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Associations of hormone-related factors with breast cancer risk according to hormone receptor status among white and African-American women

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Abstract

Background—Causes of racial disparities in breast cancer incidence and mortality between white and African-American women remain unclear. We evaluated associations of menstrual and reproductive factors with breast cancer risk by race and cancer subtypes.

Patients and Methods—Included in the study were 1,866 breast cancer cases and 2,306 controls recruited in the Nashville Breast Health Study, a population-based case-control study. Multivariable logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs).

Results—African-American women were more likely to have estrogen receptor-negative (ER−), progesterone receptor-negative (PR−), and triple-negative (ER−PR−Her2−) breast cancer than white women. Age at menarche (≥ 14 years) and multiparity (≥ 3 live births) were inversely associated with (ER+) tumors only, while late age at first live birth (>30 years) and nulliparity were associated with elevated risk; such associations were predominantly seen in whites (OR = 0.70, 95% CI = 0.55–0.88; OR = 0.72, 95% CI = 0.56–0.92; OR = 1.42, 95% CI = 1.13–1.79; OR = 1.32, 95% CI = 1.06–1.63, respectively). Age at menopause between 47 and 51 years was associated with elevated risk of ER− tumors in both whites and African Americans. Among women who had natural menopause, positive association between ever-use of hormone

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replacement therapy and breast cancer risk was seen in whites only (OR = 1.39, 95% CI = 1.03–1.87).

Conclusion—Our study suggests that certain hormone-related factors are differentially associated with risk of breast cancer subtypes, and these associations also differ by race.

Introduction

Breast cancer is the most commonly diagnosed cancer and the second-leading cause of cancer-related mortality among women in the United States (1). It has been recognized that racial disparities in breast cancer incidence and mortality between non-Hispanic white (hereafter referred to as “white”) and African-American/black (hereafter referred to as “African-American”) women exist. Overall, African-American women have a lower incidence of breast cancer than white women; however, among women between the ages of 25 and 40 years, the risk is higher among African American women than white women (2–4). Furthermore, African-American women have a higher mortality rate than white women (2–4). Data from the most recent Surveillance, Epidemiology, and End Results (SEER) Program showed that between 2006 and 2010, the average annual breast cancer incidence rates for white and African-American women were 127.4 per 100,000 and 121.4 per 100,000, respectively, whereas the average annual breast cancer death rates for white and African-American women were 22.1 per 100,000 and 30.8 per 100,000, respectively (2). The reasons for such racial disparities, however, remain unclear; limited existing evidence suggests that the explanation is likely multifactorial, including socioeconomic status, lifestyle-related factors, biological/genetic determinants, and distribution of breast cancer subtypes (5–11).

Ovarian hormones, particularly estrogens, play a pivotal role in the development of breast cancer (12). Epidemiologic studies conducted primarily among white women have consistently documented that women’s menstrual and reproductive patterns, which reflect a women’s cumulative exposure to estrogen and/or progesterone, are related to their lifetime risk of developing breast cancer. These include age at menarche, age at first full-term pregnancy, parity, age at menopause, and use of hormone replacement therapy (HRT) (13, 14). Studies on the prevalence of breast cancer risk factors have shown that African-American women are more likely to report having younger age at menarche, younger age at first full-term pregnancy, more births, and less use of HRT, compared to their white counterparts (13, 15). Differences in breast cancer risk-factor profiles related to women’s menstruation and reproduction were also observed between these two racial groups (16, 17). These findings suggest that the distributions and associations of certain menstrual and reproductive factors with breast cancer may differ between white and African-American women, which may further contribute to white/ African-American differences in the incidence and mortality rates of breast cancer.

The effects of estrogen and progesterone are mediated by their respective receptors, estrogen receptor (ER) and progesterone receptor (PR). Clinical studies have demonstrated that breast cancer cases lacking estrogen receptors (ER−) and/or progesterone receptors (PR−) are associated with an aggressive pathology and poor prognosis, compared to those having

hormone receptors (ER+ and/or PR+). Hormone-receptor status has served as an important biologic marker used in clinical practice to guide endocrine therapy for breast cancer (18). Furthermore, studies have shown that the distributions of breast cancer subtypes classified by ER, PR and human epidermal growth factor receptor 2 (Her2) vary by race, and that ER −, PR−, and triple-negative (ER−PR−Her2-) breast cancer tumors occur in African-American women more frequently than in white women (11, 19, 20). However, much less is known about the etiologic basis for this racial difference in breast cancer subtypes and their potential role in racial disparities.

