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Epidemiology of Basal-like and Luminal Breast Cancers among Black Women in the AMBER Consortium

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ABSTRACT

Background: Evidence suggests etiologic heterogeneity among breast cancer subtypes. Previous studies with six-marker IHC classification of intrinsic subtypes included small numbers of black women.

Methods: Using centralized laboratory results for estrogen receptor (ER), progesterone receptor, HER2, proliferation marker, Ki-67, EGFR, and cytokeratin (CK)5/6, we estimated case-only and case–control ORs for established breast cancer risk factors among cases ($n = 2,354$) and controls ($n = 2,932$) in the African American Breast Cancer Epidemiology and Risk (AMBER) consortium. ORs were estimated by ER status and intrinsic subtype using adjusted logistic regression.

Results: Case-only analyses by ER status showed etiologic heterogeneity by age at menarche, parity (vs. nulliparity), and age at first birth. In case–control analyses for intrinsic subtype, increased body mass index and waist-to-hip ratio (WHR) were associated with increased risk of luminal A subtype, whereas older age at menarche and parity, regardless of breastfeeding, were associated with reduced risk. For basal-like cancers, parity without breastfeeding and increasing WHR were associated with increased risk, whereas breastfeeding and age ≥25 years at first birth were associated with reduced risk among parous women. Basal-like and $ER^-/HER2^+$ subtypes had earlier age-at-incidence distribution relative to luminal subtypes.

Conclusions: Breast cancer subtypes showed distinct etiologic profiles in the AMBER consortium, a study of more than 5,000 black women with centrally assessed tumor biospecimens.

Impact: Among black women, high WHR and parity without breastfeeding are emerging as important intervention points to reduce the incidence of basal-like breast cancer.

Introduction

Basal-like breast cancer is an aggressive molecular subtype defined by a signature of genes, including those expressed in the basal layer of human breast tissue (1). Basal-like tumors typically have poor clinical outcomes and limited options for targeted treatment because of low or absent expression of estrogen receptor (ER), progesterone receptor (PR), and HER2 (2–7). Previous studies show that the relative frequency of basal-like tumors is highest among younger women and black women, especially premenopausal black women (8–11). Reproductive factors, such as parity and breastfeeding, have been shown to contribute to the risk of basal-like subtype, with parous women who do not breastfeed having an increased risk of ER-negative (ER^-) and triple-negative breast cancer (9, 12–14). Late age at menarche has been associated with reduced risk of ER^- breast cancers among black women (15). Associations with other hormone-related risk factors, such as body mass index (BMI) and oral contraceptive use, have been inconsistent across studies of black women (16–19).

Accurate and reliable methods for determining breast tumor subtype are important in studies of risk factor heterogeneity. Most prior risk factor studies have relied on ER, PR, and HER2 status from the clinical record for classification of tumors as luminal A ($ER^+/HER2^-$), luminal B ($ER^+/HER2^+$), $ER^-/HER2^+$, and triple-negative ($ER^-/PR^-/HER2^-$; refs. 20–24). However, laboratory technical variation, changes in expression cut-off values, and intratumoral heterogeneity can contribute to outcome misclassification within this schema, particularly for luminal breast cancers. Moreover, reliance on triple-negative status from the clinical record has resulted in misclassification of basal-like breast cancers in some studies (25–28). We recently showed that incorporating centrally assayed ER, PR, HER2, Ki67, EGFR, and cytokeratin (CK5/6) IHC surrogate classification improved subtype accuracy and produced subtype frequencies similar to those from the RNA-based PAM50 intrinsic subtype assay in the African American Breast Cancer and Risk (AMBER) consortium (29).

Importantly, this consortium study of black women included a large fraction of younger women, resulting in a more than 5-fold larger sample of basal-like breast cancers than previous studies ($n = 691$ basal-like breast cancers compared with $n = 122$ in Millikan and colleagues, 2008; refs. 9, 20–24). In this study, we sought to improve the precision of risk factors associations for basal-like breast cancer in this population, and compare these estimates with those from previous studies of mostly white women.

