Research Article

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History of Gestational Diabetes Mellitus and Risk of Incident Invasive Breast Cancer among Parous Women in the Nurses' Health Study II Prospective Cohort

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Abstract

Background: Type II diabetes is associated with breast cancer in epidemiologic studies. Pregnancy also modifies breast cancer risk. We hypothesized that women with a history of gestational diabetes mellitus (GDM), which shares pathogenesis and risk factors with type II diabetes, would have greater invasive breast cancer risk than parous women without a history of GDM.

Methods: We conducted a prospective analysis among parous women in the Nurses' Health Study II, with mean age 35 years in 1989. Multivariate Cox proportional hazards models were used to compare risks of incident invasive breast cancer in women with and without a history of GDM.

Results: Among 86,972 women studied, 5,188 women reported a history of GDM and 2,377 developed invasive breast cancer (100 with history of GDM, 2,277 without GDM) over 22 years of prospective follow-up. History of GDM was inversely associated with incident invasive breast cancer [HR, 0.68; 95% confidence interval (CI), 0.55–0.84; $P = 0.0004$], compared with no history of GDM, after adjustment for body mass index, reproductive history, and other breast cancer risk factors. Findings were similar by menopausal status, although observed person-time was predominantly premenopausal (premenopausal: HR, 0.73; 95% CI, 0.56–0.96; $P = 0.03$; postmenopausal: HR, 0.63; 95% CI, 0.43–0.92; $P = 0.02$). Restricting to women undergoing mammography screening modestly attenuated the relationship (HR, 0.74; 95% CI, 0.57–0.96; $P = 0.02$).

Conclusions: Among a large cohort of U.S. women, history of GDM was not associated with an elevated risk of subsequent invasive breast cancer.

Impact: Our findings highlight the need to further investigate GDM's role in breast cancer development. *Cancer Epidemiol Biomarkers Prev; 26(3); 321–7. ©2016 AACR.*

Introduction

The risk of breast cancer has long been linked to reproductive risk factors, including age at menarche, age at first birth, and age at menopause (1). Pregnancy has bidirectional effects on breast cancer risk: It increases risk over the short term, but in women with a young age at first birth, it is protective over the long term (1, 2). Hormonal changes in pregnancy are thought to induce proliferation and differentiation of the breast epithelial cells, modifying the risk of future malignancy (3–5). Identifying pregnancy-specific characteristics that modulate breast cancer risk could inform screening and prevention practices.

Type II diabetes was associated with a 27% greater overall risk of breast cancer in a meta-analysis of epidemiologic studies, although significant between-study heterogeneity suggested potential differences by menopausal status, adjustment for body mass index (BMI), or study design (prospective vs. retrospective; ref. 6). For example, no positive relationship was observed for diabetes and breast cancer among premenopausal women. Gestational diabetes mellitus (GDM) occurs in approximately 6% of pregnancies in the United States and confers a high risk of future type II diabetes (7–9). During pregnancy, women with GDM have higher glucose and C-reactive protein levels, lower sex hormone–binding globulin levels, and may be hyperinsulinemic, as

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compared with pregnant women without GDM (10, 11). These findings suggest an altered metabolic milieu, which may have biological effects on breast tissue during a critical period of differentiation (3–5). It is unclear whether GDM is associated with increased breast cancer risk, with mixed results in past studies (12–16).

We hypothesized that a history of GDM would be associated with a greater invasive breast cancer risk among parous participants in the Nurses' Health Study II (NHS II), a large prospective cohort of U.S. female nurses.

Materials and Methods

Study population

This analysis was conducted in the NHS II longitudinal prospective cohort. NHS II began in 1989 with the enrollment of 116,430 female nurses, ages 25 to 42. Questionnaires are distributed every 2 years to update information on a variety of lifestyle and health-related characteristics, with follow-up >90% of total potential person-years. This study has been approved by the Brigham and Women's Hospital Institutional Review Board, with participants' consent implied by the return of the questionnaires.

