Gestational diabetes and risk of breast cancer before age 55 years

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Abstract

Background: The history of gestational diabetes mellitus (GDM) has been associated with breast cancer risk in some studies, particularly in young women, but results of cohort studies are conflicting.

Methods: We pooled data from 257 290 young (age <55 years) women from five cohorts. We used multivariable Cox proportional-hazards regression to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between GDM history and risk of breast cancer, overall and by oestrogen receptor (ER) status, before age 55 years, adjusted for established breast cancer risk factors.

Results: Five percent of women reported a history of GDM and 6842 women reported an incident breast-cancer diagnosis (median follow-up = 16 years; maximum = 24 years). Compared with parous women without GDM, women with a history of GDM were not at increased risk of young-onset breast cancer overall (HR = 0.90; 95% CI: 0.78, 1.03) or by

ER status (HR = 0.96; 95% CI: 0.79, 1.16 for ER-positive; HR = 1.07; 95% CI: 0.78, 1.47 for ER-negative). Compared with nulliparous women, parous women with a history of GDM had a lower risk of breast cancer overall (HR = 0.79; 95% CI: 0.68, 0.91) and of ER-positive (HR = 0.82; 95% CI: 0.66, 1.02) but not ER-negative (HR = 1.09; 95% CI: 0.76, 1.54) invasive breast cancer. These results were consistent with the HRs comparing parous women without GDM to nulliparous women.

Conclusions: Results of this analysis do not support the hypothesis that GDM is a risk factor for breast cancer in young women. Our findings suggest that the well-established protective effect of parity on risk of ER-positive breast cancer persists even for pregnancies complicated by GDM.

Key words: Gestational diabetes mellitus, breast cancer, epidemiology, cohort

Key Messages

- In this pooled prospective analysis of nearly 260 000 women and 6842 incident breast cancer diagnoses, we found no evidence that history of gestational diabetes mellitus (GDM) increases risk of breast cancer among women under age 55 years.
- Compared with nulliparous women, parous women with or without a GDM-affected pregnancy were at similarly reduced risk of breast cancer, especially oestrogen receptor positive breast cancer.
- Overall, our findings do not support the hypothesis that GDM increases risk of breast cancer in women under age 55 years.

Introduction

Pregnancy and the post-partum period are times of rapid changes in circulating hormone levels, with proliferation and differentiation of mammary epithelial cells and changes in breast tissue structure, all of which may impact breast cancer risk.[1,2] In addition to hormonal and breast tissue changes, other physiologic changes during pregnancy include increases in blood volume, modulation of the immune response, low-grade inflammation and changes in metabolism. Complications of pregnancy could alter these systems and impact subsequent breast cancer risk. Previous observational studies have reported associations of pregnancy-associated factors, such as gestational hypertension, pre-eclampsia and preterm birth/gestational length with breast cancer, particularly for cancers diagnosed at younger ages.[3–7]

Gestational diabetes mellitus (GDM), a pregnancy condition characterized by hyperglycemia, occurs in an estimated 5–10% of pregnancies in the USA.[8] GDM is correlated in both pregnancy and post-partum with cardiometabolic traits that may contribute to the development or progression of breast cancer, such as hyperinsulinemia, lower sex hormone binding globulin levels, higher C-reactive protein levels and higher insulin-like growth factor 1 levels.[9–16] In particular,

women with a history of GDM have an elevated risk of subsequent type 2 diabetes, which itself is associated with an estimated 20% increase in the risk of breast cancer.[17,18] Thus, there is a strong biological rationale for an association between GDM and breast cancer risk; however, results from epidemiologic studies have been mixed.[19–31]

Three recent prospective cohort studies evaluated the possible association between GDM and breast cancer risk. In the Nurses' Health Study II (NHS II), an inverse association between history of GDM and risk of breast cancer was observed [hazard ratio (HR): 0.68; 95% confidence interval (CI): 0.55, 0.84], with similar associations for pre- and postmenopausal breast cancers.[28] In contrast, results from the Sister Study (SIS) suggest a positive association between GDM and oestrogen receptor negative (ER–) breast cancer (HR: 1.73; 95% CI: 0.98, 3.06)—a finding that was somewhat stronger among premenopausal women.[29] In the Black Women's Health Study (BWHS), there was no evidence of an association between history of GDM and risk of invasive breast cancer overall, by ER status or by menopausal status.[30] Results from earlier cohort studies based on administrative database linkages were also inconsistent.[22,24,27,31]

To address gaps in the literature, including limited numbers of ER– cases, we pooled data from five cohorts to evaluate associations of GDM with breast cancer risk, overall and by ER status. We focused exclusively on women under age 55 years, based on the hypothesis that pregnancy-related factors may play a stronger role in determining breast-cancer risk in women 0–20 years post-partum than in women who gave birth several decades prior.[1,32,33]

Methods

Study populations

The pooled study population included >270 000 women from five large cohorts who had no history of breast cancer and were aged ≤55 years at enrolment. The cohorts are part of the Premenopausal Breast Cancer Collaborative Group[34] and include BWHS,[35] NHS II,[36] SIS,[37] the Southern Community Cohort Study (SCCS)[38] and the Women's Lifestyle and Health Study (WLHS).[39] BWHS, NHS II, SIS and SCCS are US-based cohorts whereas WLHS enrolled women in Sweden. Participants in each study completed baseline and follow-up questionnaires.