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Materials and Methods

Study population

The AMBER consortium includes black cases and controls from observational studies of breast cancer: the Carolina Breast Cancer Study (CBCS; ref. 30), the Black Women's Health Study (BWHS; ref. 31), the Women's Circle of Health Study (WCHS; refs. 32, 33), and the Multi-Ethnic Cohort (MEC; ref. 34). Centralized IHC for intrinsic subtype was performed only for CBCS, BWHS, and WCHS; MEC participants were not included in the analysis. Sampling schema for each study have been reported previously (35). Each study was approved by institutional review boards at participating hospitals and academic institutions and conducted in accordance with U.S. Common Rule. Informed consent was obtained from each participant. Briefly, the CBCS is a population-based study of breast cancer cases in North Carolina that enrolled women in three phases (phase I, 1993–1996; phase II, 1996–2001; and phase III, 2008–2013) and oversampled young and black women. The study identified cases via rapid case ascertainment and recruited controls using Division of Motor Vehicle and Medicare beneficiary lists. Controls were frequency matched by age and race. Phase III did not enroll controls; as a result, use of phase III cases in this study is limited to our analyses of case-only ORs and age-at-incidence curves. Data collection included in-person interview and medical record abstraction. BWHS enrolled 59,000 cancer-free black women via a mailed questionnaire beginning in 1995 and have followed women through biennial questionnaire since. Breast cancer diagnoses were self-reported and confirmed via medical record linkage or through state cancer registries and the National Death Index. Three controls per case were included from the BWHS, frequency matched to cases by 5-year age category. The WCHS is a case–control study initially conducted in metropolitan New York and later only in 10 counties in eastern New Jersey (32). New York cases with incident breast cancer from hospitals, which served large proportions of black cases and controls, were identified through random digit dialing. Controls were frequency matched by age and recruitment site. In New Jersey, cases were identified through the New Jersey State Cancer Registry and controls using random digit dialing and community-based recruitment (33).

Eligible women for this study included 1,559 cases from the CBCS (304 from phase I, 29 from phase II, and 1,226 from phase III), 291 cases from the BWHS, and 504 cases from the WCHS. Controls included 788 from phases I and II of the CBCS, 873 from the BWHS, and 1,271 from the WCHS. Characteristics of cases and controls are described in Supplementary Table S1.

Tumor biomarkers

Eligible cases for this analysis were women diagnosed with invasive breast cancer and for whom tumor tissue was available for centralized laboratory analysis ($n = 2{,}354$). For all cases, IHC biomarker stains were carried out on paraffin-embedded tumor sections or tumor microarrays at the Translational Pathology Laboratory at the University of North Carolina at Chapel Hill (Chapel Hill, NC) using assay procedures and cut-off points as described previously (29). A 10% ER positivity threshold was used to delineate ER^+ versus ER^- tumors. Subtypes were defined using six biomarkers: luminal A [ER positive (ER^+) and/or progesterone positive (PR^+), Ki-67 < 7.1%], luminal B (ER^+ and/or PR^+, Ki-67 ≥ 7.1%), ER^-/$HER2^+$, or basal-like (ER^- and PR^- and $HER2^-$, and $EGFR^+$ or $CK5/6^+$). When ER^+ cases were missing Ki-67 (333 cases from CBCS, 0 cases from BWHS, and 51 cases from WCHS), subtypes were defined using five biomarkers, and included in case–control and case-only analyses, luminal A (ER^+ and/or PR^+ and grade 1 or grade 2), luminal B (ER^+ and/or PR^+ and grade 3), ER^-/$HER2^+$, or basal-like (ER^- and PR^- and $HER2^-$, and $EGFR^+$ or $CK5/6^+$). Twenty cases were additionally missing grade information, and were included only in analyses stratified on ER status.

Statistical analyses

ORs were calculated as the measure of association between risk factor exposure and breast cancer subtype. Multivariable binomial logistic regression was used to calculate case–control and case-only ORs and 95% confidence intervals (CI). Multivariable models were adjusted for age (continuous linear), first-degree family history of breast cancer (yes or no), parity (nulliparous, 1–2 children, or ≥3 children), breastfeeding duration (never, <6 months, or ≥6 months), and study (CBCS, WCHS, and BWHS). We conducted sensitivity analyses of fully adjusted models (adjusting for all risk factors under consideration) and found the magnitude and direction of point estimates did not change appreciably; however, the width of CIs was larger. P values were two-sided with $\alpha = 0.05$.

To compare the joint impact of parity and breastfeeding, we used a composite variable categorizing parous women by breastfeeding status (one or two children, never lactated; three or more children, never lactated; one or two children, ever lactated; and three or more children, ever lactated) and calculated case–control ORs with nulliparous controls as the reference group.

