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Original Contribution

Population-based Case-Control Study of Diabetes and Breast Cancer Risk in Hispanic and Non-Hispanic White Women Living in US Southwestern States

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Diabetes mellitus has been associated with breast cancer, although no studies appear to have adequately assessed the association in Hispanic women, a population with a high prevalence of diabetes. The authors investigated this association in a population-based case-control study of Hispanic and non-Hispanic White women living in the southwestern United States. Breast cancer cases diagnosed in 1999–2004 were identified through state cancer registries (1,526 non-Hispanic Whites, 798 Hispanics). Age- and ethnicity-matched controls (1,599 non-Hispanic Whites, 924 Hispanics) were selected from commercial mailing lists and driver's license and Social Security records. Diabetes history was assessed through interviewer-administered questionnaires. Odds ratios and 95% confidence intervals were calculated using logistic regression, adjusting for age, body mass index at age 15 years, and parity. Having any type of diabetes was not associated with breast cancer overall (odds ratio = 0.94, 95% confidence interval: 0.78, 1.12). Type 2 diabetes was observed among 19% of Hispanics and 9% of non-Hispanic Whites but was not associated with breast cancer in either group. Gestational diabetes was inversely associated with breast cancer in both ethnic groups, especially when first diagnosed at age $\leq$35 years (odds ratio = 0.54, 95% confidence interval: 0.37, 0.79). In this study, diabetes was not associated with breast cancer overall, although the inverse association with gestational diabetes warrants further investigation.

breast neoplasms; case-control studies; diabetes, gestational; diabetes mellitus; diabetes mellitus, type 2; Hispanic Americans; insulin-like growth factor I; southwestern United States

Abbreviations: CI, confidence interval; ER, estrogen receptor; OR, odds ratio; PR, progesterone receptor.

Breast cancer incidence is lower among Hispanic women than among non-Hispanic White women. In 2000–2003, the age-adjusted incidence rate of breast cancer was 89.1 per 100,000 population in Hispanics as compared with 140.6 per 100,000 in non-Hispanic Whites (1). Differences in reproductive risk factor profiles account for less than 20 percent of this difference by race/ethnicity (2). Paradoxically, the prevalence of other established breast cancer risk factors, including obesity (3, 4) and physical inactivity (3), both of which lead to increased insulin resistance, is higher among Hispanics than among non-Hispanic Whites. Insulin resistance, including some forms of non-insulin-dependent (type 2) diabetes, may affect levels of insulin-like growth factor I, which has been previously associated with breast

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cancer risk, especially among premenopausal women (5). Several groups of investigators have reported on the association between insulin resistance or type 2 diabetes mellitus and breast cancer, including those who observed a statistically significant positive association (6–16) and those who observed nonsignificant or null associations (17–31). None of these investigators studied diabetes-associated breast cancer risk specifically among Hispanic women.

Age at diabetes diagnosis may be important in defining the breast cancer risk associated with diabetes. In a large, population-based case-control study, Baron et al. (17) observed a 48 percent decreased risk of breast cancer associated with diabetes diagnosed before age 35 years and a 20 percent increased risk of breast cancer associated with diabetes diagnosed at later ages. Hispanics are diagnosed with type 2 diabetes at younger ages than non-Hispanic Whites (32, 33), and this difference in age at diabetes onset may contribute to the ethnic differences in breast cancer incidence. To investigate differences in the association between diabetes and breast cancer among Hispanics and non-Hispanic Whites, we conducted a population-based case-control study of breast cancer in the Four Corners states: Arizona, Utah, New Mexico, and Colorado.

MATERIALS AND METHODS

Study population

The design and methods of the 4 Corners Breast Cancer Study have been previously described in detail (34, 35). Briefly, a population-based case-control study of breast cancer was conducted in Colorado, New Mexico, Utah, and selected counties of Arizona. For investigation of differences in the breast cancer risk profiles of non-Hispanic Whites and Hispanics, sampling was stratified by race/ethnicity, and only women who self-reported their race as non-Hispanic White, Hispanic, or American Indian were eligible, with the exception of American Indian women living on reservations. Women diagnosed with histologically confirmed breast cancer between October 1999 and May 2004 (*International Classification of Diseases for Oncology* codes C50.0–C50.6 and C50.8–C50.9) were identified as cases through population-based cancer registries in each state. Both in situ and invasive breast cancer cases were included in these analyses. Only women diagnosed with a first primary breast cancer were included. Information on the estrogen receptor (ER) and progesterone receptor (PR) status of tumors was available through the cancer registries for approximately 70 percent of cases.

