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Menstrual and reproductive characteristics and breast cancer risk by hormone receptor status and ethnicity: The Breast Cancer Etiology in Minorities study

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Abstract

We pooled multiethnic data from four population-based studies and examined associations of menstrual and reproductive characteristics with breast cancer (BC) risk by tumor hormone receptor (HR) status [defined by estrogen receptor (ER) and progesterone receptor (PR)]. We estimated odds ratios and 95% confidence intervals using multivariable logistic regression, stratified by age (<50, ≥50 years) and ethnicity, for 5,186 HR+ (ER+ or PR+) cases, 1,365 HR− (ER− and PR−) cases and 7,480 controls. For HR+ BC, later menarche and earlier menopause were associated with lower risk in non-Hispanic whites (NHWs) and Hispanics, and higher parity and longer breast-feeding were associated with lower risk in Hispanics and Asian Americans, and suggestively in NHWs. Positive associations with later first full-term pregnancy (FTP), longer interval between menarche and first FTP and shorter time since last FTP were limited to younger Hispanics and Asian Americans. Except for nulliparity, reproductive characteristics were not

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Conflict of interest

All authors declare they have no conflicts of interest.

Additional Supporting Information may be found in the online version of this article.

associated with risk in African Americans. For HR− BC, lower risk was associated with later menarche, except in African Americans and older Asian Americans and with longer breast-feeding in Hispanics and Asian Americans only. In younger African Americans, HR− BC risk associated with higher parity (≥3 *vs.* 1 FTP) was increased fourfold in women who never breast-fed, but not in those with a breast-feeding history, suggesting that breast-feeding may mitigate the adverse effect of higher parity in younger African American women. Further work needs to evaluate why menstrual and reproductive risk factors vary in importance according to age and ethnicity.

Keywords

breast cancer; epidemiology; estrogen receptor status; progesterone receptor status; ethnicity; reproductive history

Introduction

Breast cancer incidence rates in the United States (U.S.) vary by ethnicity, with the highest rate (per 100,000) in non-Hispanic white (NHW) women (128.7), followed by African Americans (125.5), Hispanics (91.9) and Asian Americans/Pacific Islanders (90.7).[1] The incidence of breast cancer defined by hormone receptor (HR) status also differs by ethnicity,[2] with higher rates of HR negative [estrogen receptor (ER) negative and progesterone receptor (PR) negative)] breast cancer in African American and Hispanic women compared to NHW and Asian American women. The reasons underlying these ethnic disparities in breast cancer incidence overall and of specific subtypes are not understood, and ethnic differences in multiple factors likely contribute to the observed incidence patterns and differences by ethnicity.[2]

Menstrual and reproductive characteristics are well-established risk factors for breast cancer.[3] Some associations differ by age,[4] and there is growing evidence that associations differ by HR status[5] or molecular tumor markers.[6,7] Data on associations of menstrual and reproductive history with breast cancer defined by HR status come primarily from studies in NHW women. Few studies have reported on HR-specific associations in U.S. minority populations,[8–16] and those that have, often lack sufficiently large or diverse study populations to examine associations of menstrual and reproductive characteristics with risk of specific breast cancer subtypes across multiple ethnic groups. We pooled case–control data for African American, Asian American, Hispanic and NHW women to evaluate associations of menstrual characteristics, pregnancy history and breast-feeding practices with risk of breast cancer defined by joint ER and PR status and differences in associations by age and ethnicity.

Materials and Methods

Study sample

The Breast Cancer Etiology in Minorities (BEM) Study harmonized interview and cancer registry data for participants in four population-based studies of female breast cancer described in more detail elsewhere[17] and in the Supporting Information Methods. They

include three case–control studies [the San Francisco Bay Area Breast Cancer Study (SFBCS), the 4-Corners Breast Cancer Study (4-CBCS) and the Los Angeles County Asian American Breast Cancer Study (AABCS)] and a family study that also included population controls [the Northern California site of the Breast Cancer Family Registry (NC-BCFR)]. A total of 9,234 women aged 18–79 years with a first primary invasive breast cancer and 7,767 control women without a history of breast cancer participated in these studies. The studies were approved by the Institutional Review Board of each participating institution, and study participants provided written informed consent.

In NC-BCFR, we limited the analysis to cases diagnosed from 1995 to 2003 for whom population controls were available, and excluded 325 cases who also participated in SFBCS, leaving 7,895 cases and 7,767 controls with interview data. Data on ER or PR status were available for 6,928 (88%) cases, including 5,457 cases diagnosed with HR+ (ER+ or PR+) breast cancer and 1,435 cases with HR− (ER− and PR−) breast cancer (Supporting Information Fig. S1).

Data collection and harmonization

For each study, trained interviewers administered structured questionnaires in English, Spanish, Cantonese or Mandarin at the participants' home. The questionnaires assessed breast cancer risk factors in the reference year or exposure histories up to the reference year, defined as either the calendar year before diagnosis for cases, the calendar year before interview for controls in AABCS and NC-BCFR, or the calendar year before selection into the study for controls in SFBCS and 4-CBCS. Height and weight measured at interview and self-reported weight in the reference year were assessed for participants in the three case–control studies; for NC-BCFR participants, height and weight in the reference year were based on self-report. Data on ER and PR status were obtained from cancer registry records.

Study-specific data were harmonized to create derived variables using common definitions.[17] Parity was defined as the number of full-term pregnancies (FTP). Lifetime breastfeeding was calculated summing duration of breast-feeding which was reported as a continuous measure for each live birth, except for NC-BCFR which assessed breast-feeding as a categorical measure (0, 1–12, 13–24, ≥25 months); for NC-BCFR, the midpoint of a category was assigned as the continuous value and 30 months was assigned to those reporting ≥25 months of breast-feeding. Given some evidence that breast-feeding may mitigate the adverse effect of higher parity in African American women,[10,14,18] we also examined the joint association of parity and breast-feeding history. Women were classified as premenopausal if they still had menstrual periods or were pregnant, breast-feeding or perimenopausal during the reference year, and were under age 55 years. Women were classified as postmenopausal if they reported that prior to the reference year their periods had stopped naturally or due to surgery, medical treatment, or other reasons. Women who still had periods when they started using hormone therapy were classified as postmenopausal if they were ≥55 years of age; otherwise their menopausal status was classified as unknown. Body mass index (BMI) was calculated as self-reported weight (kg) in the reference year divided by measured or self-reported height (m) squared, and classified as <25.0, 25.0–29.9,

or ≥30.0 kg/m^2. Ethnicity was based on self-report and categorized as African American, Asian American (including Pacific Islanders), Hispanic (white or black and including Native Americans from 4-CBCS) or NHW.

