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ORIGINAL PAPER

Pre- and perinatal factors and incidence of breast cancer in the Black Women's Health Study

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Abstract

Purpose The purpose of the study was to investigate the association between pre- or perinatal factors and breast cancer risk among African American women.

Methods Participants in the Black Women's Health Study, a prospective cohort of 59,000 African American women, reported birth weight, preterm birth, twin or triplet status, maternal age at birth, birth order, and having been breastfed during infancy at various times during follow-up from 1997 to 2015. Numbers of incident cases ranged from 312 for breastfed analyses to 1,583 for twin or triplet analyses. Using multivariable Cox proportional hazards regression, we estimated hazard ratios (HRs) and 95% confidence intervals (CIs) for associations between each factor and breast cancer risk overall and by estrogen receptor (ER) status.

Results Compared to birth weights of 5 lbs. 8 oz.–8 lbs. 13 oz., low (< 5 lbs. 8 oz.) and high (> 8 lbs. 13 oz.) birth weights were associated with increased breast cancer risk; HRs (95% CI) were 1.19 (0.98–1.44) and 1.26 (0.97–1.63), respectively. Associations were similar by ER status. Having been born to a mother aged ≥ 35 years versus < 20 years was associated with risk of ER+ (HR 1.59, 95% CI 1.10–2.29), but not ER− breast cancer. Other perinatal factors were not associated with breast cancer.

Conclusion African American women with a low or high birth weight or born to older mothers may have increased breast cancer risk. Trends towards delayed child birth and higher birth weights, coupled with disproportionately high rates of low birth weight among African Americans, may contribute to increases in breast cancer incidence.

Keywords Prenatal factors · Perinatal factors · Breast cancer · African American women

Introduction

It has been proposed that breast cancer has early origins beginning in-utero and that greater exposure to intrauterine estrogens during fetal development may increase a woman's risk of breast cancer in adulthood [1]. Pre- or perinatal factors, such as high birth weight [2, 3], older maternal age [4], and earlier rank in birth order [5], are associated with elevated maternal pregnancy estrogens and have been used as markers of intrauterine estrogen exposure in epidemiologic studies of breast cancer. Twin or triplet (twin/triplet) status, preterm birth, and being breastfed during infancy have also been examined. Some previous research suggests that high birth weight [6–14] and older maternal age [8, 12, 15–19] are associated with modest increases in breast cancer risk, while having been breastfed during infancy may reduce a woman's risk of breast cancer [8, 17, 20, 21]. Overall, however, associations of pre- or perinatal exposures with breast cancer risk are inconsistent.

Few epidemiologic studies assessed these associations among African American women [17, 22], who are more likely to be born preterm with low birth weight [23], less likely to be breastfed [24], and have a higher incidence of estrogen receptor negative (ER−) breast cancer [25] and mortality from breast cancer compared to U.S. White women [25]. In the present study, we prospectively examined the associations between six pre- or perinatal factors

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and risk of breast cancer overall and by ER status among participants of the Black Women's Health Study.

Materials and methods

Study population

The Black Women's Health Study (BWHS) is a prospective cohort of 59,000 African American women, aged 21–69 years at enrollment in 1995. Study participants completed a comprehensive self-administered baseline questionnaire on medical history, lifestyle, demographic, and dietary factors. Follow-up questionnaires are mailed to participants biennially. Vital status is obtained from the National Death Index, U.S. Postal System, or next-of-kin. Through 2015, follow-up has been complete for 85% of potential person-years. The Boston University Institutional Review Board approved the study protocol.

Study participants answered questions related to their own birth weight, whether they were born preterm, or as a twin/triplet on the 1997 follow-up questionnaire. Questions on the age of the participant's mother at her birth (maternal age at birth), the participant's position in birth order, and whether she was breastfed during infancy were included on the 2005, 2007, and 2009 questionnaires, respectively. Those who completed the 1997 ($n = 52{,}193$), 2005 ($n = 44{,}056$), 2007 ($n = 46{,}584$), and 2009 ($n = 45{,}586$) questionnaires formed the baseline populations for each respective analysis. Participants with a cancer diagnosis before baseline of the particular analysis, those who died before baseline, or those who were missing data on the exposure of interest were excluded from each analysis. All participants were followed prospectively for cancer incidence and mortality until 2015.