Women missing data on GDM status at baseline were excluded from analysis (n = 1252, including 1091 from BWHS, 16 from SIS and 145 from SCCS), leaving an eligible sample size of 271 049 (Table 1; 51 452 in BWHS, 116 415 in NHS II, 24 028 in SIS, 30 144 in SCCS and 49 010 in WLHS). All included participants provided informed consent and individual protocols were approved by the relevant institutional review boards.

Assessment of GDM

All included studies assessed whether the participant had experienced GDM at any pregnancy, including enough information about timing to determine whether the diagnosis occurred prior to their enrolment in the study. All data were self-reported. All studies except SCCS collected information about age at first GDM diagnosis. The total number of GDM-affected pregnancies was not reliably collected for most studies and therefore is not considered in analyses.

For NHS II, SIS and SCCS, questions about GDM were included on the original enrolment questionnaire, allowing prospective ascertainment of breast-cancer status. For BWHS, GDM status was obtained on the second questionnaire (1997), but that questionnaire specifically asked about diagnoses prior to baseline (1995). Similarly, WLHS did not assess GDM status and timing until 2003, despite enrolling in 1991–1992. Under the assumption that self-reported history of GDM would be non-differential by breast-cancer status, we retained the person-time and incident breast-cancer cases accrued between enrolment and the time at which GDM was assessed in these two studies.

Three cohorts, namely BWHS, NHS II and WLHS, continued to collect information on self-reported GDM status during follow-up. These studies are included in analyses in which GDM status was treated as a time-varying exposure variable.

Assessment of incident breast cancer cases

As described in Nichols et al.,[34] information was collected on all *in situ* and invasive breast cancers diagnosed up to age 55 years. Breast cancer diagnoses were identified by linkage to cancer registries and/or by self-report followed by medical record review. All cases in WLHS and SCCS were identified through cancer registries. Medical records were available for ~80% of self-reported breast cancer

Table 1 Characteristics of eligible participants, by cohort[a]

Cohort	Sample size	Study location	Enrolment period	Baseline age (years); range (mean)	Follow-up time (years); range (median)	Number of cases/invasive cases	Ever gestational diabetes (baseline); n (% among parous)
Black Women's Health Study (BWHS)	51 452	USA	1995	20–54 (37)	0.5–19 (15)	1282/945	1334 (4)
Nurses' Health Study II (NHS II)	116 415	USA	1989	24–44 (36)	0.1–24 (20)	3765/2506	4234 (5)
Sister Study (SIS)	24 028	USA	2003–2009	35–54 (48)	0.1–11 (5)	679/483	1191 (6)
Southern Community Cohort Study (SCCS)	30 144	Southeast USA	2002–2009	40–54 (47)	0.1–13 (5)	232/184	3101 (12)
Women's Lifestyle and Health Study (WLHS)	49 010	Sweden	1991–1992	29–49 (39)	0.1–22 (15)	1192/965	905 (2)
Total	271 049		1989–2009	20–54 (38)	0.1–24 (16)	7150/5083	10 765 (5)

[a]After excluding women who had missing data for gestational diabetes at baseline (n = 1252, including 1091 from BWHS, 16 from SIS and 145 from SCCS).

cases in SIS; medical records and/or cancer registry data were available for >90% of self-reported cancer cases in BWHS and NHS II. Among those with available medical records or registry data, agreement between self-reports and medical records/registry linkage in all three cohorts was >99%; therefore, we included all self-reported diagnoses in analyses. Data on ER status and other tumour characteristics were available for all five studies.

Potential confounders and other covariates

Detailed information on participants' demographic characteristics (age, race/ethnicity, attained education), family history of breast cancer and reproductive history (parity, age at first birth, age at most recent birth and menopausal status) was available at baseline and during follow-up for all cohorts. Body mass index (BMI; kg/m^2) was calculated for each participant using data on height and weight at enrolment; we also estimated BMI during young adulthood using self-reported weight in earlier life. For BWHS, NHS II, SCCS and WLHS, this corresponded to participants' BMI at approximately ages 18–24 years and for SIS it corresponded to BMI at ages 30–39 years. We restricted all analyses to women with complete information on these covariates, resulting in a final analytic sample size of 257 290, including 191 847 parous women.