Statistical analyses

We conducted separate analyses for HR+ and HR− breast cancer and stratified the analyses by age group (<50 *vs.* ≥50 years) and ethnicity. We used unconditional logistic regression to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for menstrual variables (age at menarche, menopausal status, age at natural menopause) and pregnancy-related variables (nulliparity, age at first FTP, interval between menarche and first FTP, time since last FTP, parity, lifetime breast-feeding). All models were adjusted for age (continuous), study (AABCS, NC-BCFR, SFBCS, 4-CBCS) and year of diagnosis or selection/interview (1995–1998, 1999–2001, 2002–2007), and additionally for established breast cancer risk factors, including education (some high school or less, high school graduate, some college or vocational/technical school, college graduate or higher degree), family history of breast cancer among first-degree relatives (yes, no), personal history of benign breast disease (yes, no), alcohol consumption in reference year (none, <5, ≥5 drinks per week), BMI in reference year (<25.0, 25.0–29.9, ≥30.0 kg/m^2), age menarche, age at first FTP, parity and breast-feeding, as noted in the footnotes of the tables. Analyses for all ethnicities combined were also adjusted for ethnicity, and analyses for all ages combined were additionally adjusted for menopausal status and an interaction term between BMI and menopausal status. Analyses of time since last FTP were limited to women ages <50 years. After excluding individuals with missing covariate data (153 HR+ cases, 45 HR− cases, 252 controls), the analyses were based on 5,304 HR+ cases, 1,390 HR− cases and 7,515 controls (Supporting Information Fig. S1).

Linear trends were assessed across ordinal values of categorical variables. We tested for differences in ORs by age or ethnicity by including interaction terms in the model. To assess differences in ORs between case groups (HR+ *vs.* HR-cases), we used polytomous regression models, and tested for differences in ORs between the two case groups using the Wald statistic p value. Forest plots were used to present ORs stratified by HR status, age and ethnicity. All statistical tests were two-sided, with p values <0.05 considered statistically significant. Statistical analyses were conducted using SAS version 9.4 software (SAS Institute, Inc., Cary, NC).

Data availability

The datasets used for the current study are available upon reasonable request from the corresponding author (E.M.J.), contingent upon approval by appropriate Institutional Review Boards and study Principal Investigators.

Results

Table 1 shows that compared to HR+ cases, HR− cases were more likely to be diagnosed at a younger age (mean: 50.5 years *vs.* 53.5 years) and with higher tumor grade (grade 3 or 4: 75% *vs.* 28%). Compared to controls, HR+ cases were more likely to have a college

education, a first-degree family history of breast cancer, a personal history of benign breast disease and a BMI <25 kg/m^2. HR− cases were more likely to have a first-degree family history of breast cancer.

Menstrual and reproductive characteristics of control women differed by ethnicity (Table 2). Mean age at menarche ranged from 12.7 years (NHWs and African Americans) to 12.9 years (Asian Americans), and mean age at natural menopause ranged from 46.0 years (Hispanics) to 49.6 years (Asian Americans). Nulliparity and low parity were more frequent in NHW and Asian American controls, whereas an early first FTP and a short interval between menarche and first FTP were more frequent in African Americans and Hispanics.

Menstrual characteristics and risk of breast cancer by HR status, age and ethnicity

Age at menarche.—Among all women combined, older age at menarche was associated with reduced risk of HR+ and HRbreast cancer, and for each subtype associations differed by ethnicity ($p_{heterogeneity} < 0.01$ and 0.01, respectively; Table 3). For later menarche (≥14 *vs.* <12 years), risk reductions ranged from 25% to 42%, and statistically significant inverse trends were found for Hispanics and NHWs (both subtypes), African Americans (HR− subtype only) and younger Asian Americans (both subtypes; Supporting Information Table S1 and Fig. S2a). In African Americans, age at menarche was not associated with HR+ breast cancer risk, whereas in older Asian Americans, later menarche was associated with increased risk of HR+ ($p_{trend} = 0.01$) and HR− ($p_{trend} = 0.01$) breast cancer, and heterogeneity by age was statistically significant for both subtypes.

Menopausal status and age at natural menopause.—Menopausal status was not associated with risk of HR+ or HR− breast cancer in any ethnicity group, except Asian Americans, in whom postmenopausal women were at increased risk of HR− breast cancer (Table 3, Supporting Information Fig. S2b). In women with natural menopause, a positive association with later menopause was found for HR+ breast cancer only ($p_{heteroogeneity} = 0.06$). The association differed by ethnicity ($p_{heterogeneity} = 0.05$), with increased risks associated with later menopause (≥51 *vs.* ≤45 years) observed in NHWs (94%, $p_{trend} < 0.01$) and Hispanics (55%, $p_{trend} < 0.01$) only (Table 3, Supporting Information Fig. S2c).

Pregnancy-related characteristics and risk of breast cancer by HR status, age and ethnicity

Nulliparity.—Nulliparous women were at increased risk of HR+ breast cancer only ($p_{heterogeneity} < 0.01$), and the association differed by ethnicity ($p_{heterogeneity} < 0.01$). The increase in risk was borderline in NHWs (19%), and ranged from 48% to 85% in the other ethnicity groups (Table 4). Positive associations were found in younger and older Hispanic and Asian American women, and in older, but not younger African American women (Supporting Information Table S1 and Fig. S2d).

Age at first FTP.—A first FTP at a later age was associated with increased risk of HR+ breast cancer only ($p_{heterogeneity} < 0.01$; Table 4) and limited to younger women (Supporting Information Table S1 and Fig. S2e). The association differed by ethnicity ($p_{heterogeneity} <$

0.01), and alate first FTP (≥ 30 *vs.* <20 years) was associated with increased risk in young Hispanics (75%, p_{trend} = 0.02) and young Asian Americans (78%, p_{trend} = 0.04) only.

Interval between menarche and first FTP.—A positive association with a longer interval was found for HR+ breast cancer only ($p_{heterogeneity}$ = 0.02; Table 4), and limited to younger women (Supporting Information Table S1 and Fig. S2f). The association differed by ethnicity ($p_{heterogeneity}$ = 0.01). Risk associated with a longer interval (≥15 *vs.* <8 years) was increased in young Hispanics only (73%, p_{trend} = 0.03), and suggestively in young Asian Americans (61%, p_{trend} = 0.10).

Time since last FTP.—Positive associations with shorter time since last FTP were observed for HR+ breast cancer only, and limited to younger Hispanics (p_{trend} = 0.02) and Asian Americans (p_{trend} = 0.04)(Supporting Information Table S1 and Fig. S2g).

Parity.—Increasing number of FTPs was associated with reduced risk of HR+ (p_{trend} < 0.01) and HR− (p_{trend} < 0.01) breast cancer (Table 4). For HR+ breast cancer, the association differed by ethnicity ($p_{heterogeneity}$ < 0.01), with lower risks found in all ethnicity groups, except African Americans. Risk reductions per FTP were 14% for Hispanic, 13% for Asian American and 8% for NHW women. In Hispanics and Asian Americans, significant inverse trends were found for younger and older women (Supporting Information Table S1 and Fig. S2h), with risk reductions per FTP ranging from 12% to 20%. For HR− breast cancer, risk was reduced by 50% in Asian Americans with high parity (≥4 *vs.* 1 FTP; p_{trend} < 0.01; Table 4), but only in older women (51%, p_{trend} < 0.01).

Breast-feeding.—Longer lifetime breast-feeding was associated with reduced risk of HR+ breast cancer (p_{trend} = 0.02), and the association differed by ethnicity ($p_{heterogeneity}$ < 0.01; Table 4). Inverse trends were found in younger (p_{trend} = 0.02) and older (p_{trend} = 0.04) Hispanics, whereas in Asian Americans, inverse trends were borderline in younger (p_{trend} = 0.05) and older (p_{trend} = 0.08) women (Supporting Information Table 1 and Fig. S2i). In NHW and African American women, breast-feeding was not associated with HR+ breast cancer risk, neither in younger or older women. For HR− breast cancer (Table 4), risk reductions associated with longer breastfeeding were found in Hispanics (p_{trend} = 0.04) and Asian Americans (p_{trend} < 0.01)only.