Population-based controls were frequency-matched to cases in 5-year age groups. In New Mexico and Utah, control participants under age 65 years were randomly selected from driver's license lists; in Arizona and Colorado, controls were randomly selected from commercial mailing lists, since driver's license lists were unavailable. In all states, women aged 65 years or older were randomly selected from the lists of the Centers for Medicare and Medicaid Services (Social Security lists). Of all women contacted, 68 percent of cases and 42 percent of controls participated in the study (35). All participants gave written informed consent. The study protocol was approved by the institutional review board at each institution.

Data collection

A computerized questionnaire was administered in person by trained interviewers to obtain information on medical and reproductive histories, lifestyle factors, and family history of cancer. Study participants were given the option of having the interview administered in either English or Spanish. For several questions, women were asked to provide information for a reference period, which was defined as the year prior to diagnosis for the cases or the year prior to selection for the controls. History of diabetes was assessed through the following question: ''Before [referent date], did a doctor or other health care provider ever tell you that you had diabetes or high blood sugar?'' If the respondent answered yes, she was then asked, ''Did you have diabetes or high blood sugar only during pregnancy, at other times, or both during pregnancy and at other times?'' Subsequent questions assessed the age of onset for each type of diabetes (gestational or other types) and whether or not insulin, oral medications, diet, and/or exercise was used to control diabetes. History of diabetes in first-degree relatives was also assessed. One breast cancer case and two controls were excluded from the analysis because they did not answer the initial question about history of diabetes.

Statistical analysis

Demographic and selected breast cancer risk factors were compared between controls with and without self-reported histories of diabetes. Statistical significance testing of these differences was conducted using the chi-squared test for categorical variables, including study site (Arizona, Colorado, New Mexico, Utah), race/ethnicity (non-Hispanic White vs. Hispanic and/or Native American), menopausal status (pre-, peri-, or postmenopausal), age at first pregnancy (<30 years or ≥ 30 years), and history of breastfeeding (ever vs. never). The Mantel-Haenszel chi-squared test for trend was used to compare ordered categories between controls with and without histories of diabetes, including education ($<$12th grade, high school, or $>$12th grade), age at menarche (<13 years, 13 years, or >13 years), number of full-term pregnancies (0, 1–2, 3–4, or ≥ 5), and body mass index (weight (kg)/height $(m)^2$) at age 15 years (<20, 20–24, or ≥ 25). Age was compared between controls with and without histories of diabetes using the Wilcoxon rank-sum test to account for the nonnormal age distribution.

History of diabetes was assessed for all types of diabetes combined and separately for gestational diabetes and other types. When reporting a history of ''other'' diabetes, women were not asked to distinguish between type 1 (insulin-dependent) diabetes and type 2 (non-insulin-dependent) diabetes. To minimize misclassification of type 2 diabetes, four breast cancer cases and three controls who reported having ''other'' diabetes at age 15 years or younger were excluded from the diabetes type-specific analyses, since these women most likely had type 1 diabetes. In previous studies, investigators have used an age at diabetes diagnosis of 30 years to

differentiate between type 1 diabetes and type 2 diabetes (12, 27), although those studies were conducted among predominately non-Hispanic White women. Since Hispanics are diagnosed with diabetes at younger ages than non-Hispanic Whites (32, 33), a younger age at diabetes diagnosis (15 years) was used to exclude probable cases of type 1 diabetes in the current study population. Age at diabetes onset was first analyzed for gestational and type 2 diabetes combined, using 10-year categories. For women who reported having both types of diabetes, the younger of two ages of onset was selected for the combined analysis. For the diabetes type-specific analyses, age at diabetes onset was dichotomized at 35 years, based on a previous study that observed differences in diabetes-associated breast cancer risk among women who were younger or older than 35 years (17).

For assessment of the association between diabetes and breast cancer, odds ratios and 95 percent confidence intervals were calculated using logistic regression. Persons with no history of diabetes served as the reference group for all diabetes variables, except for family history of diabetes, for which no family history was the reference group. All odds ratios and 95 percent confidence intervals were adjusted for age in 5-year groups. Several potential confounders were considered, including study center, race, menopausal status, education, body mass index at study entry, body mass index at age 15 years, number of full-term pregnancies, age at menarche, history of breastfeeding, years since last pregnancy, physical activity, alcohol consumption, use of oral contraceptives, hormone replacement therapy, and family history of breast cancer. Each variable was tested individually in an age-adjusted model of diabetes-associated breast cancer risk, and only those variables that changed the main-effects odds ratio by a minimum of 5 percent were included in the final parsimonious model (body mass index at age 15 years and number of full-term pregnancies). Analyses were stratified by race/ethnicity, menopausal status, and the ER/PR status of the tumor for investigation of differences in the associations between diabetes and breast cancer risk by these factors.