Statistical analyses

Individual cohort analyses

We calculated covariate-adjusted HRs and 95% CIs for each individual cohort using Cox proportional hazards models with age as the timescale. Women accrued person-time from study entry until breast cancer diagnosis, study end, death or age 55 years, whichever occurred first. We computed follow-up time separately for all breast cancers and for invasive breast cancers (censoring at *in situ* diagnosis), calculating the estimated effect of ever having had GDM on breast cancer incidence. For one set of analyses, the models included all women, with nulliparous women considered as the referent group. For other analyses, we restricted to parous women and considered those without a history of GDM as the referent group. We also include sensitivity analyses restricted to *in situ* cases, censoring those who were initially diagnosed with invasive breast cancer. Here we used joint Cox models to simultaneously estimate HRs specific to invasive or *in situ* disease, testing for heterogeneity between the HRs using a Wald test.[40] When nulliparous women were included, we adjusted for race/ethnicity (non-Hispanic White, African American, other),

attained education (high school or less, some college, college graduate), young adult BMI (continuous, in kg/m^2), parity (0, 1, 2, ≥3), age at first birth (continuous, centered at 25 years), age at most recent birth (continuous, centered at 25 years), an interaction term between parity (yes or no) and age at first birth, and an interaction term between parity (yes or no) and age at most recent birth. For analyses restricted to parous women, we adjusted for race/ethnicity, attained education, young adult BMI, parity (1,2, ≥3), age at first birth and age at most recent birth. These factors were chosen for inclusion in multivariable models based on their potential for confounding. We used a Wald test to test for interaction of a GDM effect by attained age to evaluate violations of the proportional hazards assumption.

Pooled analyses

Pooled HRs and 95% CIs were calculated using cohort-stratified Cox models (i.e. with baseline hazards allowed to vary between cohorts). We again evaluated the proportional hazards assumption and also tested for between-study heterogeneity using a Wald test to test for cohort by GDM interaction in models not stratified by cohort. To further examine the impact of each individual study, we also calculated pooled estimates and between-study heterogeneity *p*-values after omitting one study at a time.

In additional pooled analyses, we estimated HRs for ER+ and ER− breast cancers separately. Here, we considered invasive breast cancers only, as a large proportion (39%) of *in situ* cases were missing ER status. We also considered whether the HRs varied by age at GDM diagnosis (<30 or ≥30 years) and conducted analyses limited to women with exactly two births. This analysis was done to limit the potential confounding influence of parity and allow each included woman an equal opportunity for exposure. Lastly, we conducted analyses of the association between history of GDM and risk of breast cancer among parous women within categories of race/ethnicity (non-Hispanic White, African American), baseline BMI (<25 or ≥25 kg/m^2), menopausal status (pre- or postmenopausal, with status updated over follow-up), age at first pregnancy (<25 or ≥25 years), parity (one or more than one birth), time since most recent pregnancy (<10 or ≥10 years) and family history of breast cancer (no first-degree relatives or at least one first-degree relative).

GDM during follow-up

For the three cohorts that continued to collect GDM data in follow-up questionnaires (BWHS, NHS II and WLHS), we conducted additional analyses updating GDM status during follow-up (i.e. treating GDM as a time-varying exposure). These analyses were limited to parous women. To improve efficiency for time-varying models, we conducted

pooled logistic regression models based on 2-year time intervals, with GDM, breast cancer status and covariates updated for each interval. We included random effects terms for cohort and reported pooled odds ratios (ORs) and 95% CIs as well as p-values for tests of heterogeneity between studies. The latter was done as a Wald test of GDM-by-cohort interaction terms in a model with no random effects.

We first calculated study-specific and pooled effect estimates for any history of GDM, adjusting for the same covariates as in the primary analysis, plus terms for age at baseline and age at the start of the 2-year follow-up interval. We also carried out an analysis limited to incident GDM diagnoses (i.e. those occurring after baseline) by excluding those with a pre-baseline diagnosis and allowing women to enter the risk set only upon experiencing a post-baseline birth. Finally, we considered only incident first births, limiting the risk set to those who were nulliparous at baseline and starting follow-up at the participant's age at first (post-baseline) birth. As the number of breast cancer cases who experienced post-baseline GDM was quite small in WLHS ($n = 3$), the latter two sets of pooled estimates include only BWHS and NHS II.

All analyses were performed using SAS 9.4 (Cary, NC).