Joint association of parity and breast-feeding in African American women.—In younger African American women, risk of HR− breast cancer was increased in those with higher parity (≥3 *vs.* 1 FTP) who never breast-fed (OR = 4.59, 95% CI = 1.69–12.5; $p_{heterogeneity}$ < 0.01; Table 5). This association was unique to African Americans and not seen in other ethnicity groups ($p_{heterogeneity}$ ≥ 0.05, data not shown).

Discussion

In this large population-based pooled dataset, we observed notable differences by ethnicity in menstrual and reproductive patterns and associations with risk of breast cancer defined by tumor HR status. Associations with HR+ breast cancer were generally consistent between Hispanic and Asian American women and largely in agreement with the

literature predominantly from studies in NHW women.[5,19–24] For NHWs, associations with reproductive characteristics were weaker, but in the expected directions, whereas in African American women, most menstrual and reproductive characteristics were not associated with HR+ breast cancer risk. For HR− breast cancer, inverse associations in the expected direction were observed for age at menarche and breast-feeding, although there were some differences by ethnicity. In younger African Americans, risk associated with higher parity was increased in the absence of breast-feeding.

Data are sparse on HR-specific associations with menstrual and reproductive characteristics in Hispanic[8] and Asian American[9] women. More data are available for African American women,[10–12,16] including from the African American Breast Cancer Epidemiology and Risk (AMBER) Consortium, the largest pooled analysis for African American women to date.[14,15] Thus, the present study contributes important new information on ethnic differences in HR-specific associations with menstrual and reproductive characteristics, which were defined in the same manner, and based on identical cut points for direct comparison.

Consistent with a meta-analysis[25] and recent studies,[5,19,20,26,27] we found lower risks of HR+ and HRbreast cancer associated with older age at menarche, although for African Americans, we found an inverse association with HR− breast cancer only, whereas other studies in African American women reported inverse associations for both subtypes.[13,15,16] For Asian Americans, we found inverse associations with HR+ and HR− breast cancer in younger women only. The positive associations with later menarche in older women were unexpected. A study of Chinese women ages 20–70 years also reported inverse associations for both subtypes, but did not stratify the analyses by age or menopausal status.[28] In Hispanic women, we found that later menarche was associated with lower risk of both subtypes. 4-CBCS previously reported borderline reduced risk associated with later menarche for ER+ breast cancer only,[8] whereas a Latin American study found an inverse association for ER− breast cancer only.[29] The present pooled analysis was based on a much larger sample size of Hispanic women, and our findings add to the evidence for Hispanic women that early menarche is likely an important risk factor for HR− breast cancer, a subtype with few known risk factors.

Later menopause has been associated with higher breast cancer risk, and consistent with other studies,[25,30,31] we found a positive association for HR+ breast cancer only, although limited to NHW and Hispanic women. Late menarche and early menopause have been related to lower lifetime exposure to sex hormones, and thus lower breast cancer risk. We saw such a risk pattern most consistently in Hispanic women.

The present results emphasize the importance of the timing of pregnancies in relation to age at diagnosis and age at menarche, although there were some differences in associations by ethnicity. Consistent with studies primarily in NHW women,[5,19–21,24,26] we found a positive association with older age at first FTP for HR+ breast cancer, but only in younger Hispanics and suggestively in younger Asian Americans. Unlike AMBER,[15] we found no association in African American women. For HR− breast cancer, we found no association with age at first FTP, consistent with the findings from AMBER,[15] whereas the Black Women’s Health

Study reported an increased risk of ER− subtype for women ages <45 years who had a first FTP at a young age.[16] For younger NHW women, we also found a trend of increasing risk of HR− breast cancer with younger age at first FTP. A very large cancer registry study from Denmark found no association of age at first live birth with risk ER− breast cancer for women ages <50 years,[24] but risk was increased for ER− HER2− breast cancer in women with a first birth before age 20 years and multiple live births. Thus, the effect of early pregnancies on risk of ER− subtypes warrants further investigation.

Our finding of a positive association between longer interval between menarche and first FTP and risk of HR+ breast cancer is consistent with studies primarily in NHW women.[21,32,33] The association, however, was limited to younger Hispanic women and suggestively to younger Asian American women. Unlike AMBER,[15] we found no association in African American women.

Previous studies have shown that a recent FTP is associated with a short-term increase in breast cancer risk that wanes after about 10 years,[5,24,34] although a recent pooled analysis of prospective data from women under age 55 years suggests that in parous compared to nulliparous women the risk of ER+ breast cancer remains elevated for more than 20 years.[35] In agreement with these findings, in women ages <50 years, we also found that a recent pregnancy (<3 *vs.* ≥20 years since last FTP) was associated with increased risk, but only for HR+ subtype and limited to Hispanic and Asian American women. In contrast, the association with a recent pregnancy did not differ by subtype in the Danish cancer registry study.[24]

Unlike our findings for Hispanic and Asian American women, associations with parity and breast-feeding were weak and nonsignificant in NHW women. Other studies in predominantly NHW women also reported relatively small risk reductions of 9%[36] and 8%[5] associated with high parity (≥4 *vs.* 1 birth) and a lack of association with breast-feeding.[36] For African American women, we found no associations between parity and breast-feeding and risk of HR+ breast cancer, consistent with the findings from AMBER,[14] suggesting that associations with parity and breast-feeding may be different for African American women compared to other ethnicity groups.

Although based on small numbers, risk of HR− breast cancer associated with higher parity (≥3 *vs.* 1) was increased fourfold in younger African Americans who never breast-fed, but not in those with a history of breast-feeding. This finding adds to the growing evidence that breast-feeding may mitigate the adverse effects of higher parity, as we and others have previously reported for ER−,[14] ER− PR−,[10,37,38] triple negative[17] and basal-like[18,36] breast cancer. This fi nding is particularly important for primary prevention, as few risk factors have been identified for ER− breast cancer which is more frequently diagnosed among African American and Hispanic women[39,40] and has worse survival than ER+ breast cancer.[40–42] Palmer *et al.* suggested that higher parity and lower prevalence of breast-feeding may contribute to the higher incidence of ER− breast cancer in African American women.[14] In the present study, a pattern of high parity (≥3 FTPs) and no breast-feeding history that was twice as common in African American controls (21%) compared to NHWs (10%). Some studies in predominantly NHW women also reported positive associations between

higher parity and ERsubtypes in younger women.[5,24,38] In the present study, however, the increased risk of HR− breast cancer associated with higher parity, in the absence of breast-feeding, was limited to younger African American women.

The associations between menstrual and reproductive characteristics and risk of HR+ breast cancer tended to be stronger for women under age 50 years, consistent with other studies,[16,43] suggesting that these factors may play a more important role in breast cancer development in younger than older women. Early-life reproductive events in particular appear to be important determinants of breast cancer risk.[44] We found that the timing of key reproductive events differed substantially by ethnicity and early menarche, early first FTP and a short interval between these two events were most common in African American controls. However, in the present analysis, these reproductive variables were not associated with risk of HR+ breast cancer in African American women, unlike AMBER which reported reduced risk associated with later menarche and shorter interval between menarche and first birth.[15] Our sample size for African American women may have not been large enough to detect significant associations.