All statistical tests were two-sided, and p values less than 0.05 were considered statistically significant. Statistical analyses were conducted using SAS software, version 8.0 (SAS Institute, Inc., Cary, North Carolina).

RESULTS

Demographic and other selected characteristics for controls with and without a history of diabetes are presented in table 1. The prevalence of diabetes among controls did not differ significantly across the four study sites. Controls with a history of diabetes were slightly older than controls without a history of diabetes and were more likely to be Hispanic and less educated (table 1). A history of diabetes was significantly associated with increased parity, a history of breastfeeding, and higher body mass index at age 15 years but not with age at menarche or age at first pregnancy.

Diabetes was self-reported by 12 percent of breast cancer cases and 13 percent of controls and was not associated with breast cancer overall (odds ratio (OR) = 0.94, 95 percent confidence interval (CI): 0.78, 1.12) (table 2). When type of diabetes was considered, a statistically significant inverse association was observed for gestational diabetes and breast cancer (OR = 0.70, 95 percent CI: 0.51, 0.96), whereas no association was observed for type 2 diabetes and breast cancer. No clear pattern in breast cancer risk was observed for age at onset for any diabetes (table 2). However, younger age at onset of gestational diabetes (<35 years) was associated with a statistically significant 46 percent decreased risk of breast cancer, whereas gestational diabetes at age 35 years or older was not associated with breast cancer risk. No associations between type 2 diabetes and breast cancer were observed by age at onset of 15–34 or ≥35 years (table 2). Only 1 percent of women (20 cases, 14 controls) reported having diabetes and having never taken insulin or oral medication to control it; of these women, all 20 cases and 11 controls reported having been prescribed a special diet or exercise regimen for the control of diabetes. Having a family history of diabetes was not associated with breast cancer (table 2). All associations were adjusted for age, number of full-term pregnancies, and body mass index at age 15 years (table 2, parsimonious model). Similar results were obtained after additional adjustment for study site, menopausal status, body mass index at study entry, age at first pregnancy, age at menarche, lifetime physical activity, family history of breast cancer, and history of breastfeeding (table 2, full model). Excluding nulliparous women from the reference group did not change the observed breast cancer risk estimates for gestational diabetes (data not shown in table).

Diabetes was more prevalent among controls who self-identified as Hispanic and/or Native American (19.4 percent) than among non-Hispanic White women (9.4 percent) (table 3). Associations between diabetes and breast cancer were similar across the two racial/ethnic groups, with no association between history of any diabetes and breast cancer being observed for either non-Hispanic White women or Hispanic and/or Native American women. History of gestational diabetes tended to be inversely associated with breast cancer in both racial/ethnic groups, although neither association was statistically significant (table 3). Nonsignificant decreased risks of breast cancer were observed for gestational diabetes among non-Hispanic White women, regardless of age at gestational diabetes onset. Among Hispanic/Native American women, a statistically significant decreased risk of breast cancer was observed for women who experienced gestational diabetes at ages younger than 35 years (OR = 0.39, 95 percent CI: 0.21, 0.73), whereas a statistically significant increased risk of breast cancer was associated with gestational diabetes at age 35 years or older (OR = 3.68, 95 percent CI: 1.33, 10.19) (table 3). Odds ratios for diabetes without use of insulin or oral medication tended to be greater than 1 for both racial/ethnic groups, although neither was statistically significant. Family history of diabetes was not associated with breast cancer, regardless of race/ethnicity (table 3).

