	
70–74	14	6.6	307	3.7	
75–79	7	3.3	156	1.9	
Family history of breast cancer					
No	167	82.3	7058	87.7	0.02
Yes	36	17.7	991	12.3	
Health insurance coverage					
None	59	28.1	2837	34.5	0.15
Medicare/Medicaid only	57	27.1	1984	24.2	
Any private/CHAMPUS/other	94	44.8	3393	41.3	
History of benign breast disease					
No	135	63.7	6254	75.7	<0.0001
Yes	77	36.3	2005	24.3	
Hypertension					
No	82	38.5	4208	50.9	0.0004
Yes	131	61.5	4067	49.1	
High cholesterol					
No	100	47.0	4529	54.8	0.02
Yes	113	53.0	3738	45.2	
Time since last mammogram (years)					
Never	13	6.2	874	10.6	0.05
3–31	33	15.7	1491	18.2	
≤2	164	78.1	5841	71.2	
Smoking					
Never	99	46.7	3458	42.0	0.11
Former	61	28.8	2201	26.7	
Current	52	24.5	2578	31.3	
Body mass index (kg/m^2)					
<25	52	24.4	2172	26.2	0.54
25–29.9	51	23.9	2207	26.7	
30–34.9	48	22.5	1818	22.0	
≥35	62	29.1	2080	25.1	
Body mass index (kg/m^2) at age 21					
<25	178	85.6	6542	80.2	0.24
25–29.9	19	9.1	903	11.1	
30–34.9	6	2.9	413	5.1	
≥35	5	2.4	295	3.6	
Blacks	Cases ($n=418$)		Noncases ($n=16,458$)		
	n	%	*n*	%	*p* value
Age (years)					
40–44	45	10.8	2640	16.0	0.0007

Table 1 (continued)

Blacks	Cases ($n=418$)		Noncases ($n=16,458$)		
	n	%	*n*	%	*p* value
45–49	85	20.3	3789	23.0	
50–54	83	19.9	3826	23.3	
55–59	85	20.3	2676	16.3	
60–64	56	13.4	1730	10.5	
65–69	36	8.6	986	6.0	
70–74	18	4.3	545	3.3	
75–79	10	2.4	266	1.6	
Family history of breast cancer					
No	338	84.1	14210	89.8	0.0002
Yes	64	15.9	1616	10.2	
Health insurance coverage					
None	125	30.2	5922	36.2	0.04
Medicare/Medicaid only	146	35.3	5390	33.0	
Any private/CHAMPUS/other	143	34.5	5027	30.8	
History of benign breast disease					
No	325	77.8	14121	86.0	<0.0001
Yes	93	22.2	2292	14.0	
Hypertension					
No	133	31.9	5798	35.2	0.16
Yes	284	68.1	10658	64.8	
High cholesterol					
No	237	56.8	10407	63.3	0.007
Yes	180	43.2	6025	36.7	
Time since last mammogram (years)					
Never	36	8.8	2166	13.3	0.03
3–31	51	12.4	1894	11.6	
≤2	324	78.8	12257	75.1	
Smoking					
Never	210	50.4	8074	49.3	0.05
Former	102	24.5	3392	20.7	
Current	105	25.2	4912	30.0	
Body mass index (kg/m^2)					
<25	45	10.8	2487	15.1	0.04
25–29.9	99	23.7	4177	25.4	
30–34.9	115	27.5	4209	25.6	
≥35	159	38.0	5585	33.9	
Body mass index (kg/m^2) at age 21					
<25	310	77.3	11961	76.0	0.73
25–29.9	60	15.0	2432	15.5	
30–34.9	22	5.5	834	5.3	
≥35	9	2.2	503	3.2	

1.04, 95% CI 0.76–1.43; black HR 1.01, 95% CI 0.82–1.24) as was done in the BWHS [7].