Results

Enrolment across these cohorts occurred over a 30-year period (1989–2009), with a median follow-up time of 16 years (range 0.1–24 years) from study baseline. Eligible participants were on average 38 years old at enrolment (range 20–54 years). Five percent of parous women reported ever having been diagnosed with GDM and 7150 women developed incident breast cancer, including 5083 invasive diagnoses (Table 1). The distribution of baseline characteristics of each participating cohort is shown in Supplementary Table S1 (available as Supplementary data at *IJE* online). Overall, ~68% of the study population were non-Hispanic White and 29% were African American. Nineteen percent of participants reported a first-degree family history of breast cancer. Seventy-five percent of participants were parous at baseline enrolment. As shown in Supplementary Table S2 (available as Supplementary data at *IJE* online), parous women with GDM had higher young adult and baseline BMI compared with both parous women without GDM and nulliparous women. Parous African American women were also more likely to report a history of GDM compared with parous non-Hispanic White women.

Among women with complete information on covariates ($n = 257\,290$, including 191 847 parous women), we identified 6842 incident breast-cancer diagnoses (4882 among parous women) (Table 2). In the pooled sample, compared with nulliparous women, parous women with a history of GDM had a decreased risk of overall (HR: 0.79; 95% CI: 0.68, 0.91) and invasive (HR: 0.85; 95% CI: 0.72, 1.02) breast cancer. Compared with parous women without GDM, the corresponding HRs were 0.90 (95% CI: 0.78, 1.03) and 0.94 (95% CI: 0.80, 1.10), respectively. Results were similar in models that adjusted only for age and cohort (data not shown) or age, young adult BMI and cohort (Supplementary Table S3, available as Supplementary data at *IJE* online). There was no evidence of violation of the proportional hazards assumption.

There was some evidence of statistical heterogeneity between studies (both p-heterogeneity <0.20). Results of pooled analyses leaving one study out at a time revealed that heterogeneity in effect estimates was driven mainly by NHS II, which generally produced the lowest HRs among the five cohorts and had the largest sample size; leaving NHS II out of pooled analyses increased summary HRs close to or slightly over 1.0 (Supplementary Table S4, available as Supplementary data at *IJE* online). Pooled multivariable-adjusted HRs for *in situ* breast cancers were more strongly inverse than those for invasive cancers: the HRs compared with nulliparous women were 0.66 (95% CI: 0.46, 0.94) for parous women with a history of GDM and 0.79 (95% CI: 0.57, 1.10) for parous women without a history of GDM. HRs for invasive vs *in situ* cancer were not different from each other, however (Supplementary Table S5, available as Supplementary data at *IJE* online).

Among invasive cancers, we found that the decreased risk of breast cancer among parous women with GDM compared with nulliparous women was observed for ER+ (HR: 0.82; 95% CI: 0.66, 1.02) but not ER– breast cancer (HR: 1.09; 95% CI: 0.76, 1.54). The corresponding HRs for parous women without GDM vs nulliparous women indicated an inverse association for ER+ (HR = 0.85; 95% CI: 0.76, 0.95) but not ER– breast cancer (HR = 1.00; 95% CI: 0.83, 1.20). Considering a referent group of parous women without GDM, there were no associations of history of GDM with either ER+ (HR: 0.96; 95% CI: 0.79, 1.16) or ER– (HR: 1.07; 95% CI: 0.78, 1.47) invasive breast cancer (Table 3).

In sensitivity analyses, results were unchanged when models were further adjusted for both young adult BMI and recent BMI or recent BMI only (data not shown). Results were similar to those in main analyses when we restricted analyses to women with exactly two births (Supplementary Table S6, available as Supplementary data at *IJE* online). Finally, we found no evidence that associations varied by age at GDM diagnosis (Table 3) or within

Table 2 Cohort-specific and pooled results for gestational diabetes mellitus (GDM) status at baseline and risk of incident breast cancer