Case ascertainment

The primary outcome, incident invasive breast cancer, excluding ductal carcinoma in situ, was identified primarily through self-report on follow-up questionnaires. Additional cases were identified from linkage to state cancer registries in 24 states in which 95% of participants lived and the National Death Index. Participants' medical records, pathology reports, and cancer registry data were reviewed by study investigators, blinded to exposure information, to confirm case status and abstract data on tumor characteristics, including ER status. The number of incident breast cancer cases in a particular analysis depended upon how many women answered the exposure question for that analysis.

Exposure ascertainment

Data on birth weight, preterm birth, and twin/triplet status were ascertained from the 1997 questionnaire. *Birth weight* Participants were asked their birth weight in pounds and ounces and also in categories (< 4 lbs., 4 lbs.–5 lbs. 8 oz., > 5 lbs. 8 oz.). Approximately 66% of participants who responded to the 1997 questionnaire answered at least one of the birth weight questions. Data from both questions were combined to create three mutually exclusive birth weight categories: < 5 lbs. 8 oz. (< 2,500 g; low), 5 lbs. 8 oz.–8 lbs. 13 oz. (2,500–3,999 g; normal), > 8 lbs. 13 oz. (≥ 4,000 g; high). Women who did not answer either question ($n = 13{,}579$) or who selected the categorical birth weight option, > 5 lbs. 8 oz., but did not report their birth weight in pounds and ounces ($n = 14{,}127$) were excluded from this analysis; the latter because whether they had a normal or high birth weight could not be determined. In a validation study among 637 Massachusetts born BWHS participants [26], the Pearson correlation coefficient between self-reported exact birth weight and Massachusetts birth registry data was 0.88. The κ coefficient of agreement between self-reported categorical birth weight and registry data was 0.80 [26]. *Preterm birth* Preterm birth (yes/no) was defined as being born ≥ 3 weeks early. *Twin/triplet status* Twin/triplet status (yes/no) included both identical and fraternal twin/triplets. *Maternal age* Continuous maternal age was reported in years in 2005. We categorized maternal age as < 20, 20–24, 25–29, 30–34, and ≥ 35 years. In stratified analyses, we collapsed maternal age categories, < 20 and 20–24, due to small numbers. Continuous maternal age was used to estimate risk associated with a 5-year increase in maternal age. *Birth order* Participants reported their position in birth order in 2007. We categorized birth order as 1st born or only child, 2nd born, and 3rd born or later. *Breastfed* Having been breastfed during infancy (yes/no) was ascertained in 2009.

Statistical analysis

Using Cox proportional hazards regression, with stratification by age (in years) and questionnaire cycle, and time to event as the underlying timescale, we calculated hazard ratios (HR) and 95% confidence intervals (CI) for the risk of overall, ER+, and ER− breast cancer, in three separate models, with respect to each pre- or perinatal factor. In analyses for birth weight, preterm birth, and twin/triplet status, participants accrued follow-up time beginning in 1997 and ending at breast cancer diagnosis, death, or end of the study period in 2015, whichever came first.

For maternal age, birth order, and having been breastfed, follow-up accrual began in 2005, 2007, or 2009, respectively, and ended at breast cancer diagnosis, death, or end of the study period, whichever came first.

Age-adjusted and multivariable hazard ratios were calculated in all analyses. For all multivariable models, we controlled for the participant's parity, age at first birth, and family history of breast cancer. We adjusted for breast cancer family history because it is an established breast cancer risk factor and precedes our exposures of interest. Parity and age at first birth were included as potential confounders because they may be associated with the mother's parity and age at first birth, which were not measured. Other established breast cancer risk factors, such as the participant's age at menarche, education, neighborhood socioeconomic status (SES), lactation, alcohol consumption, recent body mass index (BMI), BMI at age 18, height, and menopausal status were not included because they occur after the exposures and could potentially lie on the causal pathway. For each particular analysis, we also considered the other pre- or perinatal factors as potential confounders, but ultimately did not include them because their inclusion did not appreciably change estimates. However, in birth weight analyses, women who identified as a twin or triplet or preterm birth ($n=2{,}881$) were excluded to control for potential confounding by these factors. Time-varying covariates, parity, age at first birth, and family history of breast cancer, were updated with each questionnaire cycle. Missing indicators were included to account for missing covariate data.