Bimodality in age at diagnosis has been used to investigate etiologically distinct subtypes of breast cancer, therefore, we assessed bimodal age-at-diagnosis distributions to evaluate for etiologic heterogeneity among intrinsic subtypes (36). We used two-component statistical mixture models to estimate the proportions of early-onset and late-onset cases within each of the intrinsic subtypes, as described previously (36, 37). Within each subtype, we compared the fit of single-density models versus two-component mixture models. For each type of model, we implemented both normal density and semi-nonparametric density models (adding polynomial multiplier to the normal distribution to allow for skewness and heavy tails in the distributions), resulting in a total of four models for each subtype. The four models fitted for each subtype were compared using Akaike information criterion (AIC) values, with smaller AIC values indicating a better fit. We identified the best fitting single-density model and the best fitting two-component mixture model, and then compared the goodness of fit between these two models using the difference in their AIC values (ΔAIC). ΔAIC > 10 indicated a substantial difference in the goodness of fit between the two models. For each subtype, we plotted the smoothed density curve estimated from the best model overlaid with the empirical age-at-diagnosis distribution (i.e., histogram) for early onset, late onset, and overall distribution. All analyses were performed using SAS 9.4 (SAS Institute) and R (version 3.4.3, R Foundation for Statistical Computing).

Results

Case-only ORs for ER^+ and ER^- tumors

ER has been demonstrated as a strong marker of etiologic heterogeneity in previous studies of breast cancer in black and white women. To first establish the similarity of this dataset to previous studies, with respect to ER heterogeneity, we evaluated case-only ORs for a range of risk factors comparing ER^- tumors with ER^+ tumors. Multivariable ORs are presented in **Table 1**. Older age at menarche, increasing parity,

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Table 1. Case-only ORs comparing ER^- relative to ER^+ breast cancer.

Risk factor	ER^+ ($n = 1,393$) *n* (%)	ER^- ($n = 956$) *n* (%)	OR (95% CI)[a]
Family history[b]			
No	1,147 (82)	793 (83)	1.00
Yes	246 (18)	163 (17)	1.03 (0.82–1.29)
Age at menarche			
<11	164 (12)	96 (10)	1.00
11–12	630 (45)	413 (43)	1.15 (0.86–1.54)
≥13	597 (43)	446 (47)	1.35 (1.01–1.80)
Missing	2	1	
Parity			
Nulliparous	242 (17)	114 (12)	1.00
1–2 children	661 (47)	492 (51)	1.87 (1.43–2.44)
≥3 children	490 (35)	350 (37)	2.05 (1.54–2.73)
Missing	0	0	
Age at first full-term birth[c]			
<25	808 (70)	643 (76)	1.00
≥25	337 (30)	196 (23)	0.74 (0.60–0.92)
Missing	6	3	
Lifetime breastfeeding duration[c]			
Never	640 (56)	538 (64)	1.00
<6 months	205 (18)	144 (17)	0.75 (0.59–0.96)
6+ months	297 (26)	154 (18)	0.61 (0.49–0.78)
Missing	9	6	
Oral contraceptive use			
Never	559 (40)	339 (35)	1.00
Ever	823 (59)	611 (64)	1.02 (0.85–1.23)
Missing	11	0	
BMI			
<25	228 (16)	155 (16)	1.00
25–29	367 (26)	285 (30)	1.22 (0.94–1.59)
≥30	782 (56)	506 (53)	1.04 (0.82–1.33)
Missing	16	10	
WHR			
<0.77	164 (12)	116 (12)	1.00
0.77–0.83	343 (25)	287 (30)	1.18 (0.87–1.59)
≥0.84	837 (60)	528 (55)	0.97 (0.73–1.29)
Missing	49	25	

Note: Cases are from BWHS, WCHS, and CBCS phases I–III.
[a]Model includes age, family history, parity, breastfeeding duration, and study site.
[b]Family history of breast cancer in first-degree relative.
[c]Includes parous women only.

age at first full-term birth, and breastfeeding status showed etiologic heterogeneity by ER status. Family history, oral contraceptive use, BMI, and waist-to-hip ratio (WHR) did not show heterogeneity by ER status, with ORs close to 1.

Case–control ORs for IHC intrinsic subtype

Case–control ORs were estimated for subtype on the basis of six-marker central IHC (**Table 2**). Subtype distribution by study site has been reported previously (29). Luminal A subtype was positively associated with increasing BMI and increasing WHR. Older age at menarche and parity (vs. nulliparity), among both women who breastfed and women who did not, were associated with reduced risk of luminal A subtype. The magnitude of point estimates for luminal B breast cancer were close to the null, except for family history of breast cancer, which was significantly associated with luminal B risk. The direction of associations for $ER^-/HER2^+$ tumors was similar to those for luminal A, with family history, oral contraceptive use, and age ≥25 years at first birth strongly positively associated and parity with breastfeeding inversely associated with risk of $ER^-/HER2^+$. For basal-like breast cancer, increasing WHR (OR, 1.49; 95% CI, 1.00–2.21 for WHR 0.77–0.83 and OR, 1.45; 95% CI, 0.99–2.12 for WHR ≥ 0.84) and higher parity without breastfeeding (OR, 1.70; 95% CI, 1.11–2.60 for 1–2 children and never breastfed and OR, 1.84; 95% CI, 1.17–2.90 for 3+ children, never breastfed) were significantly associated with increased risk, while breastfeeding and age ≥25 years at first birth were protective among parous women.