	Person-years at risk[a]	Breast cancer cases[a] (all/ invasive)	Prevalence of GDM[a] (non-cases/all cases/ invasive cases)	Hazard ratio (95% CI): all breast cancers[b]	Hazard ratio (95% CI): invasive breast cancers[b]	Between-cohort heterogeneity p-values[c] (all cases/ invasive cases)
All women (referent = nulliparous women)						
BWHS	654 636	1254/926	2.6%/2.8%/2.6%	0.94 (0.66, 1.35)	0.90 (0.58, 1.39)	
NHS II	2 065 240	3614/2409	3.6%/2.8%/3.1%	0.63 (0.51, 0.78)	0.70 (0.54, 0.90)	
SIS	110 183	664/471	4.8%/5.9%/6.8%	0.96 (0.63, 1.45)	1.21 (0.76, 1.94)	
SCCS	145 687	215/172	10.3%/10.2%/10.5%	0.93 (0.48, 1.80)	0.76 (0.37, 1.59)	
WLHS	669 476	1095/890	1.9%/1.6%/1.6%	0.79 (0.48, 1.31)	0.72 (0.41, 1.28)	
Pooled sample	3 645 222	6842/4868	4.0%/3.2%/3.3%	0.79 (0.68, 0.91)	0.85 (0.72, 1.02)	0.17/0.06
Parous women (referent = parous women with no GDM)						
BWHS	369 334	794/609	4.2%/4.4%/3.9%	0.93 (0.66, 1.31)	0.82 (0.55, 1.24)	
NHS II	1 432 116	2475/1679	5.1%/4.1%/4.4%	0.79 (0.65, 0.96)	0.85 (0.67, 1.07)	
SIS	85 588	496/357	6.2%/7.9%/9.0%	1.20 (0.86, 1.67)	1.38 (0.95, 1.99)	
SCCS	129 306	190/149	11.6%/11.5%/12.0%	1.04 (0.66, 1.64)	1.09 (0.66, 1.80)	
WLHS	580 267	927/747	2.1%/1.9%/1.9%	0.90 (0.57, 1.44)	0.88 (0.52, 1.49)	
Pooled sample	2 596 611	4882/3541	5.4%/4.4%/4.6%	0.90 (0.78, 1.03)	0.94 (0.80, 1.10)	0.19/0.13

[a]Restricted to women with complete covariate information for the adjusted models [257 290 total (49 745 in BWHS; 110 780 in NHS II; 23 429 in SIS; 28 660 in SCCS; 44 676 in WLHS) and 191 847 total parous (30 487 in BWHS; 78 415 in NHS II; 18 344 in SIS; 25 462 in SCCS; 39 139 in WLHS)].

[b]Adjusted for age (as the timescale), race/ethnicity (non-Hispanic White, African American, other), attained education (high school or less, some college, college graduate), parity (0, 1, 2, ≥3), an interaction term between parity (yes or no) and age at first birth (continuous, centered at 25 years), an interaction term between parity (yes or no) and age at most recent birth (continuous, centered at 25 years), and body mass index at ages 18–24 years (continuous). For analyses limited to parous women, age at first birth and age at most recent birth are included as continuous variables with no interaction terms. Pooled estimates include stratification by cohort.

[c]From a Wald test of GDM-by-cohort interaction terms.

GDM, gestational diabetes mellitus; BWHS, Black Women's Health Study; NHS II, Nurses' Health Study II; SIS, Sister Study; SCCS, Southern Community Cohort Study; WLHS, Women's Lifestyle and Health Study.

strata defined by race/ethnicity, BMI, menopausal status, age at first pregnancy, parity, years since most recent pregnancy or family history of breast cancer (Table 4).

In a pooled analysis of the three cohorts (BWHS, NHS II and WLHS) that updated GDM occurrences during follow-up, the adjusted OR for risk of invasive breast cancer comparing parous women with a history of GDM to parous women without a history of GDM was 0.88 (95% CI: 0.74, 1.03). However, in an analysis of breast cancer associated with incident GDM (i.e. excluding nulliparous women and those with GDM prior to baseline), there was no association between GDM and invasive-breast-cancer risk (OR: 0.94; 95% CI: 0.67, 1.33) (BWHS and NHS II only). In analyses further restricted to women who were nulliparous at baseline and had their first birth during follow-up, the corresponding OR was 0.85 (95% CI: 0.54, 1.33). Of note, compared with women in the main analyses, women included in the analyses that considered post-baseline GDM were younger at cohort enrolment but older at first birth (Table 5).

Discussion

In this large, prospective analysis of nearly 260 000 women with >3.5 million person-years of follow-up and 6842 breast-cancer diagnoses, we found no evidence that history of GDM increases the risk of breast cancer among parous women under age 55 years, either overall or by ER status. It has been established that breast cancer risk is heightened during pregnancy and for >20 years after childbirth, especially for the first 5 years.[32] We hypothesized that complications of pregnancy, such as GDM, might further impact breast cancer risk through hormonal, immunological or inflammatory pathways.[1,41–43] Results of our analyses, however, do not support this hypothesis.