We conducted analyses stratified by parity (nulliparous and parous) and age (<45 and ≥ 45 years) at risk for all exposures. Interactions between pre- or perinatal factors and age or parity were assessed by including a categorical cross-product term in regression models and assessing the Wald statistic. In maternal age analyses, continuous maternal age was used in cross-product terms.

Wald tests were used to evaluate significance. Reported p-values are two-sided with a 0.05 level of significance. We performed analyses in SAS 9.4 (Cary, North Carolina).

Table 1 Age-standardized characteristics of the study population at the time of exposure assessment

	Birth weight, 1997			Maternal age at birth, 2005				
	< 5 lbs. 8 oz. ($n=4{,}322$)	5 lbs. 8 oz.–8 lbs. 13 oz. ($n=14{,}782$)	> 8 lbs. 13 oz. ($n=1{,}855$)	< 20 years ($n=6{,}073$)	20–24 years ($n=9{,}808$)	25–29 years ($n=6{,}924$)	30–34 years ($n=4{,}302$)	≥ 35 years ($n=3{,}537$)
Age	41.5 (10.4)	38.3 (9.7)	42.1 (11.2)	49.1 (10.9)	48.3 (10.4)	47.7 (9.9)	48.1 (9.7)	48.4 (9.9)
Family history of breast cancer (%)	8	8	11	6	7	9	10	13
Adult height: < 63 inches (%)	27	17	11	21	19	18	17	16
Age at menarche: < 12 years (%)	30	31	31	31	28	28	30	29
Body mass index at age 18 (kg/m^2)	21.3 (4.3)	21.7 (4.3)	22.5 (4.7)	21.4 (4.0)	21.4 (4.1)	21.6 (4.2)	21.5 (3.9)	21.7 (4.4)
Body mass index (kg/m^2)	28.3 (7.1)	28.4 (7.0)	29.7 (7.4)	30.6 (7.1)	30.2 (7.1)	30.0 (7.1)	29.8 (6.9)	30.5 (7.1)
Nulliparous (%)	37	34	36	21	26	29	30	30
Age at first birth: ≥ 25 years (%)	19	21	20	26	29	31	30	29
Number of births: ≥ 3 births (%)	19	19	19	25	21	19	19	20
Years of education: ≤ 12 years (%)	19	16	16	15	12	10	11	11
Neighborhood SES: lowest quintile (%)	17	18	19	17	15	15	14	15

Values are means (SD) or percentages and are standardized to the age distribution of the study population

SES socioeconomic status

Results

Characteristics of the population at the time of exposure assessment are displayed in Table 1 for birth weight and maternal age. Women with high birth weight were more likely to have a family history of breast cancer, less likely to be < 63 inches tall, and had a higher BMI at age 18 and at baseline in 1997 than women with lower birth weight. Compared to women born to a mother aged < 20 years, women born to a mother aged ≥ 35 years were more likely to have a positive family history of breast cancer and be nulliparous and less likely to have an adult height < 63 inches.

Birth weight

Among 20,959 women in the analytic cohort, 601 incident breast cancer cases occurred during follow-up from 1997 to 2015. HRs for having been born with a low or high birth weight relative to a normal birth weight were 1.19 (95% CI 0.98–1.44) and 1.26 (95% CI 0.97–1.63), respectively (Table 2). Associations were similar by ER status. Among women < 45 years old, there was no association between birth weight and risk of overall breast cancer (Table 3). However, among women aged ≥ 45 years, low birth weight was significantly associated with a 24% (95% CI 0–55%) increased breast cancer risk, and high birth weight was significantly associated with a 42% (95% CI 7–89%) increased risk. The *p*-value for interaction of age and birth weight was 0.23. Low birth weight was significantly associated with breast cancer in parous women (HR 1.27; 95% CI 1.03–1.57; Table 3), but not in nulliparous women (HR 0.91; 95% CI 0.58–1.42; *p* interaction = 0.17).