This analysis included participants reporting a previous birth on the baseline questionnaire (1989) or an incident first birth during follow-up, through 2001. Nulliparous women were excluded. The 2001 questionnaire cycle is the last in which pregnancy history was prospectively ascertained, as the majority of NHS II participants had passed reproductive age. Exclusion criteria were any history of cancer at baseline or prior to first birth, a prior multiple gestation pregnancy (i.e., twins or higher), and age at first birth <18 years of age. Women were censored during follow-up upon death, cancer diagnosis, reporting of a multiple gestation pregnancy, or being lost to follow-up. Follow-up continued through the diagnosis of breast cancer or May 31, 2013, whichever occurred first.

Ascertainment of GDM history

History of GDM was captured on the baseline questionnaire and updated every 2 years through 2001 by self-report of a physician's diagnosis. Self-reported GDM was previously validated against medical records in a subgroup of NHS II participants, with 94% of cases confirmed (17).

Ascertainment of incident breast cancer cases

Invasive breast cancer cases were identified on biennial follow-up questionnaires from baseline through the 2011 questionnaire. Medical records were obtained from willing participants to confirm the diagnosis (with >98% accuracy) as well as to capture estrogen receptor (ER) and progesterone receptor (PR) status (18). ER and PR status (positive/negative) was determined from medical records for 92% and 91% of our confirmed cases, respectively. Reasons for undetermined ER/PR status included missing information (5%), test not performed (∼2%), and borderline status (∼1%). Deaths were identified by the postal service, next of kin, or National Death Index, with medical records or death certificates used for additional documentation of breast cancer.

Covariate assessment

Detailed health, reproductive, and lifestyle histories were captured at baseline and updated every 2 years. Participants reporting a diagnosis of type II diabetes received a previously validated supplemental questionnaire (19), from which confirmation of diagnosis was made in accordance with the National Diabetes Data Group criteria through 1998 (20) and the American Diabetes Association criteria for cases thereafter (21). A family history of breast cancer in a mother or sister and family history of diabetes in a parent or sibling was updated approximately every 4 years. Participants indicated the number of years since the most recent mammogram at baseline and on follow-up questionnaires answered whether they had a mammogram in the past 2 years. Current body weight was self-reported and was highly correlated with technician-measured weight in a previous validation study (22). A validated physical activity questionnaire was distributed approximately every 4 years (23), asking participants the frequency in which they usually engaged in common recreational activities, from which we derived total metabolic equivalent task hours per week (MET-hours/week). Usual diet was ascertained every 4 years via a validated semiquantitative food frequency questionnaire, from which we estimated intake of fruits and vegetables (servings/day) and alcohol (grams/day). The birth index, which takes into account parity and the age at each birth, is inversely associated with breast cancer risk and was calculated on the basis of participants' reproductive histories (1).

Statistical analysis

Participants' person-time was calculated from age at first birth through date of breast cancer diagnosis, lost-to-follow-up, death, or return of the 2011 questionnaire, whichever occurred first. A history of GDM was determined at baseline and updated every 2 years. A participant was considered exposed from her first report of GDM through the remainder of follow-up. Women reporting a diagnosis of type II diabetes prior to a GDM pregnancy were considered not exposed to GDM.

We used age- and multivariable-adjusted Cox proportional hazards models, stratified by time since first birth and age, to estimate the HRs and 95% confidence intervals (95% CI) for the association between a history of GDM (ever vs. never) and risk of incident invasive breast cancer. Time-varying covariates were updated every questionnaire cycle. The proportional hazards assumption was met with $P > 0.05$ for the interaction of follow-up time (years) with exposure on breast cancer risk.

Our primary endpoint was invasive breast cancer. We also conducted analyses by breast cancer subgroup, including menopausal status at diagnosis and hormone receptor status. Cox proportional hazards competing risk analysis, as described by Lunn and colleagues was used to assess heterogeneity by molecular subtype (any positive receptors ER^+ or PR^+ vs. both negative receptors ER^-/PR^-; ref. 24). Briefly, data duplication methods were used, allowing the exposure variable and covariates with heterogeneity across subtypes to vary, keeping other covariate estimates constant. A likelihood ratio test is used to compare models with and without this approach to evaluate heterogeneity across subtype. We considered potential confounders in the multivariable model, including BMI (kg/m^2) at age 18 (continuous), weight gain since age 18 (continuous), height (continuous), total physical activity (MET-hours/week, quintiles), age at menarche (≤10 years old, 11–12, 13–14, ≥15), birth index (continuous; ref. 1), total lifetime breastfeeding (none, <6 months, ≥6 months), menopausal status (premenopausal, postmenopausal, unknown), hormone therapy use (never, ever use of estrogen plus progesterone, past: estrogen only or other, current: estrogen only or other), family history of breast cancer in mother