The Nashville Breast Health Study (NBHS) is a large population-based case-control study of breast cancer conducted in the United States. In this study, we evaluated the distribution of ER, PR, and Her2 in breast cancer tumors. Further, we examined the associations of hormone-related breast cancer risk factors and risk of breast cancer subtypes defined by ER status in white and African-American women. We hypothesize that differential relationships of certain menstrual and reproductive factors with breast cancer defined by ER status exist between these two racial groups, which may partially explain white/ African-American differences in incidence and mortality rates of breast cancer.

Patients and Methods

Study participants

The NBHS is a population-based, case-control study of incident breast cancer conducted in the Nashville metropolitan area of Tennessee. Eligible cases were women newly diagnosed with primary breast cancer (invasive cancer or ductal carcinoma in situ) between the ages of 25 and 75 years old. They had no prior history of cancer other than non-melanoma skin cancer. The majority of participants (92%) were residents of the eight-county Nashville metropolitan area. From February 1, 2001 through December 31, 2010, through a rapid case-ascertainment system established for this study across the five major hospitals in Nashville and the Tennessee Cancer Registry, the study identified and recruited 2,614 women (1,951 whites and 663 African-Americans) who had breast cancer. Information on ER, PR, and Her2 status of breast cancer tumors was obtained from pathology records. Controls were identified primarily via random digit dialing (RDD) of households in eight counties surrounding the Nashville metropolitan area. Controls were frequency matched to cases on five-year age groups, race, and county of residence. Approval for this study was obtained from the Institutional Review Boards of Vanderbilt University Medical Center and each of the collaborating institutions. All participants provided written informed consent prior to study enrollment.

In the NBHS, the median interval from time of breast cancer diagnosis to study enrollment was 10.4 months. Participation rates were approximately 58% for cases and 48% for controls. Reasons for nonparticipation included refusal (N=1,554), not completing the interview (N=220), death (N=206), illness (N=13), and inability to be reached (N=1) among cases, and refusal (N=614), illness (N=7), and death (N=5) and others (n=124) among controls. Among 2,614 cases, 1,866 (71.4%) had information on ER status, 1,844 (70.5%) had information on both ER and PR status, and 1,468 (55%) had information on ER, PR, and Her2 status. In both racial groups, subject characteristics were comparable between

cases with and without ER status, or between cases with ER status only and those with both ER and Her2 status, or between cases with and without Her2 status (data not shown). Included in this analysis were 2,306 controls and 1,866 breast cancer cases who had data on ER status; 748 cases (28.6%) with missing data on ER status were excluded from the analysis.

Data collection

Data on exposures was collected retrospectively during a telephone interview using a reference date, defined as the date of breast cancer diagnosis for cases, or the date of interview for controls. Information on demographic characteristics, menstrual and reproductive history, family history of breast cancer among first-degree relatives, personal history of breast diseases, medical history, current weight and height, and various lifestyle and dietary histories was obtained through a telephone interview conducted by trained interviewers using a structured questionnaire. Menstrual and reproductive history included age at menarche, age at first live birth, number of live births, age at menopause, and ever-use of HRT. Menopause was defined as the cessation of menstrual periods, excluding those caused by pregnancy and nursing, for more than 12 months before the reference date. Cause of menopause was assessed, including natural menopause, surgical menopause (hysterectomy, either uterus and/or ovaries were surgically removed), drug induced, and other (not specified). A medical record abstraction form was used to collect clinical information, including primary tumor characteristics, surgical procedure, and adjuvant treatment. TNM stage of tumors was determined based on the American Joint Committee on Cancer (AJCC) staging system (21). Tumor grade was determined based on the Nottingham grading system (21)