Maternal age

The maternal age analyses included 30,644 women in the analytic cohort, of which 572 breast cancer cases occurred during follow-up from 2005 to 2015. Risk of breast cancer increased with each 5-year increase in maternal age (HR 1.06; 95% 1.00–1.13; Table 2) to 1.34 (95% CI 1.00–1.80) for women born to mothers aged ≥ 35 years compared to women born to mothers aged < 20 years. The association was accounted for by increased risk of ER+ cancer: the multivariable-adjusted HR was 1.59 (95% CI 1.10–2.29) for maternal age ≥ 35; for every 5-year increase in maternal age, ER+ breast cancer risk increased by 10% (95% CI 2–19%). In contrast, there was no evidence of a positive association with ER− breast cancer. HRs for higher levels of maternal age in relation to ER− breast cancer were all below 1.00.

Since maternal age was associated with ER+ breast cancer only, age- and parity-stratified analyses are presented for ER+ breast cancer only. Maternal age ≥ 35 years was associated with increased risk of ER+ breast cancer (HR 2.92; 95% CI 1.53–5.57; Table 4), relative to maternal age < 25 years among women aged < 45 years, but there was only a small non-significant positive association among women ≥ 45 years old (*p* interaction = 0.10). The association between older maternal age and ER+ breast cancer was somewhat stronger among nulliparous (HR 1.97; 95% CI 1.08–3.59; Table 4) than parous women (HR 1.32; 95% CI 0.92–1.87; *p* interaction = 0.34).

Other pre- or perinatal factors

Preterm birth analyses were based on 950 breast cancer cases among an analytic cohort of 32,314 women, twin/triplet analyses on 1,583 cases among 50,983 women, birth order analyses on 561 cases among 39,610 women, and breastfed during infancy analyses on 312 cases among 31,771 women. None of these factors were associated with breast cancer risk overall (Table 2). For ER+ breast cancer, however, there was a non-significant elevation in risk among women who reported having been breastfed. Stratification by age and parity did not reveal any material associations (data not shown).

Discussion

In this prospective cohort study of African American women, both low and high birth weight were associated with non-significant increases in breast cancer risk, with no difference by ER status. However, there were stronger and statistically significant associations among women aged ≥ 45, with a stronger association for high birth weight (HR 1.42) than for low birth weight (HR 1.24). Women born to older mothers, aged 35 or greater, had a 59% elevated risk of ER+ breast cancer, and risk was higher among younger women and nulliparous women. There were no significant associations between preterm birth, twin/triplet status, birth order, or having been breastfed and breast cancer risk.

Although null findings have been reported [18, 22, 27–29], many other studies have found that risk of breast cancer increased with increasing birth weight [6, 7, 9–12, 14, 30–32]. Low birth weight, therefore, was often reported to either decrease breast cancer risk compared to high birth weight [6, 7, 9–11, 30, 32] or be unassociated with risk [12–14, 18, 22, 27, 28]. In contrast, three studies found that both low birth weight and high birth weight increased risk of breast cancer compared to normal birth weight [19, 33, 34]. Our findings align with results from these three studies. While we found a stronger positive association among older women, other studies have reported no modification by age [14] or a stronger association among younger women [6, 33].

Table 2 Association between pre- or perinatal factors and risk of overall, ER-positive or ER-negative breast cancer

