Research Article

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Differential Patterns of Risk Factors for Early-Onset Breast Cancer by ER Status in African American Women

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Abstract

Background: Given the disproportionately high incidence of early-onset breast cancer and aggressive subtypes, such as estrogen receptor (ER)-negative tumors, in African American (AA) women, elucidation of risk factors for early onset of specific subtypes of breast cancer is needed.

Methods: We evaluated associations of reproductive, anthropometric, and other factors with incidence of invasive breast cancer by age at onset (<45, ≥45) in 57,708 AA women in the prospective Black Women's Health Study. From 1995 to 2013, we identified 529 invasive breast cancers among women <45 years of age (151 ER^-, 219 ER^+) and 1,534 among women ≥45 years (385 ER^-, 804 ER^+). We used multivariable Cox proportional hazards regression to estimate hazard ratios (HRs) for associations by age and ER status.

Results: Higher parity, older age at first birth, never having breastfed, and abdominal adiposity were associated with increased risk of early-onset ER^- breast cancer: HRs were 1.71 for ≥3 births versus one birth; 2.29 for first birth after age 25 versus <20 years; 0.61 for ever having breastfed versus never; and 1.64 for highest versus lowest tertile of waist-to-hip ratio. These factors were not associated with ER^- cancer in older women or with ER^+ cancer regardless of age.

Conclusions: Differences in risk factors by ER subtype were observed for breast cancer diagnosed before the age of 45 years.

Impact: Etiological heterogeneity by tumor subtype in early-onset breast cancer, in combination with a higher prevalence of the risk factors in AA women, may explain, in part, racial disparities in breast cancer incidence. *Cancer Epidemiol Biomarkers Prev; 26(2); 270–7. ©2016 AACR.*

Introduction

Although overall breast cancer incidence is similar in African American (AA) and U.S. Caucasian women, AA women have a 70% higher incidence of the most aggressive subtypes such as estrogen receptor (ER)-negative (ER^-) tumors (1, 2), leading to higher mortality (2). In addition, relative to Caucasian women, AA women are more likely to be diagnosed at younger ages (3, 4). Among women ages 20 to 49 years, breast cancer mortality rates in the United States are now twice as high in AA women compared with Caucasian women (14.3 vs. 7.1 per 100,000; ref. 5), underlining the urgent need to understand etiology and identify modifiable risk factors for breast cancer in young AA women.

It has long been recognized that breast cancer is a heterogeneous disease and that epidemiologic risk factors differ in their associations by hormone receptor subtype (6). More recently, based on observed bimodal age distributions in breast cancer incidence, Anderson and colleagues proposed that early-onset breast cancer, enriched with ER^- tumors, and later-onset breast cancer, enriched with ER-positive (ER^+) tumors, are etiologically distinct (7–9). We and others have reported differential patterns of associations of several breast cancer risk factors by ER status overall in AA women (10–15), but whether those differences exist for early-onset breast cancer is unknown. Therefore, we assessed the relation of reproductive, anthropometric, and other factors to risk of breast cancer in young women (age < 45 years), overall and by ER status, within the Black Women's Health Study (BWHS). We conducted similar analyses for women ages 45 years and above as a comparison.

Materials and Methods

Study population

The BWHS is an ongoing prospective cohort study of 59,000 AA women (16). In 1995, women ages 21 to 69 years (median age, 38 years) enrolled in the study by completing a comprehensive self-administered baseline questionnaire. Biennial follow-up questionnaires are mailed to participants to update information on demographic, reproductive, behavioral, and lifestyle factors as well as medication use and medical history. Notices of deaths are obtained from next-of-kin, the U.S. Postal Service, and yearly searches of the National Death Index. Follow-up of the baseline cohort has been successful for 87% of potential person-years.

For this analysis, women were excluded if they had been diagnosed with breast cancer (n = 769) or any other type of cancer (except nonmelanoma skin cancer; n = 523) before baseline in 1995; the final analytic cohort included 57,708 AA women ages 21 to 69 years at baseline.

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Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

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The study protocol was approved by the Boston University Institutional Review Board.

Case ascertainment

Incident cases of invasive breast cancer in the BWHS were ascertained through self-report on biennial follow-up questionnaires (95%) or identified through death records and linkage to 24 cancer registries in states covering 95% of participants (5%). Women who reported incident breast cancer were asked for written permission to review their medical records. Study investigators blinded to exposure information reviewed all available medical records and pathology reports, as well as cancer registry data, to confirm breast cancer diagnoses and to abstract data on tumor characteristics. Of cases for which pathology records have been received to date (>80%), more than 99% were confirmed.