or sister (yes/no), personal history of benign breast disease (yes/no), white race/ethnicity (yes/no), alcohol intake (none, 1–14 grams/day, ≥15 grams/day), and mammography within the past 2 years (<40 years old, ≥40 and no mammography, ≥40 and mammography for screening, ≥40 and mammography for abnormality/symptoms). Additional supplemental models adjusted for self-reported pregnancy-associated hypertension and use of diabetes therapies (with separate terms for insulin and oral therapies). Missing covariate data for an individual were carried forward from a previous questionnaire, if available. A missing indicator category was created for categorical covariates if necessary.

In addition, we evaluated a secondary exposure definition, taking into account progression from GDM to type II diabetes, classifying women as (i) no diabetes; (ii) GDM only, without subsequent type II diabetes; (iii) type II diabetes only; or (iv) both GDM and subsequent type II diabetes. We updated participants' status prospectively over follow-up; women without either GDM or type II diabetes served as the reference group.

We next conducted stratified analyses to evaluate whether the relationship between GDM and breast cancer differed by established diabetes and breast cancer risk factors, including menopausal status (pre- vs. postmenopausal), current BMI classification (normal <25.0, overweight 25.0–29.0, and obese ≥30.0 kg/m^2), age at first birth (<30 vs. ≥30 years old), family history of breast cancer in a sister or mother (yes vs. no), family history of diabetes in a parent or sibling (yes vs. no), physical activity (quintile 1–3 vs. quintile 4–5), prepregnancy menstrual cycle regularity at ages 18 to 22 (regular to mostly regular vs. usual or always irregular), and total lifetime breastfeeding history (<6 months vs. ≥ 6 months). We hypothesized that differences in underlying risk factors, such as insulin resistance and sex steroid hormones, may modify the relationship between GDM and subsequent breast cancer risk. We calculated *P* values for interaction from a multiplicative interaction term between the exposure and modifier in the main effects model.

We assessed bias due to differences in screening practices between women with and without a history of GDM by restricting to person-time among women ≥40 years of age with mammography screening in the past 2 years. We also modeled BMI at various time points, including current BMI, BMI at age 18, or both in the multivariable model. All analyses were run on SAS Version 9.3, with α <0.05 as the level of significance.

Results

The study population consisted of 81,784 parous women without a history of GDM and 5,188 with a history of GDM. The mean (SD) age at GDM diagnosis was 33.1 (5.5) years. Overall, 63% of the 982,078 person-years was accrued prior to menopause. Baseline characteristics are shown in Table 1. Women with a history of GDM were less physically active, less likely to be white, more likely to be overweight or obese, and to have a family history of diabetes, compared with women without a history of GDM. Women with a history of GDM also had an older age at first birth, were more likely to have a history of pregnancy-induced hypertension, and were less likely to have breastfed for ≥6 months total in their lifetime. Over follow-up, women ≥40 years old with a history of GDM were slightly less likely than those without a history of GDM to report mammography screening in the past 2 years (GDM 65.5% vs. no GDM 68.1% person-years).

Table 1. Characteristics of 86,972 parous U.S. women in the NHS II cohort in 1989, by history of GDM