Statistical analysis

Proportions of ER, PR and/or Her2 positive breast tumors were examined for differences using X^2 tests by race. Differences of age at diagnosis, TNM stage, and tumor grade between white and African-American cases by ER status were compared using X^2 tests. Distributions of demographic characteristics and selected risk factors between cases (defined by ER status) and controls were compared using *t*-tests (for continuous variables) or X^2 tests (for categorical variables). Multivariable polytomous unconditional logistic regression models were used to estimate odds ratios (OR) and their 95% confidence intervals (CI) for the association between exposures and breast cancer, defined by ER status. All OR estimates were adjusted for age (years), educational attainment (high school or lower, college, above college), annual household income (US $ italic>20,000, 20,000–40,000, 40,001–60,000, >60,000), regular alcohol consumption (yes/no), regular exercise (yes/no), personal history of benign breast diseases (BBD, yes/no), history of breast cancer among first-degree relatives (yes/no), body mass index (BMI, Kg/m^2), age at menarche (years, ≤11, 12, 13, and ≥14), age at first birth (years, bold>20, 20–25, 26–30, and >30), parity (0, 1, 2, and ≥ 3), age at menopause (years), and ever-use of HRT (yes/no). Tests for trends across categories of exposure were performed by entering the categorical variables as continuous variables in the model. Interaction terms were included in the models to test for a differential effect of each variable of interest on risk of breast cancer by ER status between whites and African

Americans. All *p* values reported are two-sided. Statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC).

Results

Table 1 shows the distribution of ER, PR, and Her2 status of breast cancer among the study population as a whole and by race. As a whole, prevalence of ER+, PR+, or Her2+ tumors among the study population was 74.1%, 61.3%, and 23.2%, respectively. Compared to white women, African-American women were more likely to have ER− tumors (32.4% vs. 24.2%; $p = 0.001$), PR− tumors (46.1% vs. 36.8%; $p = 0.001$), ER− and PR− tumors (30.9% vs. 23.4%; $p = 0.005$), as well as triple-negative (ER−PR−Her2-) tumors (28.5% vs. 16.4%; $p < 0.001$). However, Her2 status in these two racial groups are similar (22.8% and 25% for Her2+ among whites and African Americans, respectively, $p = 0.444$).

As shown in Table 2, African-American women were more likely to have ER− tumors at a younger age (< 50 years) than white women (45.6% vs. 35.2%, p=0.039). Compared to their white counterparts, African-American women were less likely to be diagnosed with early stage of tumors (stages 0 and I), particularly for ER+ tumors (56.3% vs. 65.6%, p=0.041), and were more likely to have poorly differentiated tumors regardless of ER status (31.8% vs. 20.6% in ER+ tumors, p< 0.001; and 81.5% vs. 68.0% in ER− tumors, p=0.008).

Characteristics of controls and breast cancer cases by race and ER status are presented in Table 3. Cases (n = 1,866) with information on ER status were included in the analysis. Compared with controls, breast cancer cases (ER+ or ER−) in both racial groups were more likely to have lower levels of education (≤ high school) and household income (≤ 20,000 US $/year), to be physically inactive, and to have higher rates of family history of breast cancer and personal history of benign breast diseases. BMI and alcohol consumption were comparable between cases and controls in both racial groups.

Table 4 shows associations between menstrual/reproductive factors and ER status of breast cancer by race. Late menarche (age at menarche ≥ 14 years) and multiparity (number of live births ≥ 3) were significantly associated with reduced risk of ER+ breast cancer (OR = 0.76, 95% CI=0.62–0.94; OR = 0.76, 95% CI = 0.61–0.95, respectively), but not significantly associated with ER− tumors (OR = 0.88, 95% CI = 0.65–1.18; OR = 0.92, 95% CI = 0.65–1.28, respectively). These associations were seen in whites (OR = 0.70, 95% CI = 0.55–0.88, for late menarche; OR = 0.72, 95% CI = 0.56–0.92, for multiparity), but not in African Americans (OR = 1.09, 95% CI = 0.67–1.79, for late menarche; OR = 1.00, 95% CI = 0.57–1.74, for multiparity) (*p* for interaction = 0.040 and 0.087, respectively). Late age at first live birth (>30 years) among parous women was significantly associated with an increased risk of ER+ tumors (OR=1.43, 95% CI = 1.15–1.77), but not ER− tumors (OR = 0.94, 95% CI = 0.67–1.32). This association is clearly seen in white women (OR = 1.42, 95% CI = 1.13–1.79), but not in African-American women (OR=0.97, 95% CI = 0.67–1.41). A higher risk of ER+ tumors was also detected in nulliparous white women (OR=1.32, 95% CI = 1.06–1.63), but not nulliparous African-American women (OR=0.98, 95% CI = 0.59–1.63), compared to their counterparts whose age at first live birth was younger than 30 years. In addition, compared to women with early menopause (< 40 years), those whose age at

menopause was 47–51 years had higher risk for both ER+ and ER− tumors (OR = 1.39, 95% CI = 1.08–1.81; OR=1.48, 95% CI = 1.02–2.16, respectively), and no racial difference was detected (*p* for interaction = 0.278 and 0.702, respectively).