History of diabetes was not associated with pre-/perimenopausal breast cancer (OR = 0.89, 95 percent CI: 0.64, 1.26) or postmenopausal breast cancer (OR = 0.96,

TABLE 1. Selected characteristics of controls according to history of diabetes, 4 Corners Breast Cancer Study, 1999–2004

Characteristic	History of diabetes ($n = 330$)		No history of diabetes ($n = 2,193$)		p value*
	No.	%	No.	%	
Mean age (years) at study enrollment	57.0 (12.3)†		55.5 (12.1)		0.03
Study site					
Arizona	76	23.0	436	19.9	
Colorado	61	18.5	441	20.1	
New Mexico	118	35.8	824	37.6	
Utah	75	22.7	492	22.4	0.56
Race/ethnicity					
Non-Hispanic White	151	45.8	1,448	66.0	
Hispanic and/or Native American	179	54.2	745	34.0	<0.0001
Education‡					
Less than high school	73	22.1	269	12.3	
High school	89	27.0	496	22.6	
More than high school	167	50.6	1,426	65.0	<0.0001
Menopausal status‡					
Premenopausal	58	17.6	496	22.6	
Perimenopausal	25	7.6	246	11.2	
Postmenopausal	246	74.5	1,447	66.0	0.007
Age (years) at menarche‡					
≤12	156	47.3	958	43.7	
13	84	25.5	569	25.9	
>13	87	26.4	654	29.8	0.15
No. of full-term pregnancies‡					
0	30	9.1	320	14.6	
1–2	106	32.1	877	40.0	
3–4	125	37.9	734	33.5	
≥5	69	20.9	254	11.6	<0.0001
Age (years) at first pregnancy‡					
<30	283	85.8	1,804	82.3	
≥30	25	7.6	174	7.9	0.69
Breastfeeding history‡					
Never	98	29.7	782	35.7	
Ever	227	68.8	1,312	59.8	0.01
Body mass index§ at age 15 years‡					
<20	178	53.9	1,339	61.1	
20–25	113	34.2	642	29.3	
≥25	24	7.3	75	3.4	0.0003

* p values were obtained from chi-squared tests for study site, race, menopausal status, age at first pregnancy, and breastfeeding history; from Mantel-Haenszel chi-squared tests for trend for education, body mass index at age 15 years, and number of pregnancies; and from a Wilcoxon rank-sum test for age.

† Numbers in parentheses, standard deviation.

‡ Data were missing for the following variables in the controls: education ($n = 3$), menopausal status ($n = 5$), age at menarche ($n = 15$), number of full-term pregnancies ($n = 8$), age at first pregnancy ($n = 28$), breastfeeding ($n = 104$), and body mass index at age 15 years ($n = 152$).

§ Weight (kg)/height $(m)^2$.

TABLE 2. Relation between diabetes history and breast cancer risk, 4 Corners Breast Cancer Study, 1999–2004

Characteristic	Cases ($n = 2,324$)		Controls ($n = 2,523$)		Age-adjusted model		Parsimonious model*		Full model†	
	No.	%	No.	%	OR‡	95% CI‡	OR	95% CI	OR	95% CI
History of diabetes										
No§	2,053	88.3	2,193	86.9	1.00	Reference	1.00	Reference	1.00	Reference
Yes	271	11.7	330	13.1	0.90	0.76, 1.07	0.94	0.78, 1.12	0.98	0.81, 1.18
Type of diabetes¶										
Gestational	75	3.2	106	4.2	0.70	0.51, 0.94	0.70	0.51, 0.96	0.71	0.52, 0.98
Type 2	204	8.8	247	9.8	0.94	0.78, 1.15	1.00	0.81, 1.23	1.06	0.85, 1.32
Age at onset (years) for any diabetes										
<30	38	1.6	64	2.5	0.68	0.47, 0.97	0.68	0.47, 0.99	0.73	0.49, 1.06
30–39	63	2.7	64	2.5	0.97	0.68, 1.39	0.99	0.69, 1.41	1.03	0.71, 1.49
40–49	43	1.9	59	2.3	0.78	0.52, 1.16	0.81	0.54, 1.23	0.85	0.55, 1.30
50–59	62	2.7	67	2.7	1.08	0.76, 1.53	1.17	0.82, 1.68	1.19	0.82, 1.72
≥60	52	2.2	63	2.5	1.06	0.73, 1.55	1.13	0.76, 1.70	1.20	0.79, 1.83
Age at onset (years) for gestational diabetes¶										
15–34	47	2.0	86	3.4	0.54	0.37, 0.77	0.54	0.37, 0.79	0.56	0.38, 0.82
≥35	25	1.1	18	0.7	1.35	0.73, 2.48	1.39	0.74, 2.58	1.34	0.72, 2.52
Age at onset (years) for type 2 diabetes										
15–34	24	1.0	26	1.0	0.93	0.53, 1.62	0.97	0.54, 1.71	1.18	0.64, 2.17
≥35	180	7.7	221	8.8	0.94	0.77, 1.16	1.01	0.81, 1.25	1.04	0.83, 1.31
History of diabetes treatment										
Insulin and/or oral medication	125	5.4	167	6.6	0.86	0.68, 1.10	0.91	0.70, 1.17	0.95	0.72, 1.24
No insulin or oral medication	20	0.9	14	0.6	1.64	0.82, 3.25	1.78	0.89, 3.56	1.80	0.89, 3.65
Family history of diabetes¶										
No	1,142	52.8	1,157	49.7	1.00	Reference	1.00	Reference	1.00	Reference
Yes	1,019	47.1	1,168	50.2	0.90	0.80, 1.01	0.95	0.84, 1.07	1.00	0.88, 1.14