	No history of GDM *n* = 81,784	History of GDM *n* = 5,188
Age[a]	35.0 ± 4.7	33.8 ± 4.4
Lifestyle factors		
BMI	23.9 ± 4.7	25.8 ± 5.9
Normal weight (BMI < 25.0), %	71	55
Overweight (BMI 25.0–29.9), %	18	25
Obese (BMI ≥ 30), %	10	20
BMI at age 18[b]	21.0 ± 3.0	21.5 ± 3.6
Normal weight at 18 (BMI < 25.0), %	91	87
Overweight/obese at 18 (BMI ≥ 25.0), %	8	12
Height (inches)	64.9 ± 2.6	64.5 ± 2.6
Total physical activity (MET-hrs/week)	23.7 ± 35.2	21.8 ± 33.0
Alternative Healthy Eating Index score[b]	47.9 (10.7)	47.2 (10.5)
Fruit and vegetable intake (servings/day)[b]	4.2 ± 2.3	4.3 ± 2.5
Alcohol intake (g/day)[b]	2.9 ± 5.6	2.2 ± 4.8
Smoking total pack years	7.4 ± 60.7	6.9 ± 55.4
Smoking status, %		
Never	66	66
Past	22	21
Current smoker	12	13
Current multivitamin use, %	46	47
Other risk factors		
Age at menarche, %		
≤10 years	7	10
11–12 years	46	48
13–14 years	38	35
≥15 years	8	7
Regularity of menses at ages 18–22, %		
Regular or very regular	74	72
Usually or always irregular	22	25
Age at first birth (years)	26.5 ± 4.5	27.6 ± 5.0
Parity (pregnancies ≥6 months)	1.8 ± 1.1	1.8 ± 1.2
Birth index[c]	16.1 (14.3)	14.3 (14.8)
Total breastfeeding, %[b]		
None	15	13
<6 months	13	13
≥6 months	46	43
Oral contraceptive use, %		
Never	15	16
Past	73	72
Current	12	12
History of pregnancy-induced hypertension	10	20
Mammography screening among women >40 years old, %		
<40 years old	80	80
≥40 years old, with screening	11	11
≥40 years old, no screening	5	5
≥40 years old, mammography for symptoms	4	4
Hysterectomy	5	5
Bilateral oophorectomy	1	1
Family history of diabetes, %	14	28
Family history of breast cancer, %	6	5
Personal history of benign breast disease, %[b]	29	30
Race/ethnicity, %		
White	96	93
Black	2	3
Asian	2	3

NOTE: Values represent means ± SD unless otherwise indicated and are standardized to the age distribution of the study population. Values of categorical variables may not sum to 100% due to rounding.

[a]Value is not age adjusted.

[b]Missing data on BMI at age 18 in 1% of participants, food frequency and alcohol intake in 16.3% of participants, breastfeeding in 14.6% of parous participants, and history of benign breast disease in 3.6% of participants. All other data were missing in less than 1% of participants.

[c]Birth index was calculated by summing total years from each birth to current age (or age at menopause for postmenopausal women) over all births.

Table 2. Association between history of GDM and incident invasive breast cancer risk

	No GDM HR (95% CI)	GDM HR (95% CI)	*P*
Cases, no.	2,277	100	
Person-years[a]	923,694	58,384	
Age adjusted	1.00 (reference)	0.68 (0.55–0.84)	0.0003
Multivariable adjusted	1.00 (reference)	0.68 (0.55–0.84)	0.0004

NOTE: Multivariable model additionally adjusts for BMI at age 18 (continuous), weight gain since age 18 (continuous), height (continuous), total physical activity (MET-hours/week, quintiles), alcohol intake (none, 1–14 grams/day, ≥15 grams/day), age at menarche (≤10 years old, 11–12, 13–14, ≥15), birth index (continuous), total breastfeeding (none, <6 months, ≥6 months), menopausal status (premenopausal, postmenopausal, unknown), hormone therapy use (never, ever use of estrogen + progesterone, past: estrogen only or other, current: estrogen only or other), family history of breast cancer in mother or sister (yes/no), personal history of benign breast disease (yes/no), white race/ethnicity (yes/no), and mammography within the past 2 years (<40 years old, ≥40 and no mammography, ≥40 and mammography for screening, ≥40 and mammography for abnormality/symptoms).

[a]Person-years are calculated as the time from age at first birth or first GDM pregnancy, through the end of follow-up (the date of incident breast cancer diagnosis, death, or last questionnaire return through May 31, 2013).