Through 2013, we identified 529 incident cases of "early-onset" invasive breast cancer, defined for the purposes of this research as diagnosis before the age of 45 years. Of these, 151 cases were classified as ER^- and 219 as ER^+. Among women ages $\geq$45 years, there were 1,534 incident invasive breast cancers with 385 classified as ER^- and 804 as ER^+. The distribution of ER status was similar to that reported elsewhere for AA women (17–19). In addition, the distribution of breast cancer risk factors was similar in cases with known and unknown receptor status (20, 21).

Risk factor assessment

The baseline questionnaire collected information on established and putative risk factors for breast cancer including adult height, current weight, waist and hip circumferences, age at menarche, weight at age 18, oral contraceptive use, number and timing of births, duration of lactation, hysterectomy, breast cancer in first-degree relatives, alcohol consumption, cigarette smoking, physical activity, menopausal status, age at menopause, and use of menopausal female hormone supplements. Except for adult height, age at menarche, and weight at age 18, all information was updated on follow-up questionnaires. Self-reports of weight, height, waist circumference, hip circumference, and vigorous physical activity were significantly correlated with objective measures in a validation study (22). Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. We did not assess associations of menopausal status, age at menopause or use of female hormone supplements as risk factors in this report because the vast majority of women <45 years of age were premenopausal and had never used hormone supplements.

Statistical analyses

We used the Andersen-Gill data structure (23), with one record per woman per 2-year questionnaire cycle, to allow for time-varying risk factors and survival analysis with time at risk as the underlying timescale. Women contributed person-years from the beginning of follow-up in March, 1995 until diagnosis of breast cancer, death, loss to follow-up, or end of follow-up in March, 2013, whichever occurred first, for a total of 881,204 person years. We used multivariable Cox proportional hazards regression models, stratified by age in 1-year intervals and questionnaire cycle, to estimate hazard ratio (HRs) and 95% confidence intervals (CI) for risk of overall, ER^-, and ER^+ breast cancer, separately, in relation to each factor listed above. All analyses were stratified by age (<45 and $\geq$45) to compare associations for early- versus later-onset breast cancer and all models were mutually adjusted for all risk factors as well as smoking history, menopausal status and, for older women, age at menopause and duration of combination (estrogen plus progestin) menopausal hormone supplement use. HRs for age at first birth, time since last birth, and lactation were estimated from models fit among parous women only. Time-varying risk factors were updated at each questionnaire cycle. Missing indicator categories were used to account for missing information in risk factors (generally 2%–4%). To test whether the risk factor associations differed by ER status within each age group, we used the contrast test method for heterogeneity by subtype (24). Finally, we evaluated statistical interaction of risk factors with age using a likelihood ratio test, comparing main-effects only models with models including cross-product terms for age (<45 vs. $\geq$45) and each categorical risk factor. All analyses were performed using SAS 9.4.

Results

Compared with breast cancers diagnosed at age 45 and older, cancers that occurred in women under age 45 were more likely to be ER^- (41% vs. 32%) and to have other aggressive tumor features, such as advanced stage of disease (regional or distant, 50% vs. 35%), higher grade (poorly differentiated or undifferentiated, 57% vs. 46%), and larger tumor size (>2 cm, 47% vs. 34%; Table 1). Characteristics of the study population according to age group are available in the Supplementary Table. Other characteristics of the overall study population at baseline have been presented elsewhere (25, 26).

Associations of known and suspected breast cancer risk factors with incidence of breast cancer before age 45, overall and by ER subtype, are shown in Table 2. Family history of breast cancer, early age at menarche, recent oral contraceptive use, and pregnancy within the previous 10 years were associated with increased risk of both subtypes, and higher BMI at age 18 was associated with reduced risk of both subtypes. Other associations differed by ER subtype: breastfeeding was associated with a reduced risk of ER^- breast cancer [HR (95% CI): 0.61 (0.40–0.92)] but was not associated with ER^+ breast cancer; high parity was associated with increased risk of ER^- cancer [1.71 (0.98–2.99)] but with a reduced risk of ER^+ cancer [0.69 (0.41–1.14)]; and late age at first birth was associated with increased risk of ER^- cancer [2.29 (1.32–3.97)] but not ER^+ cancer ($P_{\text{heterogeneity}}$ <0.05 for each of the three factors). There was also significant heterogeneity in the results for waist-to-hip ratio, with a 64% increased risk of ER^- breast cancer for women in the top relative to the bottom tertile (95% CI, 1.04–2.59) and no apparent increase in risk of ER^+ breast cancer.