We further examined associations of breast cancer risk with menstrual and reproductive factors by estrogen-receptor status and menopausal status among white women (Table 5). Among both pre- and post-menopausal women, a reduced risk of ER+ tumors was found to be associated with late menarche (age at menarche ≥ 14 years), however, the risk was elevated in association with late age at first live birth (>30 years) or nulliparity. A reduced risk of ER− tumor was also related to late menarche among premenopausal women (OR=0.50, 95% CI = 0.27–0.94). Compared to nulliparous women, women with multiparity (number of live births ≥ 3) tend to have a lower risk for breast cancer, particularly for ER+ tumors among premenopausal women (OR=0.55, 95% CI = 0.36–0.86). Stratified analyses by menopausal status were not performed for African American women because of a small sample size.

Table 6 shows associations of HRT ever-use with risks of ER+ and ER− breast cancer among postmenopausal women by race. Overall, no significant associations were detected between HRT use and risk of ER+ or ER− tumors among postmenopausal women. However, among women who had natural menopause, ever-use of HRT showed a moderately elevated risk of ER+ tumors among whites (OR = 1.39, 95% CI = 1.03–1.87), but not among African Americans (OR = 0.57, 95% CI = 0.25–1.27) (*p* for interaction between HRT use and race for risk of ER+ tumors = 0.045).

Discussion

It is estimated that, in general, approximately 75% of breast cancers in US women are ER− positive, with a range from 60 to 85%; approximately 65% of ER− positive breast cancers are also PR− positive. Studies have consistently shown that African-American women have higher rates of ER−, ER−PR−, and triple-negative tumors than white women (7, 11, 22–25). Data from the Black Women's Health Study (BWHS) showed that the proportions of ER+, PR+, and ER−PR− tumors among African-American women were 64%, 52%, and 34%, respectively (23). Unlike the racial differences observed in the distribution of ER/PR, significant differences in the expression of Her2 between African-American and white women has not been observed (26, 27). Similarly, Her2 status in these two racial groups is similar in our study population. Clinical studies have demonstrated that ER−, ER−PR−, and triple-negative tumors are associated with poor prognosis. Our results are consistent with previous reports and support the notion that higher proportions of ER−, ER−PR−, or triple-negative tumors among African-American women contribute to their higher mortality of breast cancer.

Several studies have documented that breast cancer in African-American women is characterized by higher grade, later stage at diagnosis, and reduced survival rate (3, 6–8, 11). Our study shows that African-American women are more likely to have ER− tumors at a younger age (< 50 years), are less likely to be diagnosed in an early stage of tumors, and are more likely to have poorly differentiated tumors regardless ER status, compared to white

women. These findings are consistent with racial differences in clinical characteristics of breast cancer reported by previous studies (3, 6–8, 11). While the association of early age at menarche with breast cancer risk has been established, its association with breast cancer defined by hormone receptor status has not been consistent. In a systematic review of publications on the etiology of hormone receptor-defined breast cancer, Althuis et al. (28) concluded that older age at menarche was associated with a reduced risk of ER+PR+ tumors, but not with ER+, PR+ or ER−PR− tumors. In a meta-analysis, however, Ma et al. (29) concluded that late age at menarche was inversely associated with both ER+PR+ and ER−PR− tumors, and the protective effect was statistically significantly greater for ER+PR+ than ER−PR− cancers. The vast majority of studies included in the two reviews, however, were conducted among white women or predominately white women. In our study, a clear protective effect of late ages at menarche (≥ 14 years) against ER+ tumors was seen among white women, but not among African-American women. Our finding suggests that age at menarche may have differential effects on white and African-American women in terms of breast cancer risk, although the underlying mechanism for this racial difference is unclear.