* Adjusted for age (5-year categories), body mass index (weight (kg)/height (m)^2) at age 15 years (<20, 20–24, or ≥25), and number of full-term pregnancies (0, 1–2, 3–4, or ≥5).

† Adjusted for age (5-year categories), study site (Arizona, New Mexico, Colorado, Utah), menopausal status (pre-, peri-, or postmenopausal), body mass index at study entry (<25, 25–29, or ≥30), body mass index at age 15 years (<20, 20–24, or ≥25), number of full-term pregnancies (0, 1–2, 3–4, or ≥5), age at first pregnancy (<30 years vs. ≥30 years), age at menarche (<13, 13, or >13 years), lifetime physical activity, family history of breast cancer, and breastfeeding history (ever vs. never).

‡ OR, odds ratio; CI, confidence interval.

§ Women with no history of diabetes served as the reference group for all analyses except that for family history of diabetes.

¶ Data were missing for the following variables: type of diabetes ($n = 2$), age at gestational diabetes ($n = 5$), and family history of diabetes ($n = 361$).

95 percent CI: 0.78, 1.19) (table 4). Patterns of breast cancer risk observed with type of diabetes and age at diabetes onset in the overall study population were similar to those observed by menopausal status. History of gestational diabetes, especially when diagnosed at ages younger than 35 years, was inversely associated with both pre-/perimenopausal breast cancer and postmenopausal breast cancer; the latter finding was statistically significant (OR = 0.47, 95 percent CI: 0.27, 0.82). No associations were observed between type 2 diabetes and either pre-/perimenopausal or postmenopausal breast cancer (table 4). Having diabetes with no use of insulin or oral medication was associated with a statistically significant 2.4-fold risk of postmenopausal breast cancer, based on 18 exposed cases and 10 exposed controls. Only two pre-/perimenopausal breast cancer cases reported having diabetes without any use of insulin or oral medications. Family history of diabetes was not associated with either pre-/perimenopausal or postmenopausal breast cancer (table 4). Patterns in postmenopausal breast cancer risk associated with diabetes were similar among users and nonusers of hormone replacement therapy and across strata of body mass index (data not shown).

Gestational diabetes first diagnosed before age 35 years was significantly inversely associated with ER-positive (ER+) and PR-positive (PR+) breast cancers (table 5). Inverse associations also were observed for the less prevalent

TABLE 3. Relation between diabetes and breast cancer risk, by race/ethnicity, 4 Corners Breast Cancer Study, 1999–2004