Variables	Start of follow-up	Overall breast cancer				ER-positive breast cancer			ER-negative breast cancer		
		Person-years	Cases	Age-adjusted HR (95% CI)	MV HR (95% CI)[a]	Person-years	Cases	MV HR (95% CI)[a]	Person-years	Cases	MV HR (95% CI)[a]
Birth weight[b]	1997										
< 5 lbs. 8 oz.		73,912	148	1.17 (0.97, 1.42)	1.19 (0.98, 1.44)	73,847	89	1.18 (0.92, 1.51)	73,798	40	1.17 (0.81, 1.68)
5 lbs. 8 oz.–8 lbs. 13 oz.		256,798	383	1.00 (ref)	1.00 (ref)	256,631	227	1.00 (ref)	256,519	113	1.00 (ref)
> 8 lbs. 13 oz.		31,665	70	1.26 (0.97, 1.63)	1.26 (0.97, 1.63)	31,636	44	1.30 (0.94, 1.81)	31,611	19	1.26 (0.77, 2.06)
Preterm birth	1997										
No		506,440	878	1.00 (ref)	1.00 (ref)	506,052	513	1.00 (ref)	505,805	264	1.00 (ref)
Yes		51,242	72	0.93 (0.73, 1.18)	0.92 (0.73, 1.18)	51,211	42	0.92 (0.67, 1.27)	51,190	22	0.92 (0.60, 1.43)
Twin/triplet	1997										
No		861,491	1,549	1.00 (ref)	1.00 (ref)	860,799	898	1.00 (ref)	860,377	456	1.00 (ref)
Yes		15,918	34	1.20 (0.86, 1.69)	1.18 (0.84, 1.66)	15,904	20	1.19 (0.77, 1.86)	15,889	10	1.19 (0.64, 2.24)
Maternal age	2005										
< 20		58,952	101	1.00 (ref)	1.00 (ref)	58,909	60	1.00 (ref)	58,892	36	1.00 (ref)
20–24		95,622	169	1.04 (0.81, 1.33)	1.03 (0.81, 1.32)	95,563	112	1.15 (0.84, 1.58)	95,510	51	0.87 (0.57, 1.33)
25–29		67,559	133	1.17 (0.91, 1.52)	1.15 (0.89, 1.50)	67,506	81	1.18 (0.85, 1.66)	67,480	44	1.05 (0.68, 1.64)
30–34		41,978	88	1.23 (0.92, 1.64)	1.20 (0.90, 1.61)	41,951	61	1.41 (0.98, 2.02)	41,905	18	0.68 (0.38, 1.20)
≥ 35		34,337	81	1.38 (1.03, 1.85)	1.34 (1.00, 1.80)	34,314	57	1.59 (1.10, 2.29)	34,277	20	0.92 (0.53, 1.59)
5-year increase		298,453	572	1.07 (1.01, 1.14)	1.06 (1.00, 1.13)	298,249	371	1.10 (1.02, 1.19)	298,068	169	0.95 (0.84, 1.07)
Birth order	2007										
1st born or only child		185,695	323	0.94 (0.77, 1.15)	0.94 (0.78, 1.15)	185,591	217	0.93 (0.73, 1.18)	185,467	94	1.19 (0.80, 1.76)
2nd born		46,633	93	1.06 (0.81, 1.37)	1.06 (0.82, 1.37)	46,601	60	1.01 (0.73, 1.39)	46,565	26	1.27 (0.76, 2.12)
3rd born or later		77,715	145	1.00 (ref)	1.00 (ref)	77,664	98	1.00 (ref)	77,612	34	1.00 (ref)
Breastfed in infancy	2009										
No		110,765	163	1.00 (ref)	1.00 (ref)	110,705	105	1.00 (ref)	110,650	46	1.00 (ref)
Yes		76,940	149	1.14 (0.90, 1.44)	1.14 (0.90, 1.44)	76,898	108	1.25 (0.95, 1.66)	76,825	34	0.97 (0.61, 1.54)

HR hazard ratio, *MV* multivariable

[a]Multivariable hazard ratios are adjusted for time period, the participant's age, parity, age at first birth, and family history of breast cancer

[b]Birth weight analyses exclude women who were born preterm or as part of a multiple birth

Table 3 Association between birth weight and risk of overall breast cancer stratified by age and parity

Stratifying variables	Birth weight[a]					
	< 5 lbs. 8 oz.		5 lbs. 8 oz.–8 lbs. 13 oz.		> 8 lbs. 13 oz.	
	Cases	MV HR (95% CI)[b]	Cases	MV HR (95% CI)[b]	Cases	MV HR (95% CI)[b]
Age[c] (years)						
< 45	32	1.07 (0.72, 1.57)	132	1.00 (ref)	10	0.78 (0.41, 1.48)
≥ 45	116	1.24 (1.00, 1.55)	251	1.00 (ref)	60	1.42 (1.07, 1.89)
Parity[d]						
Nulliparous	25	0.91 (0.58, 1.42)	86	1.00 (ref)	19	1.58 (0.94, 2.65)
Parous	123	1.27 (1.03, 1.57)	297	1.00 (ref)	51	1.15 (0.85, 1.56)

MV multivariable, *HR* hazard ratio

[a]Birth weight analyses exclude women who were born preterm or as part of a multiple birth