It has been well documented that age at first birth is positively associated with breast cancer, while multiparity is inversely associated (28, 29). However, such associations vary by racial groups (15, 16) and by hormone receptor status (28–32). For example, in the Carolina Breast Cancer Study, age at first full-term pregnancy ≥ 30 was found to be positively associated with an increased breast cancer risk among white women, but not among African-American women, while multiparity was significantly associated with an increased risk of breast cancer among younger African-American women (20–49 years), but not among their white counterparts (15). In studies conducted among predominately white women, an inverse association of parity with risk of ER+ breast cancer has been consistently observed (28–32), whereas an association with the risk of ER− breast cancer has not been consistent, with studies finding either no association (28–31) or a positive association (32–35). Very few studies have examined such associations among African-American women (23) or have examined potential differential associations between African-American and white women. In our overall study population, and among white women only, age at first birth ≥ 30 years was positively associated with ER+ breast cancer, while multiparity (≥ 3) was inversely associated with ER+ tumors. No associations with ER− tumor were seen among white women. However, in African-American women a statistically non-significant increase in risk of ER− tumors was observed among those who had two live births or with age at first birth between 26–30 years. In the BWHS, late age at first birth was reported to be associated with an increased risk of both ER+ and ER− breast cancer among African-American women (23). A greater number of births and an early age at first birth appear to exert protective effects in white women, but show a tendency to increase breast cancer risk in African-American women, suggesting that the role of these two reproductive factors in the development of breast cancer may be race-dependent.

HRT use has been considered to be an established breast cancer risk factor. However, many studies failed to report significant increases in breast cancer risk (28, 36, 37). Studies investigating the effects of HRT use stratified by hormone-receptor status have yielded mix results (38–40). The Nurses' Health Study did not find an increased risk of ER+ or ER− tumors among current HRT users, but reported a stronger association of past use of HRT

with ER+ than ER− tumors (38). In other studies, an association of combined HRT with ER+PR+ only or with both ER+PR+ and ER−PR− was reported (39, 40). In the NBHS, we found that ever-users of HRT had a statistically significant increase in ER+ tumors among white women with natural menopause, but not in their African-American counterparts.

Several potential limitations of this study should be noted. First, although the NBHS is one of the largest population-based case-control studies of breast cancer in the nation, the sample size of African-American participants are still relatively small. This has limited our power to detect associations in this racial group and in potential racial differences, especially in ER− cases. Second, as with all case-control studies, our study is subject to recall bias since only self-reported information was available. However, information on reproductive factors is typically recalled with high accuracy, as determined in several previous studies (41, 42). Furthermore, the specific associations with breast cancer risk observed in this study by ER status argue against the effect of recall bias on our study results. Third, although we have carefully adjusted for a wide range of confounding variables, we cannot rule out the possible effects of residual confounding or unmeasured confounding factors on the results. In addition, data on breastfeeding was not available for this study so we were unable to investigate its effect on breast cancer subtypes.

In summary, in the NBHS we found that several hormone-related factors, such as age at menarche, parity, age at first live birth, number of live births, were associated with risk of ER+ breast cancer, and that these associations varied by race. These differences may explain in part some of the racial differences in breast cancer incidence and mortality. Further research to ascertain the underlying mechanisms is needed.

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Table 1

Distribution of ER, PR and Her2 status in breast cancer tissues among white and African-American women, the NBHS

Characteristics	[a] All, n (%)	Whites, n (%)	African Americans, n (%)	*p* value
ER status				
ER+	1,383 (74.1)	1,122 (75.8)	261 (67.6)	
ER−	483 (25.9)	358 (24.2)	125 (32.4)	0.001
Total	1,866	1,480	386	
PR status				
PR+	1,132 (61.3)	926 (63.2)	206 (53.9)	
PR−	714 (38.7)	538 (36.8)	176 (46.1)	0.001
Total	1,846	1,464	382	
ER/PR status				
ER+PR+	1,112 (60.3)	911 (62.3)	201 (53.6)	
ER+PR−	254 (13.8)	196 (13.4)	58 (15.2)	
ER−PR+	19 (1.0)	14 (1.0)	5 (1.3)	
ER−PR−	459 (24.9)	341 (23.4)	118 (30.9)	0.005
Total	1,844	1,462	382	
Her2 status				
Her2+	341 (23.2)	273 (22.8)	68 (25.0)	
Her2-	1,127 (76.8)	923 (77.2)	204 (75.0)	0.444
Total	1,468	1,196	272	
[b]**ER/PR/Her2 status**				
ER+Her2- or PR+Her2- (Luminal A)	840 (58.4)	716 (60.9)	124 (47.2)	
ER+Her2+ or PR+Her2+ (Luminal B)	215 (15.0)	169 (14.4)	46 (17.5)	
ER−Her2+ and/or PR−Her2+ (Her2 over-expression)	115 (8.0)	97 (8.3)	18 (6.8)	
ER−PR−Her2- (Triple negative)	268 (18.6)	193 (16.4)	75 (28.5)	< 0.001
Total	1,438	1,175	263	

[a] Excluded from all analyses were 471 white cases and 277 African-American cases without ER information.