Our findings are generally consistent with results from a recent meta-analysis that included six cohort and five case–control studies of women across a wider age range.[44] Individual study results were rather mixed, with some studies reporting positive associations,[20,22,29] others reporting inverse associations[23,27,28] and others reporting no clear association in either direction.[19,21,24–26,45] Some

Table 3 Pooled, multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between gestational diabetes mellitus (GDM) and risk of breast cancer

History of GDM	Person-years at risk[a]	Cases[a] (all/invasive)	All breast cancers [HR (95% CI)]	Invasive breast cancers [HR (95% CI)]	ER+ invasive cancers		ER− invasive cancers	
					Cases	HR (95% CI)	Cases	HR (95% CI)
All women[b]								
Nulliparous	1 048 610	1960/1327	1.00	1.00	904	1.00	293	1.00
Parous, no GDM	2 468 995	4666/3379	0.87 (0.81, 0.93)	0.90 (0.83, 0.98)	2235	0.85 (0.76, 0.95)	764	1.00 (0.83, 1.20)
Parous, GDM	127 616	216/162	0.79 (0.68, 0.91)	0.85 (0.72, 1.02)	110	0.82 (0.66, 1.02)	42	1.09 (0.76, 1.54)
Nulliparous[d]	1 032 229	1935/1304	1.00	1.00	888	1.00	290	1.00
Parous, no GDM[d]	2 354 960	4498/3248	0.87 (0.81, 0.93)	0.90 (0.83, 0.99)	2159	0.86 (0.77, 0.96)	721	0.98 (0.82, 1.18)
Ever, age <30 years[d]	55 288	93/68	0.83 (0.67, 1.04)	0.88 (0.68, 1.13)	47	0.89 (0.66, 1.21)	17	1.01 (0.61, 1.67)
Ever, age >30 years[d]	22 468	62/50	0.88 (0.68, 1.15)	1.03 (0.77, 1.38)	33	0.95 (0.66, 1.37)	12	1.38 (0.75, 2.51)
Parous women only[c]								
Never	2 468 995	4666/3379	1.00	1.00	2235	1.00	764	1.00
Ever	127 616	216/162	0.90 (0.78, 1.03)	0.94 (0.80, 1.10)	110	0.96 (0.79, 1.16)	42	1.07 (0.78, 1.47)
Never[d]	2 354 960	4498/3248	1.00	1.00	2159	1.00	721	1.00
Ever, age <30 years[d]	55 288	93/68	0.96 (0.78, 1.18)	0.97 (0.76, 1.23)	47	1.04 (0.78, 1.39)	17	1.02 (0.63, 1.65)
Ever, age >30 years[d]	22 468	62/50	1.00 (0.78, 1.29)	1.12 (0.84, 1.49)	33	1.09 (0.77, 1.55)	12	1.38 (0.77, 2.46)

[a]Restricted to women with complete covariate information.

[b]Models that include nulliparous women are adjusted for age (as the timescale), race/ethnicity (non-Hispanic White, African American, other), attained education (high school or less, some college, college graduate), parity (0, 1, 2, >3), age at first birth (continuous, centered at 25 years), age at most recent birth (continuous, centered at 25 years), an interaction term between parity (yes or no) and age at first birth, an interaction term between parity (yes or no) and age at most recent birth, and young adult body mass index (BMI) (continuous).

[c]Models restricted to parous women are stratified by cohort and adjusted for age, race/ethnicity (non-Hispanic White, African American, other), attained education (high school or less, some college, college graduate), parity (1, 2, >3), age at first birth (continuous, centered at 25 years), age at most recent birth (continuous, centered at 25 years) and young-adult BMI (continuous).

[d]Analysis excludes Southern Community Cohort Study (SCCS), which did not collect age information.

Table 4 Stratified, pooled, multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between gestational diabetes mellitus (GDM) and risk of breast cancer among women who were parous at baseline