Over 22 years of prospective follow-up, there were 2,377 incident cases of invasive breast cancer, with 100 occurring among women with a history of GDM. The mean (SD) age at breast cancer diagnosis was 49.5 (6.6) years. Women with a history of GDM were significantly less likely to develop invasive breast cancer (Table 2) in both the age-adjusted (HR, 0.68; 95% CI, 0.55–0.84; $P = 0.0003$) and multivariable-adjusted models (HR, 0.68; 95% CI, 0.55–0.84; $P = 0.0004$). Adjusting for oral contraceptive use, history of pregnancy-induced hypertension, and smoking status did not impact results. Similarly, inclusion of women who reported multiple gestation pregnancies in the analysis did not affect the results. Results were similar by menopausal status (premenopausal, $n = 1{,}377$ events: HR, 0.73; 95% CI, 0.56–0.96; $P = 0.03$; postmenopausal, $n = 916$ events: HR, 0.63; 95% CI, 0.43–0.92; $P = 0.02$). There was an inverse association between history of GDM and hormone receptor–positive breast cancer (either ER^+ or PR^+, $n = 71$ GDM events, $n = 1{,}690$ non-GDM events; HR, 0.65; 95% CI, 0.50–0.84; $P = 0.0009$), but not for hormone receptor–negative cancers (both ER^- and PR^-, $n = 23$ GDM events, $n = 393$ non-GDM events; HR, 0.96; 95% CI, 0.60–1.52; $P = 0.9$); however, test for heterogeneity was not statistically significant ($P_{heterogeneity} = 0.16$).

Table 3 gives results stratified by established diabetes or breast cancer risk factors. Significant effect modification was observed for BMI ($P_{interaction} = 0.04$) and total physical activity ($P_{interaction} = 0.04$), indicating an inverse relationship between GDM history and breast cancer among overweight, obese, and less physically active participants (below median MET-hours/week), with no association among normal weight or more physically active women (Table 3). There was a trend toward stronger inverse relationship between history of GDM and invasive breast cancer among women with <6 months total lifetime breastfeeding, as compared with their longer breastfeeding counterparts ($P_{interaction} = 0.08$). Findings did not differ by age at first birth, family history of breast cancer, regularity of menstrual cycles, or family history of diabetes (all $P_{interactions} > 0.05$).

Table 4 shows the risk of GDM with invasive breast cancer accounting for type II diabetes. There was a significant inverse relationship between GDM and breast cancer versus no diabetes, regardless of progression to type II diabetes (GDM only: HR, 0.72; 95% CI, 0.58–0.89; $P = 0.003$; GDM and subsequent type II diabetes: HR, 0.26; 95% CI, 0.10–0.68; $P = 0.006$). Type II diabetes only without a prior history of GDM, compared with no diabetes, was not significantly associated with breast cancer (HR, 0.69; 95% CI, 0.40–1.18; $P = 0.2$). Additional adjustment

Table 3. Association between history of GDM and incident invasive breast cancer risk, stratified by risk factors

Stratified by risk factors	Cases, no. No GDM/GDM	No GDM HR (95% CI)	GDM HR (95% CI)	$P_{interaction}$
Current BMI category (kg/m^2)[a]				
Normal (<25.0)	1,116/49	1.00 (reference)	0.97 (0.72–1.32)	0.04
Overweight (25.0–29.9)	646/25	1.00 (reference)	0.50 (0.32–0.78)	
Obese (≥30.0)	512/26	1.00 (reference)	0.50 (0.32–0.77)	
Age at first birth				
<30 years	1,707/59	1.00 (reference)	0.57 (0.39–0.83)	0.85
≥30 years	570/41	1.00 (reference)	0.89 (0.64–1.24)	
Family history of breast cancer				
No	1,900/83	1.00 (reference)	0.65 (0.52–0.83)	0.96
Yes	377/17	1.00 (reference)	0.76 (0.44–1.31)	
Family history of diabetes				
No	1,669/62	1.00 (reference)	0.75 (0.57–0.98)	0.33
Yes	608/38	1.00 (reference)	0.59 (0.41–0.85)	
Physical activity				
Low (Q1–Q3)	1,457/58	1.00 (reference)	0.56 (0.42–0.74)	0.04
High (Q4–Q5)	820/42	1.00 (reference)	0.98 (0.70–1.37)	
Total lifetime breastfeeding				
None to <6 months	933/29	1.00 (reference)	0.55 (0.37–0.81)	0.08
≥6 months	1,344/71	1.00 (reference)	0.77 (0.59–0.99)	