Case-only ORs for IHC intrinsic subtype

Case-only ORs were calculated to allow evaluation of etiologic heterogeneity by six-marker subtype. Risk factor profiles for luminal B, $ER^-/HER2^+$, and basal-like breast tumors were estimated relative to luminal A subtype (**Table 3**). Overall, consistent with case–control findings, the luminal A and luminal B subtypes showed similar risk factor profiles, demonstrated by the nonsignificant case-only ORs for luminal B tumors. Case-only analyses highlighted differences between luminal A and $ER^-/HER2^+$ and basal-like etiology. Longer

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Table 2. Case–control ORs for six-marker[a] breast cancer subtypes among cases from BWHS, WCHS, and CBCS phases I and III.

Risk factor	Controls (n = 2,932) n (%)	Luminal A (n = 471) n (%)	OR[b] (95% CI)	Luminal B (n = 240) n (%)	OR[b] (95% CI)	ER$^-$/HER2$^+$ (n = 122) n (%)	OR[b] (95% CI)	Basal (n = 295) n (%)	OR[b] (95% CI)
Family history[c]									
No	2,616 (89)	386 (82)	1.00	202 (84)	1.00	101 (83)	1.00	247 (84)	1.00
Yes	316 (11)	85 (18)	1.76 (1.34–2.30)	38 (16)	1.44 (1.00–2.10)	21 (17)	1.87 (1.15–3.05)	48 (16)	1.67 (1.20–2.35)
Age at menarche									
<11	298 (10)	55 (12)	1.00	32 (13)	1.00	13 (11)	1.00	31 (11)	1.00
11–12	1,201 (41)	221 (47)	0.97 (0.70–1.34)	98 (41)	0.78 (0.51–1.19)	53 (43)	1.03 (0.56–1.93)	127 (43)	1.04 (0.68–1.59)
≥13	1,423 (49)	110 (46)	0.70 (0.51–0.98)	110 (46)	0.71 (0.47–1.07)	56 (46)	0.95 (0.51–1.77)	137 (46)	0.93 (0.61–1.42)
Missing	10	1		1		0		0	
Age at first full-term birth[d]									
<25	1,733 (71)	255 (69)	1.00	146 (71)	1.00	57 (63)	1.00	213 (81)	1.00
≥25	716 (29)	117 (31)	1.17 (0.91–1.49)	61 (29)	1.06 (0.77–1.46)	33 (37)	1.66 (1.06–2.62)	50 (19)	0.62 (0.44–0.86)
Missing	19	4		1		2		1	
Parity and breastfeeding									
Nulliparous	464 (16)	95 (20)	1.00	32 (13)	1.00	30 (25)	1.00	31 (11)	1.00
1–2, never	833 (28)	128 (27)	0.74 (0.55–0.99)	81 (34)	1.37 (0.90–2.11)	40 (33)	0.72 (0.44–1.18)	99 (34)	1.70 (1.11–2.60)
3+, never	520 (18)	77 (16)	0.68 (0.49–0.95)	40 (17)	1.06 (0.65–1.73)	22 (18)	0.62 (0.34–1.10)	70 (24)	1.84 (1.17–2.90)
1–2, ever	582 (20)	81 (17)	0.69 (0.50–0.95)	44 (18)	1.06 (0.66–1.70)	14 (11)	0.38 (0.20–0.72)	43 (15)	1.10 (0.68–1.78)
3+, ever	510 (17)	81 (17)	0.72 (0.51–0.99)	42 (18)	1.13 (0.69–1.83)	16 (13)	0.51 (0.27–0.97)	48 (16)	1.40 (0.87–2.26)
Missing	23	9		1		0		4	
Lifetime breastfeeding duration[d]									
Never	1,353 (55)	205 (55)	1.00	121 (58)	1.00	62 (67)	1.00	169 (64)	1.00
<6 months	444 (18)	52 (14)	0.79 (0.57–1.10)	32 (15)	0.85 (0.57–1.28)	11 (12)	0.57 (0.29–1.10)	34 (13)	0.65 (0.44–0.95)
6+ months	648 (27)	110 (29)	1.11 (0.86–1.43)	54 (15)	0.90 (0.64–1.27)	19 (21)	0.71 (0.41–1.20)	57 (13)	0.73 (0.53–1.00)
Missing	23	9		1		1		4	
Oral contraceptive use									
Never	1,376 (47)	214 (45)	1.00	112 (47)	1.00	43 (35)	1.00	125 (42)	1.00
Ever	1,546 (53)	254 (54)	1.19 (0.97–1.47)	128 (53)	1.09 (0.83–1.44)	79 (65)	1.50 (1.01–2.24)	170 (58)	1.13 (0.88–1.47)
Missing	10	3		0		0		0	
BMI									
<25	578 (20)	74 (16)	1.00	41 (17)	1.00	21 (17)	1.00	62 (21)	1.00
25–29	870 (30)	131 (28)	1.16 (0.85–1.58)	65 (27)	1.02 (0.68–1.53)	42 (34)	1.51 (0.88–2.60)	93 (32)	1.03 (0.73–1.45)
≥30	1,425 (50)	260 (55)	1.41 (1.07–1.88)	129 (54)	1.19 (0.82–1.73)	57 (47)	1.26 (0.75–2.12)	133 (45)	0.87 (0.62–1.20)
Missing	59	6		5		2		7	
WHR									
<0.77	576 (20)	74 (16)	1.00	32 (13)	1.00	23 (19)	1.00	41 (14)	1.00
0.77–0.83	778 (28)	116 (25)	1.24 (0.90–1.71)	54 (23)	1.08 (0.68–1.72)	35 (29)	1.18 (0.68–2.06)	89 (30)	1.49 (1.00–2.21)
≥0.84	1,472 (52)	262 (56)	1.43 (1.06–1.94)	143 (60)	1.31 (0.85–2.01)	58 (48)	1.25 (0.74–2.11)	154 (52)	1.45 (0.99–2.12)
Missing	106	19		11		6		11	