Characteristic	Non-Hispanic White women						Hispanic and/or Native American women					
	Cases (n = 1,526)		Controls (n = 1,599)		OR*,†	95% CI*	Cases (n = 798)		Controls (n = 924)		OR†	95% CI
	No.	%	No.	%			No.	%	No.	%		
History of diabetes												
No‡	1,392	91.2	1,448	90.6	1.00	Reference	661	82.8	745	80.6	1.00	Reference
Yes	134	8.8	151	9.4	1.01	0.78, 1.30	137	17.2	179	19.4	0.92	0.71, 1.20
Type of diabetes												
Gestational	41	2.7	61	3.8	0.68	0.45, 1.03	34	4.3	45	4.9	0.75	0.46, 1.22
Type 2	96	6.3	101	6.3	1.13	0.84, 1.53	108	13.5	146	15.8	0.95	0.71, 1.27
Age at onset (years) for any diabetes												
<30	27	1.8	35	2.2	0.88	0.54, 1.42	11	1.4	29	3.1	0.49	0.27, 0.90
30–39	30	2.0	37	2.3	0.82	0.50, 1.35	33	4.1	27	2.9	1.28	0.75, 2.19
40–49	16	1.0	17	1.1	1.09	0.54, 2.20	27	3.4	42	4.5	0.75	0.44, 1.25
50–59	28	1.8	31	1.9	1.10	0.64, 1.86	34	4.3	36	3.9	1.29	0.78, 2.13
≥60	28	1.8	27	1.7	1.40	0.79, 2.49	24	3.0	36	3.9	1.01	0.56, 1.81
Age at onset (years) for gestational diabetes												
<35	31	2.0	47	2.9	0.68	0.42, 1.09	16	2.0	39	4.2	0.39	0.21, 0.73
≥35	8	0.5	13	0.8	0.60	0.25, 1.46	17	2.1	5	0.5	3.68	1.33, 10.19
Age at onset (years) for type 2 diabetes												
15–34	11	0.7	13	0.8	0.92	0.41, 2.08	13	1.6	13	1.4	1.02	0.45, 2.32
≥35	85	5.6	88	5.5	1.18	0.85, 1.62	95	11.9	133	14.4	0.93	0.68, 1.26
Diabetes treatment												
Use of insulin and/or oral medication	55	3.6	68	4.3	0.96	0.65, 1.40	70	8.8	99	10.7	0.91	0.64, 1.30
No insulin or oral medication	9	0.6	6	0.4	1.82	0.64, 5.21	11	1.4	8	0.9	1.84	0.73, 4.67
Family history of diabetes												
No	856	60.1	866	58.7	1.00	Reference	286	38.8	291	34.2	1.00	Reference
Yes	567	39.8	607	41.2	0.97	0.83, 1.13	452	61.2	561	65.8	0.97	0.78, 1.21

* OR, odds ratio; CI, confidence interval.

† Adjusted for age (5-year categories), body mass index (weight (kg)/height (m)^2) at age 15 years (<20, 20–24, or ≥25), and number of full-term pregnancies (0, 1–2, 3–4, or ≥5).

‡ Women with no history of diabetes served as the reference group for all analyses except that for family history of diabetes.

ER-negative (ER−) and PR-negative (PR−) breast cancers, although these findings did not reach statistical significance. Gestational diabetes diagnosed at age 35 years or older was significantly associated with increased risks of ER− and PR− breast cancer (table 5), whereas statistically significant associations were not observed between gestational diabetes at older ages and ER+ or PR+ cases. In the subset of 1,427 breast cancer cases for whom both ER and PR status were available, 66 percent were ER+/PR+, 12 percent were ER+/PR−, 2 percent were ER−/PR+, and 20 percent were ER−/PR−. Although non-Hispanic Whites were more likely to be ER+ and PR+ than Hispanics (data not shown), adjustment for race/ethnicity did not diminish the observed associations between gestational diabetes and breast cancer by ER/PR status.

DISCUSSION

In this study of women living in the Four Corners states, a history of any diabetes was not associated with breast cancer. Our findings are not consistent with the overall conclusion of a recent meta-analysis in which Larsson et al. (36) reported a statistically significant 20 percent increased risk of breast cancer associated with any diabetes, based on five case-control studies and 15 cohort studies. Additionally, we observed no differences in breast cancer risk by age at diabetes onset, in contrast to two previous studies in which decreased risks of breast cancer were reported among women diagnosed with diabetes at younger ages (14, 17). Among studies of diabetes and breast cancer, the present study included the largest sample of Hispanic women,

TABLE 4. Relation between diabetes and breast cancer risk, by menopausal status, 4 Corners Breast Cancer Study, 1999–2004