Menstrual and reproductive characteristics may influence breast cancer risk through effects on sex hormones,[45–47] hormonally mediated changes in breast structure,[48] or other mechanisms. The time interval between menarche and first FTP is thought to be a window of heightened breast cancer susceptibility when breast tissue is relatively undifferentiated and potentially more susceptible to carcinogens, whereas a first FTP at an early age is thought to induce protective differentiation of mammary cells in the terminal duct lobular unit, with additional pregnancies and breast-feeding inducing further differentiation, thereby protecting breast tissue from carcinogenic transformation.[48] Studies comparing breast tissue of nulliparous and parous women have shown differences in expression of genes, some of which are involved in cell differentiation, regulation of proliferation and cell growth and other processes.[49,50] Parity-related molecular changes appear to be preserved in women with ER+ breast cancer, but disrupted in those with ER− tumors.[51] It is not known whether these mechanisms differ by ethnicity and contribute to the lack of associations of pregnancies and breast-feeding with HR+ breast cancer among African American women.

Some limitations need to be considered when interpreting the present results. Tumor subtype was based on medical records and most breast cancer cases included in the present pooled analysis were diagnosed before HER2 status was routinely collected by cancer registries. We therefore defined subtype by ER and PR status only, as information on HER2 status was available only for a subset of cases in our pooled dataset.[17] It is reassuring that in a pooled analysis of prospective data associations with parity, age at first birth and interval between menarche and first birth were similar for tumors defined by joint ER and PR status or joint ER, PR and HER2 status.[5] On the other hand, Anderson et al. showed that an adverse effect of the joint variable of parity and age at first live birth only emerged when HER2 status in addition to ER status was considered,[24] with an increased risk of ER− HER2− subtype noted for women with multiple pregnancies before age 20 years. These findings underline the importance of considering more refined molecular subtypes than hormone receptor status only and the need for large sample sizes to study the less common breast cancer subtypes. In the present study, the menstrual and reproductive characteristics were assessed

by questionnaire, which is susceptible to recall bias. For 325 women who participated in both SFBCS and NC-BCFR around the same time and completed similar questionnaires on reproductive history, we found high reproducibility for age at first FTP and parity, with high proportions of cases who provided identical answers (89 and 95%, respectively) and no differences for younger and older women. However, reproducibility was somewhat lower for age at menarche (74%), which could have introduced some exposure misclassification. The extent of misclassification observed in our study is consistent with what was observed in another study of European women.[4] Finally, even though the pooled dataset was large and diverse, with 68% of study participants from ethnic minority populations, analyses of HR− breast cancer, especially those stratified by age, were based on relatively small case numbers in each ethnicity group.

Despite these limitations, the present pooled analysis has several important strengths, including case ascertainment through population-based cancer registries and the inclusion of population controls which permitted the estimation of HR-specific relative risks associated with menstrual and reproductive characteristics, unlike some studies that were limited to case–case comparisons.[27,52] With nearly 1,400 HR− cases, the present study is among those with the largest numbers of women diagnosed with this breast cancer subtype. The study population had substantial ethnic diversity and adequate sample size to conduct separate analyses for younger and older women.

To the best of our knowledge, this is the first large-scale investigation of HR-specific associations with menstrual and reproductive characteristics in multiple U.S. minority groups. Our analyses revealed consistent associations in Hispanic and Asian American women, and add to the evidence that pregnancies and breast-feeding may not protect against the development of HR+ breast cancer among African American women. We further found among African American women under age 50 years a suggestive positive association between parity and HR− breast cancer that may be mitigated by breast-feeding, as other studies have reported. The present findings emphasize the importance of studying breast cancer risk factors in diverse populations and warrant further work to understand why menstrual and reproductive risk factors vary in importance according to age and ethnicity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

4-CBCS	4-Corners Breast Cancer Study
AABCS	Los Angeles County Asian American Breast Cancer Study
AMBER	African American Breast Cancer Epidemiology and Risk
BEM	Breast Cancer Etiology in Minorities
BMI	body mass index
CI	confidence interval
ER	estrogen receptor
FTP	full-term pregnancy
HR	hormone receptor
HT	hormone therapy
NC-BCFR	Northern California Breast Cancer Family Registry
NHW	non-Hispanic white
OR	odds ratio
PR	progesterone receptor
SFBCS	San Francisco Bay Area Breast Cancer Study
U.S.	United States

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Wha's new?

To examine how breast cancer risk varies among ethnic groups, these authors pooled data from 4 population-based studies. They analyzed the relationship between menstrual and reproductive characteristics and breast cancer risk by hormone receptor status. In non-Hispanic whites, Hispanics, and Asian-Americans, associations were as expected. Characteristics such as later onset of menstruation, earlier menopause, higher parity, and longer breastfeeding were associated with lower risk of HR+ cancer in these groups. Among African Americans, however, most menstrual and reproductive characteristics showed no association with breast cancer risk, in contrast to a previous study. They did detect an increased risk for HR− cancer in African-American women with higher parity who never breast-fed.

Table 1.

Characteristics of hormone receptor positive cases, hormone receptor negative cases and controls

	HR+ cases (*n* = 5,304)	HR− cases (*n* = 1,390)	Controls (*n* = 7,515)
Study			
AABCS	1,287 (24%)	283 (20%)	1,880 (25%)
NC-BCFR	1,316 (25%)	392 (28%)	621 (8%)
SFBCS	1,558 (29%)	434 (31%)	2,656 (35%)
4-CBCS	1,143 (22%)	281 (20%)	2,358 (31%)
Ethnicity			
African American	536 (10%)	216 (16%)	663 (9%)
Asian American	1,802 (34%)	420 (30%)	1,973 (26%)
Hispanic	1,322 (25%)	418 (30%)	2,336 (31%)
Non-Hispanic white	1,644 (31%)	336 (24%)	2,543 (34%)
Year of diagnosis or selection/interview			
1995–1998	2,195 (41%)	574 (41%)	2,238 (30%)
1999–2001	1,840 (35%)	480 (35%)	2,290 (30%)
2002–2007	1,269 (24%)	336 (24%)	2,987 (40%)
Age at diagnosis or selection/interview (years)			
<40	522 (10%)	234 (17%)	794 (11%)
40–49	1,569 (30%)	430 (31%)	2,246 (30%)
50–64	2,296 (43%)	578 (42%)	2,890 (38%)
≥65	917 (17%)	148 (11%)	1,585 (21%)
Mean	53.5	50.5	53.7
Stage at diagnosis			
Localized	3,240 (61%)	823 (59%)	
Regional	1,807 (34%)	495 (36%)	
Distant	83 (2%)	23 (2%)	
Missing	174 (3%)	49 (4%)	
Histologic grade			
1	1,037 (20%)	27 (2%)	
2	2,324 (44%)	216 (16%)	