Table 4 presents age- and multivariate-adjusted HRs and 95% CIs for the association between self-reported diabetes and breast cancer risk among postmenopausal white and black women, stratified by obesity status. Among white and black women, the association between diabetes and breast cancer risk was similar regardless of obesity status (p for interaction ≥ 0.3).

Table 5 presents age- and multivariate-adjusted HRs for the association between self-reported diabetes and postmenopausal breast cancer risk among white and

Table 2 Incident breast cancer rates among white and black women with and without diabetes, Southern Community Cohort Study, 2002–2015

	Whites		Blacks	
	Diabetes ($n=2,636$)	No diabetes ($n=5,854$)	Diabetes ($n=7,382$)	No diabetes ($n=9,494$)
Incident cases (n)	66	147	185	233
Person-years (PY)	17,270	37,709	54,950	67,785
Incident rate/1,000 PY (95% CI)				
Crude	3.89 (2.98–4.83)	3.82 (3.31–4.57)	3.37 (2.91–3.88)	3.44 (3.02–3.90)
Age-adjusted	4.02 (3.24–4.81)	3.64 (2.63–4.63)	3.54 (2.90–4.18)	3.61 (3.07–4.15)

Table 3 Hazard ratio for postmenopausal breast cancer associated with diabetes measures among white and black women, Southern Community Cohort Study, 2002–2015

Characteristics	Cases		Noncases		HR[b]	95% CI[c]	HR[d]	95% CI[c]
	n	PY[a]	n	PY[a]				
White								
Self-reported diabetes								
No	147	757	5,707	36,952	1.00	Referent	1.00	Referent
Yes	66	385	2,570	16,885	1.11	0.82–1.50	1.02	0.75–1.40
Times since diabetes diagnosis (years)[e]								
< 10	50	301	1,954	13,054	1.00	Referent	1.00	Referent
≥ 10	16	84	616	3,831	0.95	0.53–1.70	0.93	0.52–1.66
Metformin[e]								
No	14	81	982	6,320	1.00	Referent	1.00	Referent
Yes	47	275	1,249	8,393	2.37	1.30–4.32	2.31	1.26–4.21
Black								
Self-reported diabetes								
No	233	1,398	9,261	66,387	1.00	Referent	1.00	Referent
Yes	185	1,195	7,197	53,755	1.07	0.88–1.31	1.00	0.81–1.22
p for interaction[f]						0.86		0.88
Times since diabetes diagnosis (years)[e]								
< 10	121	847	5,402	41,051	1.00	Referent	1.00	Referent
≥ 10	64	348	1,795	12,704	1.48	1.09–2.02	1.46	1.06–2.00
p for interaction[f]						0.18		0.18
Metformin[e]								
No	97	607	3,100	22,894	1.00	Referent	1.00	Referent
Yes	69	416	2,938	22,333	0.78	0.57–1.07	0.81	0.59–1.11
p for interaction[f]						0.001		0.003

[a]Person-years

[b]Hazard ratio adjusted for age

[c]Confidence interval

[d]Hazard ratio adjusted for age, health insurance coverage, high cholesterol, and BMI

[e]Among people with diabetes

[f]p for interaction by race

black women, stratified by tumor ER status. There were no associations between diabetes and postmenopausal breast cancer risk among all women regardless of race or ER status.

Discussion

Previous meta-analyses reported risks of postmenopausal breast cancer among women with diabetes of around

Table 4 Hazard ratio for postmenopausal breast cancer associated with diabetes among white and black women stratified by obesity status, Southern Community Cohort Study, 2002–2015