NOTE: Multivariable model adjusts for age, BMI at age 18 (continuous), weight gain since age 18 (continuous), height (continuous), total physical activity (MET-hours/week, quintiles), alcohol intake (none, 1–14 grams/day, ≥15 grams/day), age at menarche (≤10 years old, 11–12, 13–14, ≥15), birth index (continuous), total breastfeeding (none, <6 months, ≥6 months), menopausal status (premenopausal, postmenopausal, unknown), hormone therapy use (never, ever use of estrogen + progesterone, past: estrogen only or other, current: estrogen only or other), family history of breast cancer in mother or sister (yes/no), personal history of benign breast disease (yes/no), white race/ethnicity (yes/no), and mammography within the past 2 years (<40 years old, ≥40 and no mammography, ≥40 and mammography for screening, ≥40 and mammography for abnormality/symptoms).

[a]Multivariable model is adjusted for current BMI (continuous).

Table 4. Association between history of GDM and incident invasive breast cancer risk, by intermediate type II diabetes status

	No GDM or type II diabetes HR (95% CI)	GDM only HR (95% CI)	Type II diabetes only HR (95% CI)	Both GDM and type II diabetes HR (95% CI)
All women				
Cases, no.	2,224	95	53	5
Person-years	907,823	53,635	20,576	5,982
Age adjusted	1.00 (reference)	0.72 (0.58–0.90)	0.63 (0.37–1.07)	0.23 (0.09–0.61)
Multivariable model	1.00 (reference)	0.72 (0.58–0.89)	0.69 (0.40–1.18)	0.26 (0.10–0.68)

NOTE: Multivariable model adjusts for age, BMI at age 18 (continuous), weight gain since age 18 (continuous), height (continuous), total physical activity (MET-hours/week, quintiles), alcohol intake (none, 1–14 grams/day, ≥15 grams/day), age at menarche (≤10 years old, 11–12, 13–14, ≥15), birth index (continuous), total breastfeeding (none, <6 months, ≥6 months), menopausal status (premenopausal, postmenopausal, unknown), hormone therapy use (never, ever use of estrogen + progesterone, past: estrogen only or other, current: estrogen only or other), family history of breast cancer in mother or sister (yes/no), personal history of benign breast disease (yes/no), white race/ethnicity (yes/no), and mammography within the past 2 years (<40 years old, ≥40 and no mammography, ≥40 and mammography for screening, ≥40 and mammography for abnormality/symptoms).

for use of diabetes therapies (insulin and oral therapies) did not modify the estimate (HR, 0.68; 95% CI, 0.0.55–0.85; $P = 0.0005$).

When we restricted to follow-up among participants ≥40 years of age reporting mammography screening in the past 2 years, results were similar to the overall cohort (HR, 0.74; 95% CI, 0.57–0.96; $P = 0.02$; Supplementary Table S1). Results did not change when we adjusted for current BMI instead of BMI at age 18.

Discussion

In this large prospective study of parous women in the United States with >20 years of follow-up, we did not observe a greater invasive breast cancer risk among women with a history of GDM. In fact, women with history of GDM experienced a lower incident breast cancer risk. This inverse relationship was independent of intermediate progression to type II diabetes and was stronger among women who were overweight, obese, or less physically active. Our analyses also suggested that the inverse relationship may be particularly strong for hormone receptor–positive breast cancers (ER^+ or PR^+).

Results of previous studies examining GDM and breast cancer are mixed, and study populations, design, and control for potential confounders varied widely (12–16, 25). Two prior studies observed inverse relationships between GDM and breast cancer risk (15, 16). One retrospective population-based study with a median follow-up of 8 years postpartum found a lower risk of premenopausal breast cancer among women with a history of GDM (OR = 0.86; 95% CI, 0.75–0.98; ref. 16). Similarly, a retrospective U.S.-based case–control study indicated an inverse relationship between GDM and postmenopausal breast cancer (OR = 0.54; 95% CI, 0.37–0.79; ref. 15). In contrast, there was a positive relationship between a history of GDM and breast cancer risk in a retrospective cohort of live births in 1964 to 1976, limited to women ≥50 years of age (OR = 1.7; 95% CI, 1.1–2.5; ref. 12). A positive association was also observed between measures of glucose intolerance in a pregnancy cohort with long-term breast cancer (13), Three additional studies observed null associations for GDM with breast cancer risk (14, 25, 26). In the current study, we did not observe a positive association between GDM and postmenopausal breast cancer. We were able to address several limitations of prior studies with the prospective design, large sample size, and adjustment for many possible sources of bias, including lifestyle and mammography screening practices.