	HR+ cases (*n* = 5,304)	HR− cases (*n* = 1,390)	Controls (*n* = 7,515)
3	1,361 (26%)	960 (69%)	
4	86 (2%)	77 (6%)	
Missing	496 (9%)	110 (8%)	
Education			
Some high school or less	756 (14%)	246 (18%)	1,420 (19%)
High school graduate	887 (17%)	258 (19%)	1,346 (18%)
Some college or vocational/technical school	1,573 (30%)	420 (30%)	2,135 (28%)
College graduate or higher degree	2,088 (39%)	466 (34%)	2,614 (35%)
First-degree family history of breast cancer			
Yes	1,105 (21%)	237 (17%)	870 (12%)
No	4,199 (79%)	1,153 (83%)	6,645 (88%)
Personal history of benign breast disease			
Yes	1,084 (20%)	217 (16%)	1,082 (14%)
No	4,220 (80%)	1,173 (84%)	6,433 (86%)
Alcohol consumption in reference year (drinks per week)			
0	3,371 (64%)	922 (66%)	4,714 (63%)
<5	1,024 (19%)	273 (20%)	1,640 (22%)
≥5	909 (17%)	195 (14%)	1,161 (15%)
Body mass index (kg/m^2) (premenopausal women)			
<25	1,290 (64%)	336 (54%)	1,592 (57%)
25–29.9	437 (22%)	159 (25%)	685 (24%)
≥30	282 (14%)	129 (21%)	533 (19%)
Body mass index (kg/m^2) (postmenopausal women)			
<25	1,374 (44%)	309 (43%)	1,802 (41%)
25–29.9	943 (30%)	214 (30%)	1,360 (31%)
≥30	798 (26%)	193 (27%)	1,273 (29%)

Abbreviations: ER, estrogen receptor; HR+, hormone receptor positive (ER+ or PR+); HR−, hormone receptor negative (ER− and PR−); PR, progesterone receptor.

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Table 2.

Menstrual and reproductive characteristics of control women, by ethnicity

	All controls	Non-Hispanic white controls	African American controls	Hispanic controls	Asian American controls
All controls	*n* = 7,515	*n* = 2,543	*n* = 663	*n* = 2,336	*n* = 1,973
Age at menarche (years)					
<12	1,467 (20%)	475 (19%)	149 (22%)	505 (22%)	338 (17%)
12	1,887 (25%)	685 (27%)	168 (25%)	514 (22%)	520 (26%)
13	1,936 (26%)	695 (27%)	174 (26%)	570 (24%)	497 (25%)
≥14	2,225 (30%)	688 (27%)	172 (26%)	747 (32%)	618 (31%)
Mean	12.8	12.7	12.7	12.8	12.9
Menopausal status					
Premenopausal	2,810 (37%)	781 (31%)	195 (29%)	796 (34%)	1,038 (53%)
Postmenopausal	4,435 (59%)	1,683 (66%)	431 (65%)	1,414 (61%)	907 (46%)
Unknown	270 (4%)	79 (3%)	37 (6%)	126 (5%)	28 (1%)
Age at natural menopause (years)[1]					
≤45	1,048 (33%)	456 (37%)	83 (33%)	410 (40%)	99 (15%)
46–50	1,052 (33%)	375 (30%)	68 (27%)	332 (32%)	277 (42%)
>50	1,069 (34%)	409 (33%)	103 (41%)	280 (27%)	277 (42%)
Mean	47.2	46.9	47.7	46.0	49.6
Nulliparity					
Nulliparous	1,051 (14%)	448 (18%)	87 (13%)	176 (8%)	340 (17%)
Parous	6,464 (86%)	2,095 (82%)	576 (87%)	2,160 (92%)	1,633 (83%)
Age at first FTP (years), parous women					
<20	1,274 (17%)	293 (12%)	246 (37%)	644 (28%)	91 (5%)
20–24	2,373 (32%)	886 (35%)	212 (32%)	849 (36%)	426 (22%)
25–29	1,742 (23%)	571 (22%)	76 (11%)	445 (19%)	650 (33%)
≥30	1,075 (14%)	345 (14%)	42 (6%)	222 (10%)	466 (24%)
Mean	24.3	24.6	21.3	22.7	26.9
Interval between menarche and first FTP (years), parous women					
<8	1,745 (23%)	450 (18%)	288 (43%)	828 (35%)	179 (9%)
8–10	1,393 (19%)	522 (21%)	127 (19%)	501 (21%)	243 (12%)

	All controls	Non-Hispanic white controls	African American controls	Hispanic controls	Asian American controls
11–14	1,586 (21%)	563 (22%)	89 (13%)	453 (19%)	481 (24%)
≥15	1,740 (23%)	560 (22%)	72 (11%)	378 (16%)	730 (37%)
Mean	11.5	11.8	8.6	9.9	14.1
Parity, parous women[2]					
1	1,012 (13%)	331 (13%)	121 (18%)	225 (10%)	335 (17%)
2	2,107 (28%)	773 (30%)	161 (24%)	497 (21%)	676 (34%)
3	1,560 (21%)	511 (20%)	130 (20%)	561 (24%)	358 (18%)
≥4	1,785 (24%)	480 (19%)	164 (25%)	877 (38%)	264 (13%)
Mean	3.0	2.7	3.0	3.7	2.5
Lifetime breast-feeding (months), parous women					
0	2,373 (32%)	620 (24%)	308 (46%)	646 (28%)	799 (40%)
1–12	2,251 (30%)	840 (33%)	162 (24%)	705 (30%)	544 (28%)
13–24	872 (12%)	321 (13%)	54 (8%)	330 (14%)	167 (8%)
≥25	968 (13%)	314 (12%)	52 (8%)	479 (21%)	123 (6%)
Mean	11.9	11.3	8.1	17.1	7.3
Parity and breast-feeding history					
Parity 1–2					
Never	1,290 (17%)	361 (14%)	169 (25%)	263 (11%)	497 (25%)
Ever	1,829 (24%)	743 (29%)	113 (17%)	459 (20%)	514 (26%)
Parity ≥3					
Never	1,083 (14%)	259 (10%)	139 (21%)	383 (16%)	302 (15%)
Ever	2,262 (30%)	732 (29%)	155 (23%)	1,055 (45%)	320 (16%)

Abbreviation: FTP, full-term pregnancy.

[1]231 controls with missing age at menopause.

[2]Number of full-term pregnancies.

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Table 3.

Menstrual characteristics and breast cancer risk by hormone receptor status and ethnicity