[b] Additional 11 cases (7 whites and 4 African Americans) who had Her2 information, but no data on PR status, were also excluded from this analysis.

Table 2

Clinical characteristics of breast cancer tumors defined by estrogen-receptor status among white and African-American women, the NBHS

Characteristics	ER+ tumor (n=1,383)			ER− tumor (n=483)		
	Whites (n=1,122) %	African Americans (n=261) %	*p* value	Whites (n=358) %	African Americans (n=125) %	*p* value
Age at diagnosis						
< 50 yrs	31.9	31.0		35.2	45.6	
≥ 50 yrs	68.1	69.0	0.785	64.8	54.4	0.039
[a]**TNM stage**						
Stages 0 and I	65.6	56.3		51.0	44.8	
Stage II	26.9	34.5	0.041	37.7	43.7	0.537
Stages III and IV	7.5	9.22		11.3	11.5	
[b]**Tumor grade**						
Well differentiated	29.8	22.3		6.5	1.7	
Moderately differentiated	48.4	43.8		22.6	13.4	
Poorly differentiated	21.8	33.9	< 0.001	71.0	84.9	0.008

[a]266 women without information on TNM stage were excluded from this analysis.

[b]76 women without information on tumor grade were excluded from this analysis.

Table 3

Characteristics of controls and cases defined by estrogen-receptor status among white and African-American women, the NBHS

	Whites (n=3,441) %				African Americans (n=731) %			
Subject characteristics	**Controls (n=1,961)**	**ER+ tumors (n=1,122)**	**ER− tumors (n=358)**	**[c]*p* value**	**Controls (n=345)**	**ER+ tumors (n=261)**	**ER− tumors (n=125)**	**[c]*p* value**
Education								
≤High school	27.3	30.0	35.5		27.5	37.9	35.2	
Some college	30.7	30.0	26.5	0.032	37.4	34.5	40.0	0.034
≥College	42.0	40.0	38.0		35.1	27.6	24.8	
Income per annum (US$)								
≤20,000	6.1	8.6	10.0		20.7	32.1	32.3	
20,001–40,000	14.6	17.3	15.8		29.3	27.0	25.0	
40,001–60,000	24.4	22.4	21.5	0.014	19.2	17.1	24.2	0.007
>60,000	54.9	51.7	52.7		30.8	23.8	18.6	
Body mass index (kg/m^2)								
<18.5	1.8	1.7	2.5		0.3	0.4	0.8	
18.5–24.9	44.2	41.7	37.0		18.7	17.7	16.0	
25–29.9	28.3	31.3	32.5	0.171	32.0	28.1	33.6	0.833
≥ 30	25.7	25.3	28.0		49.0	53.8	49.6	
Regular Exercise	57.6	54.3	53.1	0.105	50.7	41.5	42.4	0.054
Ever consumed alcohol	21.7	19.6	18.7	0.234	10.8	16.5	14.4	0.116
Post-menopause	63.2	65.8	65.0	0.329	58.4	69.9	66.4	0.012
[a]**Family history of breast cancer**	14.5	20.1	19.8	< 0.001	12.5	20.3	21.6	0.011
[b]**Personal history of BBD**	34.3	47.7	48.6	< 0.001	24.1	31.9	30.4	0.082

[a]Family history: first-degree blood relatives with breast cancer;

[b]BBD: benign breast diseases;

[c]*p* for ER+ or ER− cases vs. controls from χ^2 test (categorical variables).