Characteristic	Cases		Noncases		HR[b]	95% CI[c]	HR[d]	95% CI[c]
	n	PY[a]	*n*	PY[a]				
White BMI < 30								
Self-reported diabetes								
No	87	430	3,624	23,604	1.00	Referent	1.00	Referent
Yes	16	89	755	4,958	0.89	0.51–1.55	0.91	0.52–1.60
White BMI ≥ 30								
Self-reported diabetes								
No	60	327	2,083	13,348	1.00	Referent	1.00	Referent
Yes	50	296	1,815	11,927	1.09	0.74–1.62	1.08	0.72–1.60
p for interaction[e]					0.57			0.64
Black BMI < 30								
Self-reported diabetes								
No	102	597	4,531	32,675	1.00	Referent	1.00	Referent
Yes	42	284	2,133	16,025	0.87	0.60–1.27	0.85	0.58–1.25
Black BMI ≥ 30								
Self-reported diabetes								
No	131	801	4,730	33,712	1.00	Referent	1.00	Referent
Yes	143	911	5,064	37,730	1.12	0.88–1.43	1.10	0.86–1.41
p for interaction[e]					0.28			0.26

[a]Person-years

[b]Hazard ratio adjusted for age

[c]Confidence interval

[d]Hazard ratio adjusted for age, health insurance coverage, and high cholesterol

[e]*p* for interaction by obesity

Table 5 Hazard ratio for postmenopausal breast cancer associated with diabetes among white and black women stratified by ER status, Southern Community Cohort Study, 2002–2015

Characteristic	Cases		Noncases		HR[b]	95% CI[c]	HR[d]	95% CI[c]
	n	PY[a]	*n*	PY[a]				
White ER positive								
Self-reported diabetes								
No	99	526	5,707	36,952	1.00	Referent	1.00	Referent
Yes	43	257	2,570	16,885	1.03	0.71–1.50	0.89	0.59–1.34
White ER negative								
Self-reported diabetes								
No	26	109	5,707	36,952	1.00	Referent	1.00	Referent
Yes	12	76	2,570	16,885	1.21	0.60–2.45	1.39	0.64–3.01
Black ER positive								
Self-reported diabetes								
No	154	931	9,261	66,387	1.00	Referent	1.00	Referent
Yes	121	829	7,197	53,755	1.07	0.84–1.37	1.02	0.79–1.32
Black ER negative								
Self-reported diabetes								
No	61	361	9,261	66,387	1.00	Referent	1.00	Referent
Yes	48	280	7,197	53,755	1.12	0.76–1.66	0.96	0.64–1.44

[a]Person-years

[b]Hazard ratio adjusted for age

[c]Confidence interval

[d]Hazard ratio adjusted for age, health insurance coverage, high cholesterol, and BMI

1.15 [1–5], while we found no association among white (HR 1.02, 95% CI 0.75–1.40) or black (HR 1.00, 95% CI 0.81–1.22) women. In the largest meta-analysis [5], 1 of the 13 studies that adjusted for BMI and 9 of the 35 studies that did not adjust for BMI reported nonsignificant inverse associations between diabetes and breast cancer risk. These studies were not restricted to postmenopausal breast cancer and are therefore complicated by the summary risk estimate of 0.86 for the five studies of premenopausal breast cancer in the largest meta-analysis [5]. The two cohort studies with large numbers of black women, although not restricted to postmenopausal breast cancer, reported risks similar to the meta-analyses (MEC [6] HR 1.14, 95% CI 0.99–1.33; BWHS [7] HR 1.18, 95% CI 1.00–1.40). However, an earlier publication from the BWHS that included two-thirds of the cases followed for 58% of the time, reported no association (0.93, 95% CI 0.73–1.19) [17] similar to our hazard ratio of 1.00.

A possible explanation for the increased risk of postmenopausal breast cancer among black women who were diagnosed with diabetes 10 or more years prior (HR 1.46, 95% CI 1.06–2.00) is the greater likelihood their diabetes was being controlled through insulin rather than an oral agent. A meta-analysis reported a neutral effect of any insulin use on breast cancer risk [18]. The MEC did not examine time since diagnosis [6], but the BWHS found a suggested increase in breast cancer risk among women diagnosed with diabetes 5 or more years prior (HR 1.20, 95% CI 1.00–1.43) [7].