	All ethnicities			Non-Hispanic white			African American			Hispanic			Asian American		
	Cs	Cn	OR (95% CI)[1,2]	Cs	Cn	OR (95% CI)[1]	Cs	Cn	OR (95% CI)[1]	Cs	Cn	OR (95% CI)[1]	Cs	Cn	OR (95% CI)[1]
Age at menarche[3,4]															
HR+ breast cancer															
<12	1,124	1,467	1.00	333	475	1.0	120	149	1.0	339	505	1.0	332	338	1.0
12	1,376	1,887	0.94 (0.84–1.05)	449	685	0.91 (0.72–1.14)	135	168	1.22 (0.83–1.79)	344	514	0.93 (0.75–1.16)	448	520	0.95 (0.76–1.17)
13	1,338	1,936	0.85 (0.76–0.95)	468	695	0.94 (0.75–1.18)	129	174	0.97 (0.66–1.43)	298	570	0.73 (0.58–0.91)	443	497	0.90 (0.72–1.12)
≥14	1,466	2,225	0.87 (0.77–0.97)	394	688	0.75 (0.59–0.94)	152	172	1.23 (0.84–1.81)	341	747	0.69 (0.55–0.85)	579	618	1.04 (0.84–1.29)
p trend			<0.01			0.02			0.53			<0.01			0.68
Per year			0.97 (0.95–0.99)			0.94 (0.89–0.98)			1.03 (0.96–1.10)			0.93 (0.88–0.97)			1.01 (0.97–1.06)
p heterogeneity by ethnicity <0.01															
HR− breast cancer															
<12	317	1,467	1.0	72	475	1.0	60	149	1.0	115	505	1.0	70	338	1.0
12	363	1,887	0.90 (0.75–1.07)	103	685	0.80 (0.54–1.18)	61	168	1.13 (0.71–1.82)	91	514	0.68 (0.49–0.95)	108	520	1.08 (0.75–1.56)
13	354	1,936	0.83 (0.69–0.99)	98	695	0.79 (0.53–1.18)	49	174	0.67 (0.40–1.12)	103	570	0.72 (0.52–0.99)	104	497	1.03 (0.71–1.50)
≥14	356	2,225	0.79 (0.66–0.94)	63	688	0.58 (0.38–0.88)	46	172	0.61 (0.36–1.03)	109	747	0.66 (0.48–0.90)	138	618	1.14 (0.79–1.63)
p trend			<0.01			0.01			0.02			0.02			0.55
Per year			0.96 (0.92–0.99)			0.87 (0.80–0.96)			0.88 (0.80–0.97)			0.93 (0.87–0.99)			1.05 (0.98–1.12)
p heterogeneity by ethnicity = 0.01															
p heterogeneity by subtype			0.33			0.17			0.04			0.80			0.85
Menopausal status[5,6]															
HR+ breast cancer															
Premenopausal	2,009	2,810	1.0	499	781	1.0	178	195	1.0	478	796	1.0	854	1,038	1.0

	All ethnicities			Non-Hispanic white			African American			Hispanic			Asian American		
	Cs	Cn	OR (95% CI)[1,2]	Cs	Cn	OR (95% CI)[1]	Cs	Cn	OR (95% CI)[1]	Cs	Cn	OR (95% CI)[1]	Cs	Cn	OR (95% CI)[1]
Postmenopausal	3,115	4,435	1.01 (0.89–1.14)	1,085	1,683	1.09 (0.85–1.40)	334	431	0.91 (0.58–1.40)	776	1,414	0.91 (0.71–1.16)	920	907	0.88 (0.71–1.11)
p heterogeneity by ethnicity <0.01															
HR− breast cancer															
Premenopausal	624	2,810	1.0	153	781	1.0	82	195	1.0	197	796	1.0	192	1,038	1.0
Postmenopausal	716	4,435	1.14 (0.95–1.38)	176	1,683	0.86 (0.56–1.33)	126	431	1.26 (0.71–2.21)	194	1,414	0.89 (0.62–1.28)	220	907	1.45 (1.01–2.09)
p heterogeneity by ethnicity <0.01															
p heterogeneity by subtype			0.10			0.49			0.17			0.83			<0.01
Age at natural menopause (years)[5]															
HR+ breast cancer															
≤45	501	1,048	1.0	181	456	1.0	73	83	1.0	166	410	1.0	81	99	1.0
46–50	775	1,052	1.34 (1.15–1.56)	254	375	1.56 (1.19–2.05)	54	68	0.89 (0.52–1.53)	181	332	1.28 (0.96–1.72)	286	277	1.26 (0.87–1.84)
≥51	871	1,069	1.58 (1.35–1.84)	309	409	1.94 (1.48–2.54)	79	103	0.82 (0.50–1.33)	178	280	1.55 (1.15–2.08)	305	277	1.28 (0.87–1.87)
p trend			<0.01			<0.01			0.41			<0.01			0.31
Per year			1.03 (1.02–1.04)			1.04 (1.02–1.05)			0.98 (0.95–1.01)			1.03 (1.02–1.05)			1.03 (1.00–1.06)
p heterogeneity by ethnicity = 0.05															
HR− breast cancer															
≤45	126	1,048	1.0	37	456	1.0	17	83	1.0	46	410	1.0	26	99	1.0
46–50	186	1,052	1.30 (1.00–1.68)	47	375	1.31 (0.79–2.19)	21	68	1.21 (0.54–2.74)	58	332	1.46 (0.94–2.26)	60	277	0.73 (0.40–1.31)
≥51	152	1,069	1.22 (0.93–1.60)	35	409	1.24 (0.73–2.11)	21	103	1.02 (0.47–2.22)	38	280	1.17 (0.72–1.89)	58	277	0.78 (0.43–1.43)
p trend			0.16			0.41			0.98			0.46			0.59
Per year			1.02 (1.00–1.04)			1.01 (0.98–1.04)			1.00 (0.96–1.05)			1.03 (1.00–1.06)			1.00 (0.95–1.05)
p heterogeneity by ethnicity = 0.93															
p heterogeneity by subtype			0.06			0.09			0.75			0.29			0.25

Covariates were categorized as follows: Study (AABCS, NC-BCFR, SFBCS, 4-CBCS); year of diagnosis or selection/interview (1995–1998, 1999–2001, 2002–2007); ethnicity (non-Hispanic white, African American, Hispanic, Asian American); education (some high school or less, high school graduate, some college or vocational/technical school, college graduate or higher degree); first-degree family history of breast cancer (yes, no); personal history of benign breast disease (yes, no); alcohol consumption in reference year (none, <4, ≥5 drinks per week); BMI in reference year (<25.0, 25.0–29.9, ≥30.0 kg/m^2); age at menarche (<12, 12, 13, ≥14 years); menopausal status (premenopausal, postmenopausal, unknown); age at first FTP (nulliparous, <20, 20–24, 25–29, ≥30 years); parity (nulliparous, 1, 2, 3, ≥4 FTPs); lifetime breast-feeding (nulliparous, 0, 1–12, 13–24, ≥25 months).

[1]Adjusted for age at diagnosis or selection/interview (continuous), study, year of diagnosis or selection/interview, education, first-degree family history of breast cancer, personal history of benign breast disease, alcohol consumption, BMI, age at first FTP, parity and breast-feeding.

[2]Additionally adjusted for ethnicity.

[3]Additionally adjusted for menopausal status and interaction between menopausal status and BMI.

[4]Additionally adjusted for age at first FTP, parity and breast-feeding.

[5]Additionally adjusted for age at menarche, age at first FTP, parity and breast-feeding.

[6]Excludes 180 HR+ cases, 50 HR− cases and 270 controls with unknown menopausal status.

Abbreviations: BMI, body mass index; CI, confidence interval; Cs, cases; Cn, controls; ER, estrogen receptor; FTP, full-term pregnancy; HR+, hormone receptor positive (ER+ or PR+); HR−, hormone receptor negative (ER− and PR−); OR, odds ratio; PR, progesterone receptor.

Table 4.