Characteristic	Pre- and perimenopausal women						Postmenopausal women					
	Cases ($n = 871$)		Controls ($n = 825$)		OR*,†	95% CI*	Cases ($n = 1,448$)		Controls ($n = 1,693$)		OR†	95% CI
	No.	%	No.	%			No.	%	No.	%		
History of diabetes												
No‡	794	91.2	742	89.9	1.00	Reference	1,254	86.6	1,447	85.5	1.00	Reference
Yes	77	8.8	83	10.1	0.89	0.64, 1.26	194	13.4	246	14.5	0.96	0.78, 1.19
Type of diabetes												
Gestational	46	5.3	54	6.5	0.79	0.52, 1.21	29	2.0	52	3.1	0.60	0.37, 0.97
Type 2	38	4.4	38	4.6	0.98	0.61, 1.59	166	11.5	208	12.3	1.01	0.80, 1.27
Age at onset (years) for any diabetes												
<30	20	2.3	26	3.2	0.82	0.45, 1.49	18	1.2	38	2.2	0.62	0.38, 1.01
30–39	33	3.8	33	4.0	0.91	0.55, 1.52	30	2.1	30	1.8	1.09	0.65, 1.83
40–49	16	1.8	16	1.9	1.06	0.52, 2.21	27	1.9	43	2.5	0.68	0.41, 1.13
50–59	6	0.7	7	0.8	0.75	0.25, 2.28	56	3.9	60	3.5	1.21	0.83, 1.78
≥60							52	3.6	63	3.7	1.19	0.79, 1.78
Age at onset (years) for gestational diabetes												
<35	27	3.1	42	5.1	0.61	0.36, 1.02	20	1.4	44	2.6	0.47	0.27, 0.82
≥35	18	2.1	12	1.5	1.41	0.67, 2.98	7	0.5	6	0.4	1.33	0.44, 4.02
Age at onset (years) for type 2 diabetes												
15–34	10	1.1	8	1.0	1.37	0.50, 3.74	14	1.0	17	1.0	0.88	0.43, 1.81
≥35	28	3.2	30	3.6	0.89	0.52, 1.54	152	10.5	191	11.3	1.02	0.80, 1.29
Diabetes treatment												
Insulin and/or oral medication	17	2.0	23	2.8	0.73	0.38, 1.43	108	7.5	143	8.4	0.94	0.72, 1.24
No insulin or oral medication	2	0.2	4	0.5	0.47	0.08, 2.58	18	1.2	10	0.6	2.42	1.11, 5.33
Family history of diabetes												
No	477	54.8	428	51.9	1.00	Reference	661	45.6	728	43.0	1.00	Reference
Yes	337	38.7	347	42.1	0.92	0.75, 1.13	682	47.1	819	48.4	0.96	0.82, 1.12

* OR, odds ratio; CI, confidence interval.

† Adjusted for age (5-year categories), body mass index (weight (kg)/height (m)^2) at age 15 years (<20, 20–24, or ≥25), and number of full-term pregnancies (0, 1–2, 3–4, or ≥5).

‡ Women with no history of diabetes served as the reference group for all analyses except that for family history of diabetes.

a population with a high prevalence of diabetes. However, differences in the racial/ethnic compositions of previously reported study populations cannot entirely explain the discrepancy with the present study findings, given that genetic admixture was not associated with breast cancer risk among Hispanics in this population (37) and diabetes was not associated with breast cancer in either Hispanic women or non-Hispanic White women.

Estimates from the National Health and Nutrition Examination Survey suggest that approximately one third of diabetes in the United States is undiagnosed (32). History of diabetes was measured by self-report in the current study, and if diabetes was underdiagnosed to a similar extent in cases and controls, the observed findings for breast cancer and diabetes overall could have been biased toward the null. However, in their meta-analysis, Larsson et al. (36) observed no difference in risk estimates for diabetes-associated breast cancer among studies that measured diabetes through self-report versus those that used clinical measurements.

When gestational diabetes was analyzed separately from other types of diabetes in the current study, a decreased risk of breast cancer was observed. This inverse association was particularly strong and statistically significant among women who were first diagnosed with gestational diabetes at ages younger than 35 years (OR = 0.54, 95 percent CI: 0.37, 0.79). Underdiagnosis may be less problematic for the measurement of gestational diabetes, since screening for gestational diabetes is more universally conducted in pregnant women. However, recall bias may have affected study results if controls were more likely to accurately report a history of gestational diabetes at younger ages than cases. Selection bias could also have affected our results if control participants were more likely to have had gestational diabetes than nonparticipants, although it is unlikely that this bias

TABLE 5. Relation between history of diabetes and breast cancer risk, by estrogen receptor/progesterone receptor status of the tumor, 4 Corners Breast Cancer Study, 1999–2004