Table 4

Odds ratios for breast cancer according to menstrual and reproductive factors by race and estrogen-receptor status, the NBHS

Variables	[a] Adjusted OR (95%CI)		[a] Adjusted OR (95%CI)		[a] Adjusted OR (95%CI)	
		All	Whites	African Americans	Whites	African Americans
ER status of breast cancer	**ER+ tumors**	**ER− tumors**	**ER+ tumors**	**ER+ tumors**	**ER− tumors**	**ER− tumors**
Number of subjects	n=1,383	n=483	n=1,122	n=261	n=358	n=125
[b]**Age at menarche (yrs)**						
≤ 11	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
12	0.96 (0.79–1.16)	0.92 (0.69–1.22)	0.94 (0.76–1.17)	0.96 (0.61–1.52)	1.01 (0.72–1.42)	0.68 (0.39–1.21)
13	1.06 (0.87–1.29)	1.17 (0.88–1.56)	1.02 (0.82–1.26)	1.20 (0.73–1.96)	1.27 (0.91–1.76)	0.93 (0.50–1.71)
≥ 14	0.76 (0.62–0.94)	0.88 (0.65–1.18)	0.70 (0.55–0.88)	1.09 (0.67–1.79)	0.85 (0.59–1.22)	1.05 (0.59–1.89)
p for trend	0.036	0.808	0.008	0.544	0.691	0.707
[*]*p* for interaction			0.040		0.470	
[c]**Parity and number of live births**						
0 (Nulliparous)	1.00 (ref.)	1.00 (ref.)	1,00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
1	0.88 (0.69–1.12)	1.05 (0.74–1.49)	0.85 (0.65–1.10)	1.07 (0.60–1.92)	1.00 (0.67–1.48)	1.22 (0.56–2.65)
2	0.88 (0.71–1.08)	1.04 (0.76–1.43)	0.84 (0.67–1.05)	1.11 (0.63–1.94)	0.90 (0.63–1.28)	1.71 (0.83–3.55)
≥ 3	0.76 (0.61–0.95)	0.92 (0.65–1.28)	0.72 (0.56–0.92)	1.00 (0.57–1.74)	0.87 (0.60–1.28)	1.09 (0.51–2.32)
p for trend	0.019	0.518	0.010	0.954	0.377	0.848
[*]*p* for interaction			0.087		0.416	
[c]**Nulliarity and age at 1st live birth**						
<30	1.00 (ref.)	1.00 (ref.)	1,00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
≥ 30	1.43 (1.15–1.77)	0.94 (0.67–1.32)	1.42 (1.13–1.79)	1.30 (0.67–2.52)	0.97 (0.67–1.41)	0.70 (0.27–1.86)
Nulliparity	1.27 (1.04–1.54)	0.96 (0.71–1.29)	1.32 (1.06–1.63)	0.98 (0.59–1.63)	1.05 (0.76–1.47)	0.72 (0.37–1.43)
[*]*p* for interaction			0.094		0.143	
[d]**Age at menopause (yrs)**						
Q1 (<40)	1.00 (ref.)	1.00 (ref.)	1,00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Q2 (40–46)	1.02 (0.79–1.30)	1.16 (0.82–1.66)	0.95 (0.72–1.26)	1.23 (0.69–2.19)	1.19 (0.78–1.81)	1.16 (0.58–2.31)

Variables	[a] Adjusted OR (95%CI)		[a] Adjusted OR (95%CI)		[a] Adjusted OR (95%CI)	
		All	Whites	African Americans	Whites	African Americans
ER status of breast cancer	**ER+ tumors**	**ER− tumors**	**ER+ tumors**	**ER+ tumors**	**ER− tumors**	**ER− tumors**
Q3 (47–51)	1.39 (1.08–1.80)	1.48 (1.02–2.16)	1.35 (1.02–1.80)	1.28 (0.66–1.49)	1.39 (0.90–2.16)	1.94 (0.90–4.15)
Q4 (≥ 52)	1.14 (0.87–1.48)	1.07 (0.72–1.60)	1.09 (0.82–1.46)	0.94 (0.47–1.88)	1.08 (0.68–1.70)	1.01 (0.41–2.51)
p for trend	0.131	0.489	0.236	0.971	0.671	0.494
[*] *p* for interaction			0.278		0.702	

[a] Adjusted for age, education, income, menopausal status, personal history of benign breast diseases, first-degree family history of breast cancer, regular exercise, body mass index, alcohol consumption, oral contraceptive use, and hormone replacement therapy use.

[b] Also adjusted for parity and number of live birth and parity and age at first live birth.

[c] Also adjusted for age at menarche.

[d] Among postmenopausal women; Also adjusted for age at menarche, parity and number of live birth, parity and age at first live birth, and reasons for menopause.

[*] *p* for interactions between variables of interest (age at menarche, parity and number of live birth, parity and age at first live birth, and age at menopause) and race for risks of ER+ and ER− tumors.