Strata	All cases		Invasive cases		ER+ invasive cases	ER− invasive cases
	Never/ever GDM[a]	HR (95% CI)[b]	Never/ever GDM[a]	HR (95% CI)[b]	HR (95% CI)[b]	HR (95% CI)[b]
Overall	4666/216	0.90 (0.78, 1.03)	3379/162	0.94 (0.80, 1.10)	0.95 (0.79, 1.16)	1.06 (0.78, 1.45)
Race/ethnicity						
Non-Hispanic White	3558/153	0.91 (0.78, 1.07)	2549/117	0.99 (0.82, 1.19)	0.96 (0.77, 1.20)	1.26 (0.86, 1.83)
African American	1108/63	0.87 (0.67, 1.12)	830/45	0.83 (0.61, 1.13)	0.96 (0.65, 1.42)	0.79 (0.45, 1.38)
BMI at baseline						
<25 kg/m^2	2967/107	0.95 (0.78, 1.15)	2092/78	1.00 (0.80, 1.26)	1.02 (0.78, 1.34)	1.08 (0.67, 1.73)
≥25 kg/m^2	1649/108	0.87 (0.71, 1.06)	1246/84	0.91 (0.73, 1.13)	0.91 (0.69, 1.21)	1.08 (0.71, 1.65)
Menopausal status[c]						
Premenopausal	4153/184	0.98 (0.82, 1.16)	3034/137	1.00 (0.82, 1.23)	1.05 (0.82, 1.33)	0.96 (0.61, 1.50)
Postmenopausal	508/32	0.86 (0.68, 1.08)	340/25	0.93 (0.72, 1.20)	0.90 (0.66, 1.23)	1.29 (0.83, 1.99)
Age at first pregnancy						
<25 years	2055/86	0.98 (0.79, 1.21)	1542/62	0.94 (0.73, 1.22)	1.03 (0.75, 1.41)	1.07 (0.67, 1.70)
≥25 years	2611/130	0.86 (0.72, 1.03)	1837/100	0.95 (0.78, 1.16)	0.94 (0.73, 1.19)	1.05 (0.69, 1.61)
Parity at baseline						
1 birth	1254/45	0.83 (0.62, 1.12)	880/34	0.91 (0.65, 1.29)	0.97 (0.64, 1.46)	0.67 (0.29, 1.51)
≥2 births	3412/171	0.92 (0.79, 1.07)	2499/128	0.95 (0.79, 1.13)	0.96 (0.77, 1.19)	1.19 (0.85, 1.68)
Time since most recent pregnancy, at baseline						
<10 years	2691/153	0.93 (0.79, 1.09)	1853/111	0.97 (0.80, 1.18)	0.98 (0.78, 1.24)	1.04 (0.69, 1.54)
≥10 years	1975/63	0.84 (0.65, 1.08)	1526/51	0.90 (0.68, 1.19)	0.91 (0.64, 1.29)	1.15 (0.69, 1.91)
Breast cancer family history						
No first-degree relatives	3449/152	0.89 (0.75, 1.04)	2523/112	0.90 (0.75, 1.09)	0.92 (0.72, 1.16)	1.08 (0.75, 1.55)
≥1 first-degree relative	1209/63	0.95 (0.73, 1.22)	848/50	1.07 (0.81, 1.43)	1.08 (0.77, 1.52)	1.12 (0.61, 2.06)

[a]Restricted to women with complete covariate information.

[b]Stratified by cohort and adjusted for age (as the timescale), race/ethnicity (non-Hispanic White, African American, other), attained education (high school or less, some college, college graduate), parity (1, 2, >3), age at first birth (continuous, centered at 25 years), age at most recent birth (continuous, centered at 25 years) and young adult body mass index (BMI) (continuous).

[c]Counts based on menopausal status at baseline, but menopausal status coded as a time-varying factor. There were 3261 premenopausal breast-cancer cases (3124 without GDM, 137 with) and 1616 postmenopausal breast-cancer cases (1537 without GDM, 79 with GDM). When limited to invasive cases, there were 2362 premenopausal (2263 without GDM and 99 with) and 1174 postmenopausal (1111 without GDM and 63 with GDM). We excluded 650 women with inconsistent data for age at menopause.

	Mean age at baseline (years)	Mean age at first birth (years)	Non-cases[a]	All breast cancers/invasive breast cancers (n)	Had GDM (n non-cases/n all cases/n invasive cases)	Adjusted odds ratio, all BC (95% CI)	Adjusted odds ratio, invasive BC (95% CI)	Between-cohort heterogeneity p-value (all/invasive)
All parous women	36	25	162 736	4728/3387	8606/213/154	0.84 (0.73, 0.97)	0.88 (0.74, 1.03)	0.45/0.74
Women with >1 post-baseline birth and no history of GDM at baseline	30	28	33 422	979/635	2104/49/35	0.85 (0.64, 1.14)[c]	0.94 (0.67, 1.33)[c]	0.95/0.35
Women nulliparous at baseline with >1 post-baseline birth	29	32	14 862	437/280	1369/30/21	0.77 (0.53, 1.12)[c]	0.85 (0.54, 1.33)[c]	0.26/0.09

[a]Restricted to women with complete covariate information for the adjusted models.

[b]Adjusted for age (as the timescale), race/ethnicity (non-Hispanic White, African American, other), attained education at baseline (high school or less, some college, college graduate), time-updated age at first birth (continuous, centered at 25 years), time-updated parity (1, 2, >3), time-updated body mass index, with cohort modeled as a random effect. Heterogeneity p-value is a test for between-study heterogeneity in effect estimates between cohorts (in models without cohort random effects).

[c]Includes Black Women's Health Study (BWHS) and Nurses' Health Study II (NHS II) only.

earlier reports of positive associations in predominantly postmenopausal populations lacked adjustment for important confounders, such as BMI,[20,22] or were based on small numbers of GDM-affected cases.[29]

Compelling epidemiologic evidence suggests distinct etiologic pathways and risk factor profiles for ER– and ER+ breast cancer,[46–49] including among younger women.[32,50,51] Few previous studies, however, considered possible etiologic heterogeneity in associations of GDM with breast cancer risk by ER status. In a previous analysis within SIS, history of GDM was positively associated with risk of ER– breast cancer.[29] A similar finding was reported in the BWHS, but only among women whose most recent birth was within 10 years of breast cancer diagnosis.[30] Statistical power was limited in these studies because of relatively few exposed ER– cases. In NHS II, the inverse association reported for overall breast cancer was restricted to ER+ breast cancer.[28] Other studies that evaluated associations by ER status found no differences in associations.[23,25] In each of these studies, findings were similar among both pre- and postmenopausal women.