Results from analyses of women $\geq$45 years of age are shown in Table 3. BMI $\geq$25 kg/m^2 at age 18 was associated with decreased risk, whereas family history of breast cancer, early age at menarche, and recent oral contraceptive use were associated with increased risk of both ER^- and ER^+ breast cancer. HRs for nulliparity relative to one birth were 0.71 (0.48–1.07) for ER^- breast cancer and 1.17 (0.90–1.52) for ER^+ cancer ($P_{\text{heterogeneity}} =$ 0.05). The other factors examined were not associated with breast cancer risk in women over 45, regardless of ER subtype. In fact, the lack of association for high waist-to-hip ratio with risk of ER^- breast cancer in women age 45 and older was in contrast to the strong positive association observed among younger women ($P_{\text{interaction}} = 0.03$).

As noted, having a first-degree family history of breast cancer was associated with increased risk of breast cancer in both age

Table 1. Breast cancer tumor characteristics by age

	Age < 45 ($n = 529$) n (%)	Age ≥ 45 ($n = 1,534$) n (%)
ER Status		
Positive	219 (59.2%)	804 (67.6%)
Negative	151 (40.8%)	385 (32.4%)
SEER Stage		
Localized	225 (49.7%)	832 (64.6%)
Regional	211 (46.6%)	401 (31.1%)
Distant	17 (3.8%)	55 (4.3%)
Grade		
Well differentiated	36 (8.5%)	187 (15.2%)
Moderately differentiated	146 (34.4%)	473 (38.4%)
Poorly or undifferentiated	243 (57.2%)	571 (46.4%)
Tumor size		
≤1.0 cm	81 (19.8%)	339 (27.7%)
>1–2.0 cm	135 (32.9%)	474 (38.7%)
>2 cm	194 (47.3%)	411 (33.6%)

NOTE: ER status was unknown or missing for 159 cases <45 years and 345 cases ≥45 years; SEER stage was unknown or missing for 76 cases <45 years and 246 cases ≥45 years; grade was unknown or missing for 104 cases <45 years and 303 cases ≥45 years; tumor size was missing for 119 cases <45 years and 310 cases ≥45 years.

groups and for both ER subtypes; however, the positive association was significantly stronger in the younger women ($P_{\text{interaction}} = 0.02$).

Discussion

In this large prospective cohort study of AA women, we identified breast cancer risk factor profiles that differed by age at diagnosis and ER status. Higher parity, older age at first birth, never having breastfed, and greater abdominal adiposity were important risk factors for early-onset ER$^-$ breast cancer. These factors were not associated with increased risk of later-onset ER$^-$ breast cancer or with ER$^+$ cancers in either age group. Other factors were associated with both ER$^-$ and ER$^+$ breast cancer, regardless of age.

In a recent case–control study in Seattle-Puget Sound with approximately 1,000 breast cancer cases diagnosed before the age of 45 years, Li and colleagues reported that parity was associated with reductions in risk of both ER$^+$ and "triple-negative" tumors and that increasing number of live births was similarly associated with reduced risk of both subtypes (27). NonHispanic Caucasian women comprised approximately 80% of that study population. In contrast, in an analysis of reproductive factors and premenopausal breast cancer diagnosed before age 40 in the predominantly Caucasian Nurses' Health Studies (NHS), Warner and colleagues found a nonsignificant inverse association of parity with ER$^+$/PR$^+$ breast cancer ($n = 118$) but a suggestive positive association with ER$^-$/PR$^-$ breast cancer ($n = 71$; ref. 28). In this study of AA women diagnosed before age 45, we found that higher parity was associated with increased risk of ER$^-$ breast cancer. The current analysis updates our earlier reports of parity and lactation in relation to breast cancer in the BWHS (20, 29), and is also consistent with findings of a recent large pooled analysis of AA women, which included the BWHS, in which parity relative to nulliparity was associated with increased risk of ER$^-$ breast cancer with risk increasing with number of births (12). Although increased risks for parous versus nulliparous were observed across age strata, the association appeared stronger for early-onset ER$^-$ disease, consistent with the current findings. Breastfeeding was associated with reduced risk of early-onset ER$^-$ breast cancer in this study, consistent with our earlier reports (20, 29) with findings from the NHS (28) and with the Seattle-Puget Sound study (27).