[a]Includes 384 cases with missing Ki-67, which were classified using grade as a surrogate as described by Allott and colleagues (29).
[b]Model adjusted for age, family history, parity, breastfeeding duration, and study site.
[c]Family history of breast cancer in first-degree relative.
[d]Among parous women only.

breastfeeding duration was associated with decreased odds for both ER$^-$/HER2$^+$ and basal-like breast cancers relative to luminal A. Parity (vs. nulliparity), particularly among women who did not breastfeed, was associated with higher odds of basal-like compared with luminal A subtype (OR, 3.04; 95% CI, 2.11–4.37 for 1–2 children, never breastfed). Similar to case–control analyses, age ≥25 years at first birth was protective for basal-like cancers among parous women. Age at menarche, oral contraceptive use, BMI, and WHR did not show significant heterogeneity by intrinsic subtype with case-only ORs not significantly different from 1.

Age-at-incidence curves

Bimodal frequency distributions for age at incidence have been interpreted as evidence of etiologic heterogeneity for basal-like versus luminal A tumors (36). We found that luminal cancers were best represented by a two-component mixture model (Supplementary Table S2). For the basal-like group, ΔAIC lay between 4 and 10, still indicating that the two-component mixture model provided better fit, albeit with slightly lower certainty than for luminal cancers. For ER$^-$/HER2$^+$, we could not distinguish which model provided the better fit, with ΔAIC < 4. Broadly, luminal A tumors showed a strongly bimodal pattern in age at diagnosis, with enrichment for both early- and late-onset disease. Luminal B subtype had a less pronounced late-onset peak. ER$^-$/HER2$^+$ subtype was skewed toward earlier age at incidence, with a strong early-onset peak. Basal-like subtype was similarly enriched for early-onset disease, showing a small late-onset peak (**Fig. 1**).

Discussion

We estimated associations between breast cancer risk factors and tumor subtypes defined by six-marker IHC classification among black

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Table 3. Case-only ORs comparing six-marker[a] subtypes of breast cancer among cases from BWHS, WCHS, and CBCS phases I–III.