To our knowledge, no other investigators have found that race modified the effect of current metformin use on postmenopausal breast cancer risk. Of the 12 studies included in the recent meta-analysis that found no association between metformin use and breast cancer incidence [12], only one reported an increased risk of breast cancer associated with metformin use among primarily white Medicare recipients [19]. Wide confidence intervals among whites in our study argue for a cautious interpretation. However, given that metformin may result in better glycemic control among blacks than among whites [20] emphasizes the need to confirm our finding.

In agreement with the Nurses' Health Study (NHS) [21] and the MEC [6], we found no evidence that obesity modified the effect of diabetes on breast cancer risk. Among postmenopausal women in the NHS, the risks for nonobese (HR 1.15, 95% CI 0.93–1.43) and obese (HR 1.17, 95% CI 0.91–1.49) women were nearly identical. Among all women in the MEC, the HR for the diabetes and breast cancer risk association among obese women (HR 1.12, 95% CI 1.00–1.26) was within the range of the HRs for the underweight, normal weight, and overweight women (HRs 0.97–1.17) (95% CIs 0.73–1.89) (p for interaction = 0.31) [6]. Although large percentages of women in our study population were obese (white 47.2%, black 59.2%), limited study power could explain our failure to identify effect modification.

Our finding of no association with diabetes for white or black women with ER positive (+) or ER negative (−) disease is comparable with one of the three cohort studies that have examined the diabetes and breast cancer risk association by tumor subtype [6, 7, 21]. The MEC found no association for the diabetes and breast cancer risk relation among all women who were ER+/progesterone receptor (PR) + (1.06, 95% CI 0.95–1.18) or among women of other subtypes (ER−/PR− 1.02, 95% CI 0.83–1.27; ER+/PR− and ER-/PR+ 1.00, 95% CI 0.79–1.26) after adjustment for BMI [6]. The NHS found a stronger association between diabetes and breast cancer risk among all women with ER+ tumors (1.22, 95% CI 1.01–1.47) than among women with ER- tumors (1.13, 95% CI 0.79–1.62) [21]. In their analysis of black women, BWHS investigators reported no association in women with ER+ disease (HR 1.02, 95% CI 0.80–1.31) but a positive association in women with ER- disease (HR 1.43, 95% CI 1.03–2.00) [7].

Possible explanations for our different findings include small sample size, restriction to postmenopausal breast cancer, inclusion of women with type 1 diabetes, and adjustment for different confounders. Our number of breast cancer cases (white $n = 213$, black $n = 418$) was substantially less than the number in the BWHS ($n = 1{,}851$) [7] and the number of all women in the MEC ($n = 6{,}599$) [6]. Sensitivity analyses indicated that other possible explanations for our findings did not affect our results.

Additional limitations of our study included possible misclassification of self-reported diabetes and BMI, underreporting of current use of metformin, detection bias, and limited study power due to small numbers of white women with diabetes. Validation sub-studies of the SCCS found that 96% of self-reported diabetes could be confirmed through medical records or elevated HbA1c measurements, and correlations between self-reported and clinic-recorded height and weight exceeded 0.95 [14]. Nevertheless, approximately, one-fourth of diabetes in the U.S. is undiagnosed so our results could be partially explained if cases were more likely than controls to have undiagnosed diabetes [22]. Current use of metformin was not collected on the first follow-up survey; however, fewer than 4% of women completed the first follow-up survey but not the second follow-up survey. Women may have switched from metformin to another formulation due to side effects and ever use of metformin was not collected. Although we previously found no effect of diabetes on mammography screening in the SCCS [10], we excluded women whose diabetes and breast cancer diagnoses were within 1 year of each other to minimize the effect of detection bias. Our study is one of the largest to investigate the joint effect of diabetes and obesity on postmenopausal

breast cancer among white and black women, separately; nonetheless, study power was an issue. Thus, larger studies may assist in elucidating the role of obesity in the insulin signaling pathway in breast cancer.

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Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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