Older age at first birth has been fairly consistently positively associated with ER$^+$ breast cancer (30–34), and this association has been observed among both younger and older women (28, 31–33, 35, 36). Although we observed a weak positive association for later-onset ER$^+$ breast cancer, we found no apparent association between age at first birth and risk of early-onset ER$^+$ breast cancer. For overall ER$^-$ breast cancer, most previous studies have shown no clear association with age at first birth (31, 32), whereas results from studies in young women have been mixed, with reports of positive (28, 37), inverse (27, 36), and null associations (35, 38). In this analysis, we found that later age at first birth was associated with more than twice the risk of early-onset ER$^-$ breast cancer, but not later-onset ER$^-$ cancer. These findings suggest that nonhormonal mechanisms of carcinogenesis may contribute to the associations with ER$^-$ breast cancer, which may be particularly relevant for younger women.

We also observed a positive association of waist-to-hip ratio with early-onset ER$^-$ breast cancer. The existing literature on central adiposity and breast cancer risk is not consistent (17, 39–47). In the Nurses' Health Study II, Harris and colleagues reported a significant two-fold increased risk of ER$^-$ breast cancer ($n = 131$) for women in the highest quintile of waist-to-hip ratio compared to the lowest, after adjustment for BMI (40); similar positive associations with ER$^-$ disease were observed in a U.S. case–control study (48) and a Finnish case–control study (49). Other studies in premenopausal Caucasian or multiethnic populations, however, found no associations (37, 43, 50). Current findings from the BWHS are consistent with results from the Carolina Breast Cancer Study (CBCS; ref. 17) and the Women's Circle of Health Study (WCHS; ref. 41), both of which reported increased risk of premenopausal ER$^-$ breast cancer in AA women associated with measures of central adiposity (e.g., waist circumference and waist-to-hip ratio).

There is consistent evidence that higher BMI in young adulthood is associated with decreased risk of both pre- and postmenopausal breast cancer (51–60), although few studies have examined this association by age at onset (52, 61–63) or ER status (57, 58, 63). In this study, we found strong inverse associations of BMI at age 18 with both ER$^-$ and ER$^+$ breast cancer diagnosed before age 45. These findings are consistent with results from other studies of younger women that evaluated overall breast cancer (52, 61, 62). In the Seattle-Puget Sound study, there was a nonsignificant inverse association of BMI at age 18 with risk of triple-negative breast cancer (OR 0.7; 95% CI, 0.4–1.2) but no association with ER$^+$ breast cancer (63). Although the mechanisms underlying the association between BMI in young adulthood and breast cancer risk are not well understood, proposed hypotheses include less cumulative exposure to endogenous estrogens due to anovulatory cycles in overweight women (64), faster clearance of free estradiol by the liver in overweight women (65), or greater susceptibility to carcinogenic influences in lean women.

Some limitations of this study are worth noting. First, although we were interested in identifying risk factors for early-onset ER$^-$ and ER$^+$ breast cancer in AA women, and

Table 2. Multivariable analyses for associations of risk factors with invasive breast cancer among women age <45 years, by ER status[a]