Findings from SIS also suggested that parous women with two or more GDM pregnancies were at increased risk of breast cancer overall (HR: 1.68; 95% CI: 1.15, 2.44), but women with only one GDM-affected pregnancy were not at increased risk relative to parous women without a history of GDM.[29] Results were similar for premenopausal breast cancer. The BWHS, NHS II, SCCS and WLHS did not have information on the number of GDM-affected pregnancies so we were unable to evaluate this possible association in pooled analyses.

In the present analysis, compared with nulliparous women, women with a GDM-affected pregnancy were at reduced risk of breast cancer, especially *in situ* and ER+ invasive breast cancer. This finding suggests that the long-term protective effect of parity on breast cancer risk observed in many previous epidemiologic studies[32,52] persists even for pregnancies complicated by GDM. One previous study reported results from analyses that considered a reference group that included both parous women without GDM and nulliparous women (OR: 0.71; 95% CI: 0.52, 0.98).[23] However, other reports of inverse associations have been observed in analyses restricted to parous women.[27,28] Given established inverse associations between being overweight or obese and premenopausal breast cancer, Powe et al.[28] hypothesized that GDM could reflect an underlying metabolic state that is protective against premenopausal breast cancer. Although we were unable to address this hypothesis directly, we considered potential confounding by both recent BMI and young adult BMI and found no evidence that associations varied by BMI. As both measures are imperfect proxies for BMI during a woman's reproductive years, however, residual

confounding by BMI remains a possible explanation for our findings.

An important limitation of this study is the possibility of exposure misclassification due to reliance on self-report of GDM and the possibility of undiagnosed GDM. In a NHS II validation study, 94% of self-reported GDM diagnoses were confirmed by medical records.[53] Information on screening for GDM or on fasting plasma glucose levels was not available; clinical practice patterns with respect to GDM screening have changed over time,[54] which could account for some discrepancies across studies. We also lacked data on the treatment for or severity of GDM; however, most women manage their GDM through diet and exercise, and only 15–30% of women require insulin treatment.[54] Previous studies that considered progression to Type II diabetes, a possible marker of severity of GDM, did not find differences in associations for those who later developed Type II diabetes vs those who did not.[28–30] Our primary exposure of interest was history of GDM in any pregnancy; however, this may not reflect the relevant timing of exposure for breast cancer risk. To evaluate whether associations might differ by timing of GDM, we conducted analyses stratified by age at GDM diagnosis as well as time since last pregnancy, finding no differences. Most births, and thus most GDM diagnoses, however, occurred many years prior to cohort enrolment and we cannot rule out a possible short-term increase in breast-cancer risk during this unobserved period.

Major strengths of this study include the prospective design, a large racially diverse population and adjustment for many potential confounders, including careful consideration of BMI at various age periods and other established breast cancer risk factors. Importantly, we focused specifically on young-onset breast cancer because younger women may have unique breast-cancer risk factor profiles, particularly with regard to pregnancy-related factors. We were also able to evaluate the ER status of breast cancer diagnoses and potential effect modification by a number of factors, including race/ethnicity (African American and non-Hispanic White). Overall, our findings do not support the hypothesis that GDM increases the risk of breast cancer in women under age 55 years. Based on these data, it appears that the long-term protective effect of pregnancy on breast cancer risk persists even in the presence of GDM.

Supplementary data

Supplementary data are available at *IJE* online.

Ethics approval

Individual study protocols were approved by the relevant institutional review boards.

Data availability

The data underlying this article cannot be shared publicly due to privacy or ethical reasons. The data will be shared on reasonable request to the senior authors.

Author contributions

K.A.B., K.M.O., A.J.S., M.J.S., H.B.N. and D.P.S. conceived of and designed the study. L.B.W., J.R.P., W.J.B., A.H.E., L.R., S.S., E.W., W.Z., A.J.S., M.J.S. and D.P.S. collected the data. A.J.S., M.J.S., H.B.N. and D.P.S. assembled the data. K.A.B. and K.M.O. developed the analytic strategy with input from A.J.S., M.J.S., H.B.N. and D.P.S. K.M.O. conducted the statistical analyses. All authors contributed to interpretation of data. K.A.B. and K.M.O. drafted

the manuscript, which was critically revised and approved by all authors. All authors jointly serve as guarantors of the paper.

Conflict of interest

None declared.

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