

# Gestational Diabetes and Risk of Breast Cancer in African American Women

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## ABSTRACT

**Background:** Gestational diabetes mellitus (GDM) has been hypothesized to increase breast cancer risk, but results from the few prior epidemiologic studies are conflicting, and no studies have examined the association in African American women.

**Methods:** We analyzed data from the prospective Black Women's Health Study to evaluate associations of history of GDM with breast cancer risk among 41,767 parous African American women, adjusting for potential confounders. HRs and 95% confidence intervals (CI) were estimated from multivariable Cox proportional hazards regression models.

**Results:** There was no evidence of an association between history of GDM and risk of invasive breast cancer, overall or by estrogen receptor status.

**Conclusions:** Results of this study do not support the hypothesis that GDM is an important risk factor for breast cancer in African American women overall.

**Impact:** On the basis of these data, breast cancer risk is not increased among African American women with a history of GDM compared with parous women without a history of GDM.

## Introduction

Type 2 diabetes (T2D) is an emerging risk factor for breast cancer (1, 2). Breast cancer risk may also be influenced by a woman's history of gestational diabetes mellitus (GDM) via endocrinologic, immunomodulatory, and proinflammatory changes in the breast microenvironment during pregnancy. To date, epidemiologic studies on this topic have yielded conflicting results. An analysis in the Nurses' Health Study II (2,377 invasive breast cancers; 2% of cohort is Black) showed a statistically significant inverse association (3) while the Sister Study (1,609 invasive breast cancers; 9% of cohort is Black) reported a positive association for estrogen receptor (ER)-negative breast cancer (4). Prior studies have not evaluated associations of GDM with breast cancer risk among African American (AA) women, who have an increased risk of complications due to GDM compared to women of other racial/ethnic groups. AA women also have high incidence of aggressive breast cancers.

## Methods

Since 1995, 59,000 participants in the Black Women's Health Study (BWHS) have completed biennial self-administered questionnaires about their medical history and demographic, lifestyle, and reproductive factors, including pregnancy complications (5). For this analysis, the study population was restricted to women who were parous (or had their first birth during follow-up) and cancer-free at baseline [ $n = 41,767$  AA women ages 21–69 (median age, 38)]. Incident diagnoses of

invasive breast cancer ( $n = 1,679$ , including 954 ER-positive and 519 ER-negative cases) were ascertained via self-report, death certificates, or linkage to state cancer registries and confirmed by medical records and cancer registry records. The study protocol was approved by the Boston University Institutional Review Board.

Parous women contributed person-years from the beginning of follow-up in March 1995 (or year of first birth, if first birth occurred during follow-up) until diagnosis of breast or other cancer, death, or end of follow-up in March 2017, whichever occurred first (793,356 total person-years). We used Cox proportional hazards regression models, with age as the time scale and stratification by questionnaire cycle, to estimate hazard ratios (HR) and 95% confidence intervals (CI) for history of GDM (ever vs. never) in relation to risk of overall, ER-negative, and ER-positive invasive breast cancer, separately. Multivariable models included adjustment for established breast cancer risk factors and potential confounders: recent and age 18 body mass index (BMI; continuous,  $\text{kg}/\text{m}^2$ ), age at menarche, parity, age at first birth, oral contraceptive use, and first-degree family history of breast cancer. Except for BMI at age 18 and age at menarche, covariates were treated as time-varying in the models. We also conducted analyses stratified by age, BMI, T2D, menopausal status, years since last birth, and breastfeeding history. Analyses were performed using SAS 9.3.

## Results

Among 41,767 parous women in the BWHS, 2,059 (4.9%) reported ever having been diagnosed with GDM. At baseline, women with a history of GDM were on average younger (mean age 36.5 vs. 41.0 years) and heavier (mean BMI 30.2 vs. 28.2  $\text{kg}/\text{m}^2$ ) than parous women without a history of GDM. Women with GDM were also more likely to report more births (32% had 3 or more births compared with 26% of women without GDM) and more likely to have been older at the time of their first birth (48% were 25 years or older at first birth compared with 38% of women without GDM). Distributions of other breast cancer risk factors, such as age at menarche, oral contraceptive use, and breastfeeding history were similar in GDM-affected and unaffected women.

Seventy of 1,679 incident breast cancer diagnoses occurred in women with a history of GDM. In multivariable-adjusted analyses,

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**Table 1.** Multivariable-adjusted HRs (95% CI) for associations of gestational diabetes with breast cancer risk in the BWHs, overall and by ER status, 1995–2017.