Risk factor	Luminal A ($n = 827$)	Luminal B ($n = 626$)		$ER^-/HER2^+$ ($n = 210$)		Basal ($n = 691$)	
	n	*n*	OR (95% CI)	*n*	OR (95% CI)	*n*	OR (95% CI)
Family history[b]							
No	664	535	1.00	177	1.00	568	1.00
Yes	163	91	0.70 (0.53–0.93)	33	0.84 (0.55–1.27)	123	0.93 (0.71–1.21)
Age at menarche							
<11	90	79	1.00	22	1.00	70	1.00
11–12	386	269	0.81 (0.57–1.14)	91	0.97 (0.57–1.64)	298	0.99 (0.69–1.42)
≥13	350	277	0.92 (0.65–1.31)	97	1.23 (0.73–2.09)	322	1.19 (0.83–1.71)
Missing	1	1		0		1	
Age at first full-term birth[c]							
<25	483	361	1.00	111	1.00	498	1.00
≥25	193	156	1.12 (0.87–1.46)	50	1.13 (0.77–1.67)	135	0.70 (0.54–0.92)
Missing	5	1		2		1	
Parity and breastfeeding							
Nulliparous	146	108	1.00	47	1.00	57	1.00
1–2, never	218	190	1.16 (0.84–1.59)	63	1.00 (0.64–1.55)	252	3.04 (2.11–4.37)
3+, never	158	107	0.89 (0.62–1.27)	38	0.90 (0.55–1.49)	153	2.58 (1.74–3.81)
1–2, ever	152	124	1.06 (0.75–1.50)	28	0.55 (0.32–0.93)	118	1.89 (1.27–2.80)
3+, ever	144	96	0.91 (0.63–1.31)	33	0.85 (0.51–1.42)	107	2.06 (1.37–3.09)
Missing	9	1		1		4	
Lifetime breastfeeding duration[c]							
Never	376	297	1.00	101	1.00	405	1.00
<6 months	111	101	1.12 (0.82–1.53)	28	0.81 (0.50–1.31)	110	0.84 (0.62–1.14)
6+ months	185	119	0.84 (0.64–1.11)	33	0.64 (0.42–1.00)	115	0.60 (0.45–0.79)
Missing	9	1		1		4	
Oral contraceptive use							
Never	336	252	1.00	69	1.00	243	1.00
Ever	484	370	0.89 (0.71–1.12)	140	1.13 (0.81–1.58)	443	1.01 (0.81–1.27)
Missing	7	4		1		5	
BMI							
<25	132	104	1.00	37	1.00	110	1.00
25–29	224	160	0.94 (0.67–1.32)	74	1.32 (0.83–2.09)	196	1.11 (0.80–1.55)
≥30	462	355	1.01 (0.75–1.37)	96	0.89 (0.57–1.38)	378	1.04 (0.77–1.41)
Missing	9	7		3		7	
WHR							
<0.77	101	74	1.00	32	1.00	73	1.00
0.77–0.83	204	158	0.89 (0.61–1.31)	64	1.03 (0.62–1.70)	206	1.24 (0.85–1.82)
≥0.84	493	373	0.90 (0.63–1.28)	107	0.84 (0.52–1.37)	395	1.06 (0.74–1.52)
Missing	29	21		7		17	

[a]Includes 384 cases with missing Ki-67, which were classified using grade as a surrogate as described by Allott and colleagues (29).
[b]Family history of breast cancer in first-degree relative.
[c]Includes parous women only.

women in the AMBER consortium. We found breastfeeding to be protective for basal-like and $ER^-/HER2^+$ breast cancer in both case–control and case-only analyses. Parity and later age at menarche were associated with reduced risk of luminal A breast cancer, while increased BMI and WHR conferred increased risk. Luminal B subtype was not significantly associated with any risk factors other than family history, although the direction of association was similar for luminal A breast cancers, and in case-only analyses did not exhibit a risk factor profile distinct from luminal A. Age-at-incidence curves overall showed bimodal distributions with pronounced early-onset peaks for all subtypes, but $ER^-/HER2^+$ and basal-like subtypes showed earlier age at diagnosis compared with luminal subtypes, in keeping with their distinct risk factor profiles. In a large, black population with centrally assessed, six-marker IHC-based breast cancer subtypes, risk factor profiles by intrinsic subtype suggest distinct risk factors for basal-like breast cancer and highlight breastfeeding as a plausible intervention to reduce risk of this aggressive subtype of breast cancer.

Breastfeeding has consistently demonstrated a protective effect for triple-negative and basal-like breast cancers in prior literature (38–45). In our study, we observed that women who were parous, but did not breastfeed, had the highest ORs for basal-like breast cancer, further reinforcing the importance of breastfeeding to reduce risk of basal-like breast cancer. A number of prior studies have found similar results, including earlier analyses with clinical markers in the AMBER consortium, which found breastfeeding to be associated with reduced risk for ER^-, basal-like, and triple-negative subtypes, while parous women who did not breastfeed were at increased risk for these subtypes (9, 13, 39, 46). We also found increased WHR to be associated with increased risk of basal-like subtype, in agreement with earlier analyses in the AMBER consortium (16, 18). A previous study among participants of the Women's Health Initiative showed no association