Table 5

Odds ratios for breast cancer associated with selected menstrual and reproductive factors by estrogen-receptor status and menopausal status among white women, the NBHS

Variables	[a] Adjusted OR (95%CI)		[a] Adjusted OR (95%CI)	
	Premenopausal women	Postmenopausal women	Premenopausal women	Postmenopausal women
ER status of breast cancer	**ER+ tumors**	**ER+ tumors**	**ER− tumors**	**ER− tumors**
Number of subjects	N=382	n=736	n=125	n=232
[b]**Age at menarche (yrs)**				
≤ 11	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
12	0.87 (0.60–1.28)	0.98 (0.75–1.28)	0.77 (0.45–1.35)	1.16 (0.76–1.80)
13	0.77 (0.53–1.14)	1.17 (0.90–1.52)	0.89 (0.52–1.55)	1.54 (1.02–2.34)
≥ 14	0.65 (0.43–0.98)	0.74 (0.56–0.99)	0.50 (0.27–0.94)	1.10 (0.71–1.72)
p for trend	0.027	0.151	0.065	0.400
[*]*p* for interaction				
[c]**Parity and number of live births**				
0 (Nulliparous)	1,00 (ref.)	1,00 (ref.)	1.00 (ref.)	1.00 (ref.)
1	0.73 (0.47–1.12)	0.94 (0.67–1.32)	1.58 (0.84–2.99)	0.72 (0.43–1.22)
2	0.90 (0.63–1.28)	0.81 (0.60–1.08)	1.25 (0.70–2.25)	0.72 (0.46–1.13)
≥ 3	0.55 (0.36–0.86)	0.82 (0.60–1.12)	0.85 (0.43–1.70)	0.81 (0.51–1.29)
p for trend	0.038	0.149	0.467	0.567
[*]*p* for interaction				
[c]**Age at 1st live birth**				
<30	1,00 (ref.)	1,00 (ref.)	1.00 (ref.)	1.00 (ref.)
≥ 30	1.48 (1.07–2.06)	1.50 (1.08–2.08)	1.39 (0.87–2.24)	0.51 (0.25–1.04)
Nulliparity	1.50 (1.05–2.13)	1.26 (0.95–1.66)	0.91 (0.51–1.60)	1.26 (0.83–1.90)
[*]*p* for interaction				

[a] Adjusted for age, education, income, personal history of benign breast diseases, first-degree family history of breast cancer, regular exercise, body mass index, alcohol consumption, cigarette smoking status, oral contraceptive use, and hormone replacement therapy use.

[b] Also adjusted for parity, number of live birth, and age at first live birth.

[c] Also adjusted for age at menarche.

* p for interactions between variables of interest (age at menarche, parity and number of live birth, and age at first live birth) and menopausal status for risks of ER+ and ER− tumors

Table 6

Associations of ER+ and ER− breast cancer tumors with use of hormone replacement therapy among postmenopausal white and African-American women who had natural or surgical menopause, the NBHS

Variables	Adjusted OR (95%CI)		Adjusted OR (95%CI)		Adjusted OR (95%CI)	
	All		Whites	African Americans	Whites	African Americans
[a]All post-menopausal women	ER+ (n=872)	ER− (n=302)	ER+ (n=697)	ER+ (n=175)	ER− (n=225)	ER− (n=77)
Never use of HRT	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Ever use	1.01 (0.83–1.24)	0.96 (0.72–1.29)	1.13 (0.90–1.42)	0.74 (0.46–1.17)	0.98 (0.70–1.37)	0.89 (0.50–1.59)
[b]*p* for interaction			0.016		0.381	
[a]Natural menopause	ER+ (n=469)	ER− (n=142)	ER+ (n=387)	ER+ (n=82)	ER− (n=111)	ER− (n=31)
Never use of HRT	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Ever use	1.26 (0.96–1.66)	0.85 (0.57–1.28)	1.39 (1.03–1.87)	0.57 (0.25–1.27)	0.93 (0.59–1.46)	0.32 (0.10–1.03)
[b]*p* for interaction			0.045		0.219	

[a]Adjusted for age, education, income, personal history of benign breast diseases, first-degree family history of breast cancer, regular exercise, body mass index, alcohol consumption, age at menarche, age at menopause, age at first live birth, number of live births, oral contraceptive use; for all race (white and African Americans), race was also adjusted; for all postmenopausal women, cause of menopause was also adjusted.

[b]*p* for interaction between HRT use and race for risks of ER+ and ER− tumors.