Characteristic	Controls (%) (n = 2,575)	ER*-positive cases (n = 1,181)			ER-negative cases (n = 341)			PR*-positive cases (n = 1,035)			PR-negative cases (n = 481)		
		%	OR*,†	95% CI*	%	OR†	95% CI	%	OR†	95% CI	%	OR†	95% CI
No history of diabetes‡	88.3	87.7	1.00	Reference	88.3	1.00	Reference	88.6	1.00	Reference	86.1	1.00	Reference
Type of diabetes													
Gestational	3.2	3.4	0.73	0.49, 1.09	5.3	0.94	0.55, 1.62	3.4	0.68	0.45, 1.04	4.8	0.99	0.61, 1.61
Type 2	8.8	9.8	1.08	0.84, 1.39	7.8	0.96	0.61, 1.50	9.0	0.98	0.75, 1.28	10.1	1.25	0.88, 1.77
Age at onset (years) for gestational diabetes													
<35	2.0	2.0	0.52	0.31, 0.85	2.5	0.53	0.25, 1.11	2.2	0.53	0.32, 0.89	2.0	0.50	0.25, 1.00
≥35	1.1	1.3	1.68	0.82, 3.44	2.5	2.52	1.07, 5.93	1.0	1.30	0.59, 2.85	2.6	3.08	1.45, 6.54
Age at onset (years) for type 2 diabetes													
15–34	1.0	0.9	0.88	0.42, 1.85	1.2	0.98	0.33, 2.89	0.9	0.87	0.40, 1.88	1.1	1.02	0.38, 2.73
≥35	7.7	8.9	1.11	0.85, 1.45	6.5	0.96	0.59, 1.56	8.1	1.00	0.75, 1.33	9.0	1.30	0.90, 1.87
Diabetes treatment													
Use of insulin and/or oral medication	5.4	5.6	0.88	0.64, 1.22	6.2	1.19	0.71, 1.98	5.1	0.79	0.55, 1.12	7.0	1.33	0.88, 2.00
No use of insulin or oral medication	0.9	1.0	1.98	0.88, 4.44	0.9	1.94	0.53, 7.06	0.9	1.88	0.80, 4.43	1.1	2.34	0.82, 6.68

* ER, estrogen receptor; PR, progesterone receptor; OR, odds ratio; CI, confidence interval.

† Adjusted for age (5-year categories), body mass index (weight (kg)/height (m)^2) at age 15 years (<20, 20–24, or ≥25), and number of full-term pregnancies (0, 1–2, 3–4, or ≥5).

‡ Women with no history of diabetes served as the reference group for all analyses except that for family history of diabetes.

would have occurred only among women with a history of gestational diabetes at ages younger than 35 years. Additionally, the inverse association between gestational diabetes at younger ages and breast cancer risk was observed for each of the four study centers. The similarity of risks by study center and across strata of race/ethnicity, menopausal status, and hormone receptor status suggests that this inverse association was not due to chance. Although results were similar after adjustment for multiple breast cancer risk factors, confounding by unmeasured factors may also explain the observed findings.

To the best of our knowledge, the association between gestational diabetes and breast cancer has only been investigated in three previous studies. In a population-based case-control study of pregnancy characteristics and breast cancer, Troisi et al. (38) observed no association between self-reported history of gestational diabetes and breast cancer among 1,239 cases under age 45 years and 1,166 controls residing in New Jersey, Atlanta, Georgia, and Seattle, Washington. In a New Zealand cohort study of 753 pregnant women who underwent glucose testing at 13 weeks of pregnancy, Dawson (39) observed a statistically significant association between higher glucose levels and increased risk of breast cancer diagnosed up to 20 years later. In an Israeli cohort study, Perrin et al. (40) also observed a positive association between gestational diabetes and breast cancer, particularly among women diagnosed at age 50 years or older. None of these studies investigated differences in breast cancer risk by age at onset for gestational diabetes.

Prevalence estimates for gestational diabetes are lower among non-Hispanic White women than among Mexican-American women, the predominate subgroup of Hispanic women in the current study population (1.5 percent vs. 4.5 percent) (41). Additionally, Hispanics have been shown to be at increased risk for gestational diabetes as compared with non-Hispanic Whites, even after accounting for differences in body mass index (42, 43). An inverse association between gestational diabetes at young ages and breast cancer could partially explain the lower incidence of breast cancer in Hispanics, since a higher proportion of Hispanic controls with gestational diabetes were under age 35 years at onset (89 percent) as compared with non-Hispanic Whites (78 percent).

Previous studies have demonstrated that women with a history of gestational diabetes are at greater risk of developing type 2 diabetes later in life (44, 45). If younger age at gestational diabetes onset served as a surrogate marker for younger age at onset of type 2 diabetes in the current study, the observed inverse association between earlier-onset gestational diabetes and breast cancer may reflect an underlying inverse association between undermeasured earlier-onset type 2 diabetes and breast cancer (14, 17). Alternatively, there may be something specific about the biology of gestational diabetes at a younger age that may be related to breast cancer risk. Should the inverse association between gestational diabetes and breast cancer be observed in future studies, potential biologic explanations should be further investigated.

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