Pregnancies and breast-feeding and risk of breast cancer by hormone receptor status and ethnicity

	All ethnicities			Non-Hispanic white			African American			Hispanic			Asian American		
	Cs	**Cn**	**OR (95% CI)[1,2]**	**Cs**	**Cn**	**OR (95% CI)[1]**	**Cs**	**Cn**	**OR (95% CI)[1]**	**Cs**	**Cn**	**OR (95% CI)[2]**	**Cs**	**Cn**	**OR (95% CI)[2]**
Nulliparity															
HR+ breast cancer															
Parous	4,204	6,464	1.0	1,298	2,095	1.0	431	576	1.0	1,148	2,160	1.0	1,327	1,633	1.0
Nulliparous	1,100	1,051	1.46 (1.32–1.62)	346	448	1.19 (0.97–1.45)	105	87	1.48 (1.03–2.13)	174	176	1.57 (1.21–2.02)	475	340	1.85 (1.56–2.19)
p heterogeneity by ethnicity <0.01															
HR− breast cancer															
Parous	1,170	6,464	1.0	263	2,095	1.0	188	576	1.0	373	2,160	1.0	346	1,633	1.0
Nulliparous	220	1,051	1.02 (0.86–1.22)	73	448	1.00 (0.68–1.45)	28	87	0.78 (0.45–1.35)	45	176	1.22 (0.82–1.81)	74	340	1.13 (0.83–1.53)
p heterogeneity by ethnicity = 0.29															
p heterogeneity by subtype			<0.01			0.24			0.04			0.08			<0.01
Age at first FTP (years), parous women[3]															
HR+ breast cancer															
<20	694	1,274	1.0	178	293	1.0	174	246	1.0	279	644	1.0	63	91	1.0
20–24	1,414	2,373	1.04 (0.91–1.17)	517	886	1.07 (0.83–1.40)	152	212	1.04 (0.74–1.46)	440	849	1.14 (0.93–1.40)	305	426	0.95 (0.65–1.40)
25–29	1,231	1,742	1.13 (0.98–1.30)	372	571	1.02 (0.76–1.36)	61	76	1.06 (0.66–1.70)	249	445	1.11 (0.87–1.42)	549	650	1.14 (0.77–1.68)
≥30	865	1,075	1.15 (0.98–1.35)	231	345	0.99 (0.70–1.40)	44	42	1.60 (0.90–2.83)	180	222	1.38 (1.02–1.86)	410	466	1.14 (0.76–1.72)
p trend			0.045			0.78			0.2			0.07			0.17
p heterogeneity by ethnicity = 0.17															
HR− breast cancer															
<20	264	1,274	1.0	50	293	1.0	83	246	1.0	111	644	1.0	20	91	1.0
20–24	391	2,373	0.84 (0.69–1.01)	90	886	0.66 (0.42–1.03)	63	212	0.96 (0.61–1.51)	152	849	0.98 (0.73–1.31)	86	426	0.87 (0.48–1.59)
25–29	323	1,742	0.91 (0.73–1.12)	78	571	0.61 (0.36–1.01)	26	76	0.97 (0.51–1.83)	77	445	0.91 (0.64–1.31)	142	650	1.01 (0.55–1.84)

	All ethnicities			Non-Hispanic white			African American			Hispanic			Asian American		
	Cs	Cn	OR (95% CI)[1,2]	Cs	Cn	OR (95% CI)[1]	Cs	Cn	OR (95% CI)[1]	Cs	Cn	OR (95% CI)[2]	Cs	Cn	OR (95% CI)[2]
≥30	192	1,075	0.74 (0.57–0.96)	45	345	0.49 (0.27–0.92)	16	42	0.83 (0.38–1.83)	33	222	0.68 (0.41–1.11)	98	466	0.85 (0.45–1.61)
p trend			0.08			0.03			0.67			0.18			0.78
p heterogeneity by ethnicity = 0.89															
p heterogeneity by subtype			<0.01			0.11			0.50			0.01			0.35
Interval between menarche and first FTP (years), parous women[4]															
HR+ breast cancer															
<8	899	1,745	1.0	239	450	1.0	208	288	1.0	342	828	1.0	110	179	1.0
8–10	885	1,393	1.17 (1.03–1.33)	304	522	1.11 (0.86–1.44)	88	127	0.98 (0.67–1.44)	288	501	1.23 (0.99–1.54)	205	243	1.26 (0.90–1.77)
11–14	1,057	1,586	1.12 (0.98–1.28)	363	563	1.12 (0.86–1.46)	68	89	1.06 (0.68–1.66)	245	453	1.02 (0.80–1.28)	381	481	1.18 (0.85–1.62)
≥15	1,363	1,740	1.21 (1.05–1.39)	392	560	1.15 (0.86–1.54)	67	72	1.33 (0.83–2.15)	273	378	1.24 (0.96–1.60)	631	730	1.31 (0.94–1.82)
p trend			0.02			0.38			0.3			0.26			0.2
p heterogeneity by ethnicity = 0.51															
HR− breast cancer															
<8	319	1,745	1.0	61	450	1.0	92	288	1.0	129	828	1.0	37	179	1.0
8–10	242	1,393	0.97 (0.80–1.18)	55	522	0.82 (0.52–1.30)	33	127	0.79 (0.47–1.33)	95	501	1.08 (0.78–1.50)	59	243	1.24 (0.74–2.06)
11–14	274	1,586	0.94 (0.76–1.15)	65	563	0.76 (0.47–1.23)	34	89	1.08 (0.60–1.92)	81	453	0.96 (0.68–1.36)	94	481	0.98 (0.60–1.61)
≥15	335	1,740	0.90 (0.72–1.12)	82	560	0.64 (0.37–1.09)	29	72	0.95 (0.50–1.79)	68	378	0.91 (0.61–1.36)	156	730	1.00 (0.60–1.67)
p trend			0.34			0.1			0.97			0.59			0.66
p heterogeneity by ethnicity = 0.77															
p heterogeneity by subtype			0.02			0.06			0.87			0.22			0.32
Parity (number of FTPs), parous women[4]															
HR+ breast cancer															
1	819	1,012	1.0	212	331	1.0	102	121	1.0	194	225	1.0	311	335	1.0
2	1,619	2,107	0.96 (0.85–1.08)	566	773	1.17 (0.91–1.50)	129	161	0.94 (0.62–1.42)	343	497	0.86 (0.66–1.12)	581	676	0.89 (0.72–1.09)