		All invasive ($n = 529$)		ER$^-$ ($n = 151$)		ER+ ($n = 219$)	
	Person-years	Cases	HR (95% CI)	Cases	HR (95% CI)	Cases	HR (95% CI)
Age at menarche (y)							
≤11	124,385	168	1.00 (reference)	53	1.00 (reference)	75	1.00 (reference)
12–13	221,987	275	0.86 (0.71–1.04)	72	0.73 (0.51–1.04)	110	0.79 (0.58–1.06)
≥14	73,990	83	0.73 (0.56–0.96)	25	0.70 (0.43–1.13)	32	0.67 (0.44–1.01)
Oral contraceptive use							
Never	70,615	79	1.00 (reference)	19	1.00 (reference)	29	1.00 (reference)
Ever, ≥10 years ago	116,719	180	0.93 (0.71–1.21)	54	1.21 (0.71–2.07)	74	1.02 (0.66–1.58)
Ever, 5–10 years ago	63,872	82	1.07 (0.78–1.46)	19	1.03 (0.54–1.97)	34	1.12 (0.67–1.85)
Ever, within 5 years	171,110	188	1.25 (0.95–1.64)	59	1.53 (0.90–2.62)	82	1.40 (0.90–2.16)
Family history of breast cancer							
No	397,064	456	1.00 (reference)	131	1.00 (reference)	190	1.00 (reference)
Yes	25,280	73	2.27 (1.77–2.90)	20	2.11 (1.32–3.39)	29	2.16 (1.46–3.20)
Parity							
Nulliparous	163,006	156	1.11 (0.80–1.55)	43	1.30 (0.69–2.47)	68	0.90 (0.54–1.48)
1 birth	111,372	148	1.00 (reference)	40	1.00 (reference)	72	1.00 (reference)
2 births	90,252	135	1.07 (0.84–1.37)	40	1.30 (0.82–2.05)	51	0.80 (0.54–1.16)
≥3 births	54,927	90	1.21 (0.89–1.64)	28	1.71 (0.98–2.99)	28	0.69 (0.41–1.14)
Age at first birth (years)[b]							
<20	64,929	86	1.00 (reference)	22	1.00 (reference)	35	1.00 (reference)
20–24	76,126	92	1.01 (0.74–1.36)	28	1.42 (0.80–2.50)	28	0.65 (0.39–1.09)
≥25	110,113	190	1.44 (1.08–1.94)	58	2.29 (1.32–3.97)	85	1.06 (0.67–1.67)
Years since last birth[b]							
≥10 years	114,915	186	1.00 (reference)	54	1.00 (reference)	75	1.00 (reference)
<10 years	132,817	178	1.43 (1.13–1.81)	53	1.39 (0.90–2.16)	72	1.44 (1.00–2.07)
Lactation[b]							
Never	133,107	199	1.00 (reference)	64	1.00 (reference)	70	1.00 (reference)
Ever	121,551	174	0.87 (0.70–1.08)	44	0.61 (0.40–0.92)	81	1.22 (0.87–1.73)
BMI at age 18 (kg/m^2)							
<20	152,177	216	1.00 (reference)	69	1.00 (reference)	87	1.00 (reference)
20–24	192,897	259	0.97 (0.80–1.18)	62	0.68 (0.47–0.99)	111	1.04 (0.77–1.41)
≥25	71,914	49	0.51 (0.36–0.72)	19	0.55 (0.31–0.99)	21	0.52 (0.31–0.88)
Current BMI (kg/m^2)							
<25	147,559	168	1.00 (reference)	40	1.00 (reference)	73	1.00 (reference)
25–29.9	125,668	174	1.03 (0.83–1.29)	57	1.47 (0.97–2.25)	63	0.87 (0.62–1.24)
≥30	145,616	183	1.04 (0.81–1.33)	53	1.24 (0.76–2.01)	83	1.10 (0.76–1.60)
Waist:hip ratio							
Tertile 1 (<0.76)	113,945	123	1.00 (reference)	33	1.00 (reference)	55	1.00 (reference)
Tertile 2 (0.76–0.84)	102,018	114	1.00 (0.77–1.29)	28	0.89 (0.54–1.48)	53	1.00 (0.68–1.47)
Tertile 3 (>0.84)	101,901	141	1.30 (1.01–1.68)	50	1.64 (1.04–2.59)	45	0.88 (0.58–1.33)
Alcohol consumption (drinks)							
<1/week	300,559	372	1.00 (reference)	114	1.00 (reference)	151	1.00 (reference)
1–6/week	104,727	130	0.96 (0.78–1.18)	29	0.69 (0.46–1.05)	56	0.94 (0.69–1.29)
≥7/week	16,542	27	1.28 (0.86–1.91)	5	0.73 (0.30–1.83)	12	1.39 (0.76–2.55)
Vigorous exercise							
None	155,744	211	1.00 (reference)	64	1.00 (reference)	86	1.00 (reference)
<5 hours/week	215,857	258	0.96 (0.80–1.16)	73	0.97 (0.69–1.37)	110	0.93 (0.28–3.02)
≥5 hours/week	47,631	55	1.00 (0.74–1.35)	13	0.87 (0.47–1.59)	23	1.00 (0.75–1.33)