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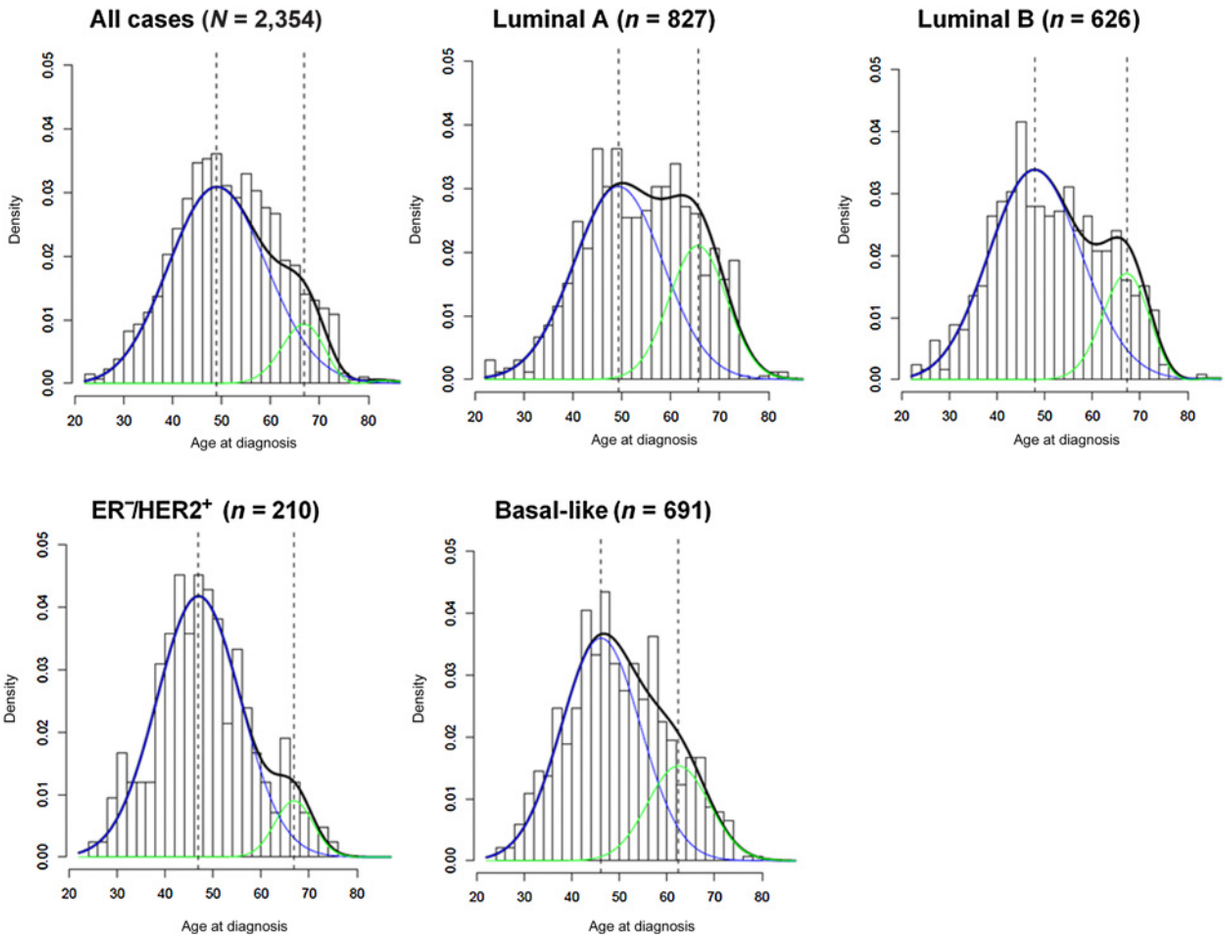

Figure 1.
Density plots showing age frequency distributions at diagnosis for invasive breast cancer cases from AMBER consortium, overall and by six-marker IHC-based subtype. Smoothed density curve is plotted in black, early-onset density is plotted in blue, and late-onset density is plotted in green, with dotted lines representing median age at diagnosis for early- and late-onset density curves. Bar plot shows empirical distribution of age at diagnosis. It includes 384 cases missing Ki-67, which were classified using grade as a surrogate, as described by Allott and colleagues (29).

between WHR and risk for triple-negative breast cancer; however, this study included a small number of black women ($n = 199$ cases; ref. 47). The relationship between adiposity and breast cancer risk appears to vary by race and ethnicity, and WHR, commonly used to represent central adiposity, may more strongly influence breast cancer risk than BMI among black women (48). It will be important to consider obesity-related biomarkers in future studies to better understand how body mass distribution and race influence breast cancer etiology.