[b]Multivariable hazard ratios are adjusted for time period, the participant's age, parity, age at first birth, and family history of breast cancer

[c]p interaction = 0.23

[d]p interaction = 0.17

Table 4 Association between maternal age and risk of ER-positive breast cancer stratified by age and parity

Stratifying variables	Maternal age (years)								
	< 25		25–29		30–34		≥ 35		5-year increase
	Cases	MV HR (95% CI)[a]	Cases	MV HR (95% CI)[a]	Cases	MV HR (95% CI)[a]	Cases	MV HR (95% CI)[a]	MV HR (95% CI)[a]
Age[b] (years)									
< 45	25	1.00 (ref)	14	1.26 (0.66, 2.44)	9	1.40 (0.65, 3.01)	15	2.92 (1.53, 5.57)	1.27 (1.06, 1.51)
≥ 45	147	1.00 (ref)	67	1.05 (0.79, 1.41)	52	1.27 (0.92, 1.75)	42	1.23 (0.87, 1.73)	1.07 (0.99, 1.16)
Parity[c]									
Nulliparous	30	1.00 (ref)	25	1.59 (0.93, 2.72)	14	1.29 (0.67, 2.47)	17	1.97 (1.08, 3.59)	1.17 (1.01, 1.37)
Parous	142	1.00 (ref)	56	0.95 (0.70, 1.30)	47	1.28 (0.92, 1.78)	40	1.32 (0.92, 1.87)	1.08 (0.99, 1.17)

MV multivariable, *HR* hazard ratio

[a]Multivariable hazard ratios are adjusted for time period, the participant's age, parity, age at first birth, and family history of breast cancer

[b]p interaction = 0.10

[c]p interaction = 0.34

Birth weight has been positively associated with maternal circulating concentrations of hormones, such as estrogens [35, 36], but less so with concentrations in umbilical cord serum [35, 36]. Studies of the relation between maternal and fetal estrogen concentrations have found weak [37, 38] or no [39] correlations. However, fetal estrogen levels measured in umbilical cord blood or amniotic fluid at birth may not accurately reflect fetal estrogen exposure during the critical exposure window, which has not been established, likely due to the fact that measuring fetal circulation prior to delivery could harm the fetus [40]. Other potential mechanisms underlying observed associations of birth weight and breast cancer risk, such as pathways involving growth factors, endocrine factors, and growth patterns in childhood and adulthood [40], have been explored to a lesser extent.

Hilakivi-Clarke and de Assis [41] hypothesized that fetal exposure to elevated hormone levels may alter mammary gland development and increase mammary cell susceptibility to carcinogenic factors, such as endogenous estrogen, in adulthood. This hypothesis could explain our results for high birth weight, but not low birth weight. The observed association between low birth weight and increased breast cancer risk may operate through growth mechanisms in childhood. Low birth weight has been linked to rapid pubertal growth [42] and earlier age at menarche [42, 43], which have been associated with breast cancer [44, 45]. Reasons why associations of birth weight with breast cancer risk might be stronger in older women are unknown; however, there were relatively few cases in the younger age group and this result could be a chance finding.

In the United States, giving birth to higher birth weight babies has become more common, while rates of low birth weight have slightly decreased [46]. However, low birth weight rates are still disproportionately high among African

Americans compared to other races [46]. With overall increasing trends toward having high birth weight babies and a high rate of low birth weight among African Americans, associations between low or high birth weight and breast cancer may contribute to increased breast cancer incidence among African American women [25].

In some [15, 18, 19, 22, 29, 34, 47], but not all [12, 16, 17, 32, 33, 48] studies, maternal age has been positively associated with breast cancer in the daughters. In two prior analyses including Black women, no association [17] and a more than threefold increase in risk [22] were reported for Black women born to older mothers. In our study, ER+ breast cancer risk increased linearly with increasing maternal age and women born to mothers ≥ 35 years old had a 59% increase in risk. Among a subset of White women aged < 45 years, Weiss et al. observed a small non-significant positive association between older maternal age and breast cancer [17], which is similar to our finding of a stronger association among younger versus older women. In the present study, the positive association of maternal age with breast cancer risk was stronger among nulliparous women compared to parous women, which is inconsistent with reports by Thompson and Janerich [15].