[a]Multivariable HRs adjusted for age, smoking history (never active or passive, passive only, never active/unknown passive, 1 to <10 packyears, 10+ packyears), menopausal status (premenopausal, hysterectomy only, postmenopausal, missing), and all factors in Table 2.
[b]Among parous women only. Estimates for age at first birth adjusted for age, smoking history, menopausal status, and all factors in Table 2 except years since last birth; estimates for years since last birth adjusted for age, smoking history, menopausal status, and all factors in Table 2 except age at first birth; estimates for lactation adjusted for age, smoking history, menopausal status, and all factors in Table 2.

comparing them to factors associated with breast cancer in older women, we may have been underpowered to detect significant interactions by age. Second, although we had nearly complete data for most risk factors of interest (generally ~2% missing data), there was a fair amount of missing data for waist-to-hip ratio (16%), which required participants to have a tape measure on hand. Third, we did not have information on ER status for 24% of cases; however, the risk factor distribution was similar in cases with and without known ER status, suggesting that any potential selection bias is likely small. We were not able to evaluate associations with triple-negative breast cancer due to small numbers, once we stratified by age.

Despite some limitations, the strengths of this study are considerable, including the prospective design, the large sample size with high follow-up, and high accuracy of reporting of breast cancer diagnoses and risk factor information. Because of the availability of detailed questionnaire data, we were able to perform multivariable analyses including established and suspected risk factors for breast cancer to account for potential confounding. Most importantly, there are very few studies of breast cancer in AA women and even fewer that are able to evaluate risk factors in

Table 3. Multivariable analyses for associations of risk factors with invasive breast cancer among women age ≥45 years, by ER status[a]

	Person-years	All invasive (n = 1,534) Cases	HR (95% CI)	ER$^-$ (n = 385) Cases	HR (95% CI)	ER+ (n = 804) Cases	HR (95% CI)
Age at menarche (y)							
≤11	124,056	442	1.00 (reference)	122	1.00 (reference)	227	1.00 (reference)
12–13	238,248	818	0.94 (0.84–1.06)	192	0.80 (0.63–1.00)	444	1.00 (0.85–1.18)
≥14	94,487	270	0.77 (0.66–0.90)	71	0.72 (0.53–0.97)	131	0.73 (0.59–0.91)
Oral contraceptive use							
Never	113,214	397	1.00 (reference)	72	1.00 (reference)	220	1.00 (reference)
Ever, ≥10 years ago	304,717	1008	1.07 (0.95–1.22)	281	1.54 (1.17–2.03)	518	0.99 (0.84–1.17)
Ever, 5–10 years ago	17,513	56	1.34 (1.00–1.80)	16	1.95 (1.10–3.46)	25	1.08 (0.70–1.66)
Ever, within 5 years	23,408	73	1.37 (1.05–1.80)	16	1.51 (0.85–2.69)	41	1.38 (0.96–1.98)
Family history of breast cancer							
No	411,591	1292	1.00 (reference)	331	1.00 (reference)	677	1.00 (reference)
Yes	47,269	242	1.57 (1.36–1.80)	54	1.39 (1.04–1.86)	127	1.55 (1.28–1.88)
Parity							
Nulliparous	85,033	275	1.02 (0.84–1.24)	51	0.71 (0.48–1.07)	156	1.17 (0.90–1.52)
1 birth	105,685	377	1.00 (reference)	91	1.00 (reference)	198	1.00 (reference)
2 births	134,026	449	0.93 (0.81–1.07)	131	1.09 (0.83–1.43)	228	0.90 (0.74–1.09)
3+ births	132,098	432	0.84 (0.71–0.98)	112	0.92 (0.68–1.26)	221	0.80 (0.64–0.99)
Age at first birth (years)[b]							
<20	125,426	397	1.00 (reference)	112	1.00 (reference)	200	1.00 (reference)
20–24	128,929	430	1.00 (0.87–1.15)	120	1.01 (0.77–1.31)	215	0.98 (0.80–1.19)
≥25	111,747	412	1.14 (0.98–1.33)	99	0.97 (0.72–1.32)	221	1.20 (0.97–1.49)
Years since last birth[b]							
≥10 years	350,948	1198	1.00 (reference)	325	—	617	1.00 (reference)
<10 years	10,107	26	1.09 (0.73–1.65)	2	—	14	1.18 (0.67–2.08)
Lactation[b]							
Never	220,478	746	1.00 (reference)	202	1.00 (reference)	373	1.00 (reference)
Ever	145,885	497	1.04 (0.93–1.18)	128	1.01 (0.80–1.27)	266	1.12 (0.95–1.32)
BMI at age 18 (kg/m^2)							
<20	202,790	727	1.00 (reference)	191	1.00 (reference)	382	1.00 (reference)
20–24	196,533	640	0.90 (0.81–1.01)	159	0.87 (0.70–1.09)	331	0.88 (0.76–1.03)
≥25	50,353	135	0.76 (0.63–0.93)	31	0.73 (0.49–1.09)	75	0.80 (0.61–1.04)
Current BMI (kg/m^2)							
<25	96,942	337	1.00 (reference)	84	1.00 (reference)	169	1.00 (reference)
25–29.9	158,660	527	0.95 (0.82–1.09)	148	1.04 (0.79–1.37)	279	1.00 (0.82–1.21)
≥30	198,604	659	1.00 (0.87–1.16)	151	0.87 (0.65–1.17)	352	1.08 (0.88–1.32)
Waist:hip ratio							
Tertile 1 (<0.76)	105,204	324	1.00 (reference)	81	1.00 (reference)	167	1.00 (reference)
Tertile 2 (0.76–0.84)	116,588	383	1.05 (0.91–1.22)	106	1.17 (0.87–1.57)	209	1.11 (0.90–1.36)
Tertile 3 (>0.84)	115,305	380	1.07 (0.92–1.25)	98	1.11 (0.82–1.51)	195	1.04 (0.84–1.29)
Alcohol consumption (drinks)							
<1/week	317,121	1079	1.00 (reference)	274	1.00 (reference)	565	1.00 (reference)
1–6/week	118,361	376	0.94 (0.83–1.06)	90	0.90 (0.71–1.15)	203	0.96 (0.82–1.13)
≥7/week	22,950	79	1.01 (0.80–1.27)	21	1.07 (0.68–1.68)	36	0.88 (0.63–1.24)
Vigorous exercise							
None	243,272	858	1.00 (reference)	223	1.00 (reference)	450	1.00 (reference)
<5 hours/week	178,581	562	0.94 (0.84–1.04)	134	0.83 (0.67–1.04)	297	0.95 (0.82–1.10)
≥5 hours/week	33,355	103	0.94 (0.76–1.16)	26	0.88 (0.58–1.33)	51	0.92 (0.68–1.23)