	Person-years	All invasive (n = 1,679)		ER-positive (n = 954)		ER-negative (n = 519)	
		Cases	HR <sup>a</sup> (95% CI)	Cases	HR <sup>a</sup> (95% CI)	Cases	HR <sup>a</sup> (95% CI)
History of GDM							
Never	753,933	1,609	1.00 (Reference)	913	1.00 (Reference)	493	1.00 (Reference)
Ever	39,423	70	1.00 (0.78–1.27)	41	1.03 (0.75–1.41)	26	1.16 (0.78–1.72)
Age at GDM							
Never	753,933	1,609	1.00 (Reference)	913	1.00 (Reference)	493	1.00 (Reference)
Ever, age <30	19,519	36	1.04 (0.74–1.45)	22	1.12 (0.74–1.72)	13	1.18 (0.68–2.04)
Ever, age 30+	19,904	34	0.95 (0.68–1.34)	19	0.93 (0.59–1.47)	13	1.14 (0.66–1.99)

<sup>a</sup>Adjusted for age and questionnaire cycle.<sup>b</sup>Additionally adjusted for BMI at age 18, recent BMI, parity, menarche, age at first birth, oral contraceptive duration, and family history of breast cancer.

there was no evidence of an association between GDM and risk of invasive breast cancer, overall or by ER status ( $P_{\text{heterogeneity}} = 0.58$ ). Findings were similarly null when we considered age at diagnosis of GDM (<30 vs.  $\geq 30$  years; **Table 1**).

There was little evidence of effect modification by BMI, breastfeeding history, T2D, or menopausal status. For ER-negative breast cancer only, the HR for GDM versus no history of GDM was elevated among women with a recent birth (<10 years ago) (multivariable HR: 1.99; 95% CI: 0.99–3.98;  $n = 10$  GDM-affected cases), but not among women whose most recent births were 10 or more years ago ( $P_{\text{interaction}} = 0.08$ ; **Table 2**).

## Discussion

On the basis of these data, history of GDM does not appear to be associated with breast cancer in AA women. Breast cancer risk is heightened during the years following childbirth (6) while T2D also increases risk (1). Positive, inverse, and null associations for GDM were reported in previous studies, mostly in populations of European ancestry (7). Possible reasons for conflicting results in previous studies are recall bias, small sample sizes, differences in exposure assessment, inadequate adjustment for confounders, and lack of consideration of subtype heterogeneity (8).

Limitations of the present study include possible misclassification of GDM diagnosis due to self-report, which could have biased results. We also lacked data on severity of and treatment for GDM; therefore, we were unable to assess whether severity of GDM influences breast cancer risk. Statistical power was limited for stratified analyses. Strengths of the study include the large sample size, prospective study design, and adjustment for potential confounders, including BMI. To our knowledge, this is the first report on associations of gestational diabetes and breast cancer risk in AA women.

Results of this study do not support the hypothesis that GDM is an important risk factor for total invasive breast cancer in AA women. Given the relatively small number of affected cases, however, larger studies are warranted to provide additional insight into the role of pregnancy characteristics in the etiology of breast cancer.

## Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

## Disclaimer

The content is solely the responsibility of the authors and does not necessarily represent the official views of the NCI, the NIH, or the state cancer registries.

## Authors' Contributions

**Conception and design:** K.A. Bertrand, J.R. Palmer

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**Table 2.** Multivariable-adjusted HRs (95% CI) for associations of gestational diabetes with breast cancer risk in the BWHS, overall and by ER status, 1995–2017, stratified by risk factors.

	All invasive		ER-positive		ER-negative	
	Cases Never/ever GDM	HR <sup>a</sup> (95% CI)	Cases Never/ever GDM	HR <sup>a</sup> (95% CI)	Cases Never/ever GDM	HR <sup>a</sup> (95% CI)
BMI						
<30 kg/m <sup>2</sup>	939/31	0.94 (0.65–1.34)	506/14	0.80 (0.47–1.36)	316/15	1.28 (0.76–2.17)
≥30 kg/m <sup>2</sup>	658/38	1.02 (0.73–1.42)	401/27	1.17 (0.79–1.74)	173/10	0.99 (0.52–1.89)
Type 2 diabetes						
Yes	230/23	1.07 (0.68–1.69)	141/14	1.12 (0.63–2.01)	65/9	1.23 (0.57–2.65)
No	1,341/45	0.96 (0.71–1.30)	755/26	1.02 (0.69–1.51)	416/17	1.14 (0.70–1.86)
Menopausal status						
Premenopausal	496/35	1.11 (0.78–1.56)	256/19	1.11 (0.69–1.78)	158/16	1.58 (0.94–2.66)
Postmenopausal	907/26	0.98 (0.66–1.46)	551/15	0.92 (0.55–1.55)	262/10	1.30 (0.68–2.46)
Years since last birth						
<10 years	171/21	1.13 (0.71–1.79)	89/10	1.00 (0.52–1.94)	48/10	1.99 (0.99–3.98)
≥10 years	1,421/49	0.92 (0.69–1.22)	810/31	1.00 (0.70–1.44)	444/16	0.93 (0.56–1.53)
Breastfeeding history						
Ever	714/34	0.80 (0.60–1.21)	420/21	0.85 (0.54–1.32)	215/13	1.16 (0.66–2.05)
Never	895/36	1.16 (0.83–1.63)	493/20	1.23 (0.78–1.93)	278/13	1.23 (0.70–2.17)

<sup>a</sup>Adjusted for age, questionnaire cycle, BMI at age 18, recent BMI, parity, menarche, age at first birth, oral contraceptive duration, and family history of breast cancer.

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