	All ethnicities			Non-Hispanic white			African American			Hispanic			Asian American		
	Cs	Cn	OR (95% CI)[1,2]	Cs	Cn	OR (95% CI)[1]	Cs	Cn	OR (95% CI)[1]	Cs	Cn	OR (95% CI)[2]	Cs	Cn	OR (95% CI)[2]
3	905	1,560	0.76 (0.66–0.87)	275	511	0.83 (0.62–1.12)	95	130	1.03 (0.66–1.61)	267	561	0.60 (0.45–0.80)	268	358	0.75 (0.58–0.96)
≥4	861	1,785	0.67 (0.58–0.78)	245	480	0.81 (0.60–1.10)	105	164	1.03 (0.65–1.63)	344	877	0.55 (0.41–0.74)	167	264	0.57 (0.42–0.77)
p trend			<0.01			0.01			0.79			<0.01			<0.01
Per FTP			0.89 (0.86–0.91)			0.92 (0.86–0.98)			0.99 (0.91–1.08)			0.86 (0.82–0.91)			0.87 (0.81–0.93)
p heterogeneity by ethnicity <0.01															
HR− breast cancer															
1	223	1,012	1.0	48	331	1.0	46	121	1.0	45	225	1.0	84	335	1.0
2	422	2,107	0.91 (0.75–1.10)	103	773	0.99 (0.63–1.56)	59	161	0.73 (0.43–1.22)	118	497	1.06 (0.70–1.61)	142	676	0.74 (0.53–1.04)
3	289	1,560	0.88 (0.71–1.09)	75	511	1.07 (0.65–1.76)	47	130	0.89 (0.50–1.57)	90	561	0.79 (0.51–1.22)	77	358	0.67 (0.45–1.00)
≥4	236	1,785	0.65 (0.51–0.82)	37	480	0.60 (0.34–1.05)	36	164	0.60 (0.33–1.10)	120	877	0.83 (0.52–1.30)	43	264	0.50 (0.30–0.81)
p trend			<0.01			0.1			0.17			0.17			<0.01
Per FTP			0.92 (0.88–0.97)			0.87 (0.76–0.99)			0.93 (0.82–1.05)			0.97 (0.90–1.04)			0.86 (0.77–0.97)
p heterogeneity by ethnicity = 0.68															
p heterogeneity by subtype			0.57			0.93			0.31			0.048			0.98
Lifetime breast-feeding (months), parous women[5]															
HR+ breast cancer															
0	1,732	2,373	1.0	442	620	1.0	236	308	1.0	432	646	1.0	622	799	1.0
1–12	1,538	2,251	0.99 (0.90–1.10)	530	840	0.88 (0.72–1.07)	120	162	0.89 (0.63–1.24)	398	705	0.85 (0.70–1.03)	490	544	0.82 (0.68–1.0)
13–24	463	872	0.88 (0.76–1.01)	169	321	0.75 (0.56–1.00)	38	54	0.95 (0.56–1.62)	151	330	0.79 (0.61–1.03)	105	167	0.63 (0.47–0.86)
≥25	471	968	0.86 (0.74–1.00)	157	314	0.88 (0.65–1.19)	37	52	1.06 (0.62–1.80)	167	479	0.69 (0.54–0.89)	110	123	0.76 (0.54–1.07)
p trend			0.02			0.17			0.96			<0.01			<0.01
Per 12 months			0.96 (0.93–0.99)			0.99 (0.92–1.06)			0.99 (0.88–1.11)			0.95 (0.91–0.99)			0.92 (0.86–0.99)

	All ethnicities			Non-Hispanic white			African American			Hispanic			Asian American		
	Cs	Cn	OR (95% CI)[1,2]	Cs	Cn	OR (95% CI)[1]	Cs	Cn	OR (95% CI)[1]	Cs	Cn	OR (95% CI)[2]	Cs	Cn	OR (95% CI)[2]
p heterogeneity by ethnicity <0.01															
HR− breast cancer															
0	484	2,373	1.0	80	620	1.0	111	308	1.0	125	646	1.0	168	799	1.0
1–12	432	2,251	1.00 (0.86–1.17)	110	840	0.94 (0.65–1.36)	52	162	0.95 (0.61–1.48)	140	705	0.87 (0.65–1.16)	130	544	0.75 (0.55–1.02)
13–24	113	872	0.77 (0.61–0.97)	34	321	0.89 (0.52–1.51)	13	54	0.80 (0.39–1.63)	46	330	0.69 (0.46–1.03)	20	167	0.43 (0.25–0.74)
≥25	141	968	0.88 (0.69–1.11)	39	314	1.17 (0.69–1.99)	12	52	0.92 (0.42–2.01)	62	479	0.71 (0.48–1.04)	28	123	0.58 (0.34–0.99)
p trend			0.09			0.72			0.59			0.04			<0.01
Per 12 months			0.92 (0.88–0.97)			1.00 (0.88–1.14)			0.88 (0.74–1.06)			0.93 (0.87–1.00)			0.79 (0.68–0.91)
p heterogeneity by ethnicity = 0.72															
p heterogeneity by subtype			0.64			0.61			0.29			0.81			0.12

Covariates were categorized as follows: Study (AABCS, NC-BCFR, SFBCS, 4-CBCS); year of diagnosis or selection/interview (1995–1998, 1999–2001, 2002–2007); ethnicity (non-Hispanic white, African American, Hispanic, Asian American); education (some high school or less, high school graduate, some college or vocational/technical school, college graduate or higher degree); first-degree family history of breast cancer (yes, no); personal history of benign breast disease (yes, no); alcohol consumption in reference year (none, <4, ≥5 drinks per week); BMI in reference year (<25.0, 25.0–29.9, ≥30.0 kg/m^2); age at menarche (<12, 12, 13, >14 years); menopausal status (premenopausal, postmenopausal, unknown); age at first FTP (nulliparous, <20, 20–24, 25–29, >30 years); parity (nulliparous, 1, 2, 3, ≥4 FTPs); lifetime breast-feeding (nulliparous, 0, 1–12, 13–24, ≥25 months).

[1]Adjusted for age at diagnosis or selection/interview (continuous), study, year of diagnosis or selection/interview, education, first-degree family history of breast cancer, personal history of benign breast disease, age at menarche, menopausal status, alcohol consumption, BMI and interaction between menopausal status and BMI.

[2]Additionally adjusted for ethnicity.

[3]Additionally adjusted for parity and breast-feeding.

[4]Additionally adjusted for age at first FTP and breast-feeding.

[5]Additionally adjusted for age at first FTP and parity.

Abbreviations: BMI, body mass index; CI, confidence interval; Cs, cases; Cn, controls; ER, estrogen receptor; FTP, full-term pregnancy; HR+, hormone receptor positive (ER+ or PR+); HR−, hormone receptor negative (ER− and PR−); OR, odds ratio; PR, progesterone receptor.

Table 5.

Parity and breast-feeding and risk of HR− breast cancer among African American women, by age

	African American					
	<50 years			≥50 years		
	Cs	Cn	OR (95% CI)[1]	Cs	Cn	OR (95% CI)[1]
Nulliparity						
Nulliparous	15	40	1.0	13	47	1.0
Parous	79	186	1.55 (0.68–3.51)	109	390	1.00 (0.48–2.11)
Nulliparity and breast-feeding history						
Nulliparous	15	40	1.0	13	47	1.0
Parous, never	44	99	1.76 (0.74–4.23)	67	209	1.07 (0.49–2.32)
Parous, ever	35	87	1.36 (0.57–3.29)	42	181	0.94 (0.42–2.07)
Parity						
1	24	54	1.0	22	67	1.0
2	26	73	1.00 (0.46–2.17)	33	88	0.64 (0.31–1.33)
≥3	29	59	1.81 (0.73–4.51)	54	235	0.55 (0.28–1.08)
p trend			0.23			0.09
Parity and breast-feeding history						
Parity 1–2						
Never	24	75	1.0	35	94	1.0
Ever	26	52	1.41 (0.63–3.15)	20	61	1.24 (0.61–2.54)
Parity ≥3						
Never	20	24	4.59 (1.69–12.5)	32	115	0.92 (0.46–1.81)
Ever	9	35	0.62 (0.21–1.84)	22	120	0.64 (0.31–1.32)
p heterogeneity by parity and breast-feeding history			<0.01			0.26

[1]Adjusted for age at diagnosis or selection/interview (continuous), study, year of diagnosis or selection/interview, education, first-degree family history of breast cancer, personal history of benign breast disease, age at menarche, alcohol consumption and BMI.