There are several potential explanations for our unexpected observation of lower breast cancer risk among women with prior GDM. It is possible that the altered hormonal milieu of a GDM complicated pregnancy confers protection on breast tissue. Pregnancy is known to induce proliferation and functional differentiation of breast lobules and ducts, thought to mediate the epidemiologic association between pregnancy history and breast cancer risk (3–5). It follows that differences in circulating growth factors or hormones in GDM-affected pregnancies may impact these processes and the future risk for breast cancer. Preeclampsia is a pregnancy-associated condition linked with GDM that may be associated with lower breast cancer risk (27, 28). However, adjusting for a history of pregnancy-induced hypertension did not impact our findings.

Beyond pregnancy, GDM may be a manifestation of chronic subclinical abnormal glucose metabolism. We hypothesized, based on epidemiologic literature and rodent models, that a history of abnormal glucose metabolism in pregnancy would be associated with a higher risk of breast cancer. However, obesity (itself strongly associated with type II diabetes and abnormal glucose metabolism) is known to be inversely associated with the risk of premenopausal breast cancer (29, 30). Consistent with this, a trend toward an inverse association between midlife fasting insulin levels (a marker of insulin resistance) and premenopausal breast cancer risk was observed in the NHS II (31), in contrast to a previously observed positive relationship between fasting insulin levels and postmenopausal breast cancer risk (29, 30). It is possible that GDM reflects an underlying metabolic state that specifically impacts premenopausal breast cancer risk, which accounted for the majority of the cases in this study. Notably, the magnitude of the reduction in breast cancer risk associated with a history of GDM appeared to be greatest among women with additional diabetes risk factors: low physical activity, overweight/obesity, and less lifetime breastfeeding (32). Previous studies suggest that the physiology underlying GDM differs in obese versus lean women; thus, different subtypes of GDM may have different associations with breast cancer (33, 34).

Alternate explanations for our observations include residual or unmeasured confounding and screening bias. Unmeasured factors underlying the inverse relationship between obesity and premenopausal breast cancer risk may partially explain our findings. Some oral diabetes therapies have been associated with a lower cancer risk (35), but adjusting for this factor did not account for our findings. A recent analysis identified three type II diabetes genetic risk variants as inversely related to breast cancer risk, although the overall diabetes genetic risk score was null; this suggests there may be some potential for shared pathways between diabetes and lower breast cancer risk that were uncontrolled for in our analysis (36). We explored the potential for

screening bias in sensitivity analyses. Women with GDM were slightly less likely to have been recently screened for breast cancer, which might lead to fewer diagnoses. However, mammography screening was included in our multivariate model. Furthermore, when restricting to women ≥40 years old reporting mammography screening in the past 2 years, breast cancer risk remained lower among women with a history of GDM, suggesting that differences in screening did not account for our findings.

Strengths of the current study include its large sample size, prospective nature, and rigorous ascertainment of exposures and outcomes. We also captured information on numerous potential confounders. Analyses of breast cancer subtypes and subgroup stratification were limited in statistical power by the number of events; thus, we must interpret these with caution. Another limitation to note is the potential for misclassification of GDM exposure status, given that of the women deemed "probable GMD," 21% had medical records indicating a physician's diagnosis, but no oral glucose tolerance test values to verify the diagnosis. Finally, because <5% of the participants in this study were from ethnic/racial minority groups, generalizability to nonwhite populations may be limited.

In summary, in contrast to our hypothesis, we found that a history of GDM was not associated with greater breast cancer risk among a large cohort of U.S. women, followed prospectively for >20 years. In fact, GDM appeared inversely associated with breast cancer risk, even after adjustment for the many known breast cancer risk factors. It is possible that the hormonal milieu of a GDM pregnancy protects the breast from future malignancy or that GDM is representative of an underlying metabolic state (including obesity), which is protective against premenopausal breast cancer. Further research is needed to validate our unexpected findings in other large prospective cohorts.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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