[a]Multivariable HRs adjusted for age, smoking history (never active or passive, passive only, never active/unknown passive, 1–<10 packyears, 10+ packyears), menopausal status (premenopausal, hysterectomy only, postmenopausal age <40, postmenopausal age 40–44, postmenopausal age ≥45, postmenopausal age unknown or missing), postmenopausal hormone use (never, E+P <5 years duration, E+P 5+ years duration, other type), and all factors in Table 3.
[b]Among parous women only. Estimates for age at first birth adjusted for age, smoking history, menopausal status, and all factors in Table 3 except years since last birth; estimates for years since last birth adjusted for age, smoking history, menopausal status, and all factors in Table 3 except age at first birth; estimates for lactation adjusted for age, smoking history, menopausal status, and all factors in Table 3.

younger AA women. We have reported on many of the risk factors evaluated in prior analyses (20, 21, 56, 66–68). Now, with the accrual of sufficient numbers of breast cancer cases in the BWHS, the current analysis represents the first study to prospectively characterize risk factor profiles for early-onset ER$^-$ and ER$^+$ breast cancer in AA women.

Differential associations of risk factors by age for ER$^-$ and ER$^+$ breast cancers in AA women suggest etiological heterogeneity by tumor subtype and are supportive of the hypotheses by Anderson and colleagues of age-specific subtypes (7–9). Higher parity, never having breastfed, and abdominal adiposity were associated with increased risk of early-onset ER$^-$ breast cancer but not with later onset ER$^-$ or with ER$^+$ cancer regardless of age. The distribution of these risk factors differs appreciably between AA and Caucasian women: AA women tend to have higher parity (69, 70), lower rates of breastfeeding (71–73), and greater abdominal adiposity (74). Therefore, these differences could explain, in part, disparities in breast cancer incidence between AA and Caucasian women, especially for younger women. Some of the identified risk factors, including lactation and higher waist-to-hip ratio, are potentially modifiable, suggesting opportunities for prevention.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

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

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Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): K.A. Bertrand, T.N. Bethea, L.L. Adams-Campbell, L. Rosenberg
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