Maternal age appears to be associated with estrogen levels. There is some evidence that maternal estrogen levels are higher in older mothers. In 1990, Panagiotopoulou et al. observed that pregnant women aged ≥ 20 years had higher concentrations of total estrogen and estradiol compared to pregnant women aged < 20 years [4]. This correlation between maternal estrogens and maternal age may explain why we found an association with ER+ and not ER− breast cancer. There are other possible mechanisms through which older maternal age may lead to breast cancer. Advanced maternal age can result in the accumulation of germline mutations [49], and chromosome abnormalities [50], and has been linked to childhood cancer [51]. The average age of U.S. mothers of all races has steadily increased, as cultural norms surrounding contraception, pregnancy, and educational attainment have shifted [52, 53]. Our results suggest that with more women bearing children at older ages, risk of breast cancer among their daughters may become a greater concern.

Having been breastfed during infancy was not associated with breast cancer overall, although a small non-significant positive association with ER+ breast cancer was observed. Most studies report no association [27, 54–56], non-significant reductions [21], or significant reductions [17, 20] in risk associated with having been breastfed. Because factors in breastmilk play roles in detoxification, immunity, and disease prevention [57], an inverse association, if any, between having been breastfed and risk of breast cancer would have been expected. However, breastmilk has been shown to contain hormones and persistent organic pollutants or pesticides, which can be transferred to the infant [57, 58]. The relation between transmission of these factors through breastmilk and breast cancer incidence has not been established [58].

As in previous studies [6, 13, 27, 29, 33], prematurity was not associated with breast cancer risk in the present study. Two early studies reported that severe prematurity (birth at < 31 or < 33 gestational weeks) increased breast cancer risk [18, 59]. Another reported a protective effect of severe prematurity (birth at < 33 gestational weeks) [19]. We did not have appropriate data to assess severe prematurity.

Previous studies reported that maternal estrogens and other hormone levels were higher in twin pregnancies compared to singleton pregnancies [60–63], suggesting that twins may have an increased risk of breast cancer. We found no significant association between twin/triplet status and breast cancer risk, which is consistent with some [18, 19, 33, 64], but not all [17, 47, 65, 66], previous studies. The small number of twin/triplets in the present study limited our statistical power.

Bernstein et al. reported that women in their first pregnancy had significantly higher serum estrogen concentrations compared to women in their second pregnancy [5]. Researchers hypothesized that women with an earlier rank in birth order may have higher intrauterine estrogen exposure and increased breast cancer risk. Only a few studies support this hypothesis [48, 67]. Our results are consistent with prior studies reporting no relation between birth order and breast cancer [12, 22, 29, 32–34].

Exposures in the present study were self-reported and misclassification would have tended to dilute associations. Birth weight measurements were found to be reasonably accurate in a validation study. However, the remaining exposures have not been validated. Since these data were collected prospectively, any misclassification is likely non-differential. Therefore, associations with dichotomous exposures would be biased toward the null. Although we considered mutual confounding by the pre- or perinatal factors and adjusted for established breast cancer risk factors, confounding by other factors, such as nutritional status of the participant's mother, cannot be ruled out. While we had sufficient statistical power to detect modest associations overall, power was more limited for stratified analyses. Limited power also prevented us from evaluating twin/triplet type and breastfed duration as potential exposures. Also, we could not examine the estrogen hypothesis directly since we did not have biomarker data representing participants' in-utero estrogen exposure.

Strengths of this study include its prospective design, and large number of breast cancer cases for some analyses. Detailed information on breast cancer risk factors and covariates were collected, allowing for confounder control. We had sufficient power to investigate associations by ER

status, which allowed for a more complete characterization of associations between each pre- or perinatal factor and breast cancer risk. Furthermore, this study was conducted among African American women, broadening our understanding of the estimated effects of these factors in this minority population.

In sum, our results support the hypothesis that early life exposures, birth weight and maternal age, influence subsequent risk of breast cancer in African American women. The recent U.S. trends towards higher birth weight babies and childbearing at older ages, coupled with the persisting disproportionately high occurrence of low birth weight babies among African Americans, may lead to further increases in breast cancer incidence in this population.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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

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

Research involving human and animal participants This article does not contain any studies with animals performed by any of the authors.

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