Compared with luminal A and basal-like subtypes, risk factor profiles for luminal B and ER$^-$/HER2$^+$ breast cancer have been less consistently reported, likely due to the lower prevalence of these subtypes. However, considering the magnitude of associations in prior literature, there appears to be an overlapping risk factor profile for luminal A and B subtypes, in-line with our case-only ORs, which were very close to 1 (38, 40, 41, 49). As for the ER$^-$/HER2$^+$ subtype, we found several significant associations, including a protective effect of parity with breastfeeding. This is in contrast to a study among a multiethnic cohort of women that found parity (vs. nulliparity) to be associated with 43% (95% CI, 1.08–1.89) higher odds of ER$^-$/HER2$^+$ breast cancer relative to luminal A (46). That study included a larger number ($n = 493$) of ER$^-$/HER2$^+$ tumors and a lower proportion (less than 6%) of black women relative to our study. In the Nurses' Health Study, a cohort of largely non-Hispanic white women, Fortner and colleagues also found parity (vs. nulliparity) to be associated with increased risk of ER$^-$/HER2$^+$ tumors (40). Our discrepant findings may be due to differences in tumor classification schema and/or patient population, as reproductive factors are known to vary by race and ethnicity (50, 51). Of note, we found an increased risk for ER$^-$/HER2$^+$ subtype with oral contraceptive use, a finding that has been reported previously among white and Asian women, but not among black women (52–54).

Age-at-incidence curves offer additional perspectives on etiologic heterogeneity among breast tumor subtypes. Recent evidence has suggested that breast cancer can be divided into two etiologic subtypes defined by age at onset, and that the difference in the relative distribution of those two subtypes underpins the biological characteristics of any given breast cancer categorization (55). We saw that, compared with the luminal subtypes, ER$^-$/HER2$^+$ and basal-like subtypes exhibited strong early-onset peaks, which supports the distinct risk factor associations found in case-only analyses. However,

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it is notable that predominant early-onset enrichment was observed among all subtypes in this study of black women. This is in contrast to an earlier study using data from the Molecular Taxonomy of Breast Cancer International Consortium, which enrolled mostly white women, and showed luminal A and luminal B subtypes to have predominant late-onset modes (55). Our findings confirm a consistent trend toward earlier age at breast cancer incidence for black women compared with white women and suggest that it persists across all subtypes (36, 56, 57).

Strengths of this study include a large population of black women from throughout the United States and the use of central laboratory, six-marker IHC classification. The sample size of $ER^-/HER2^+$ and basal-like breast cancers is also higher than in previous studies of these subtypes in diverse populations. However, despite being one of the largest cohorts of black women with breast cancer, we still lacked precision in measuring risk factor associations for the less common luminal B and $ER^-/HER2^+$ subtypes. Likewise, the sample size of our study did not allow sufficient power for analysis stratified by menopausal status. For example, examining parity and lactation or breastfeeding duration and stratifying by menopausal status would have resulted in fewer than 10 women in multiple categories. In addition, some associations were not statistically significant in case–control analyses, but the magnitude of these associations is important for interpretation of case-only analyses, which included larger sample sizes. It is also important to note that the modes for early and late age at incidence cannot be generalized to women in the source populations because some studies in the AMBER consortium oversampled for younger women. However, the modes were stable across intrinsic subtype, allowing for comparison of age-at-incidence curves by subtype.

Our findings suggest that previously identified risk factors for basal-like breast cancer also hold for black women. In earlier analyses, aggregation of risk factor patterns by race, including a trend toward earlier births and lower breastfeeding rates in black women, remained a concern for etiologic inference. This study shows that even among a population entirely composed of black women, reproductive and body size patterns were associated with this more aggressive breast cancer subtype. Future research to understand the mechanisms underlying these associations is needed. Additional approaches, such as studies of second primary breast cancers, may offer more direct evidence for etiologic heterogeneity. However, these results suggest that continued promotion of breastfeeding, as well as improved understanding of the biologic mechanisms linking adiposity and basal-like breast cancer risk, should be part of a comprehensive strategy to address breast cancer disparities.

Authors' Disclosures

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Authors' Contributions

H.C. Benefield: Conceptualization, formal analysis, investigation, methodology, writing-original draft, writing-review and editing. **G.R. Zirpoli:** Conceptualization, data curation, formal analysis, investigation, methodology, writing-review and editing. **E.H. Allott:** Formal analysis, methodology, writing-review and editing. **Y. Shan:** Formal analysis, methodology, writing-review and editing. **A.N. Hurson:** Methodology, writing-review and editing. **A.R. Omilian:** Conceptualization, methodology, writing-review and editing. **T. Khoury:** Conceptualization, writing-review and editing. **C.-C. Hong:** Conceptualization, writing-review and editing. **A.F. Olshan:** Resources, writing-review and editing. **T.N. Bethea:** Conceptualization, methodology, writing-review and editing. **E.V. Bandera:** Conceptualization, resources, methodology, writing-review and editing. **J.R. Palmer:** Conceptualization, resources, supervision, methodology, writing-review and editing. **C.B. Ambrosone:** Conceptualization, resources, supervision, methodology, writing-review and editing. **M.A. Troester:** Conceptualization, resources, supervision, funding acquisition, methodology, writing-review and editing.

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