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Research Article

Cancer Epidemiology, Biomarkers & Prevention

Biology and Etiology of Young-Onset Breast Cancers among Premenopausal African American Women: Results from the AMBER Consortium

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Abstract

Background: African American (AA) women have higher incidence of aggressive, young-onset (<40 years) breast cancers. Young- and older-onset disease may have distinct tumor biologies and etiologies; however, studies investigating age differences among AA women have been rare and generally underpowered.

Methods: We examined tumor characteristics and breast cancer risk factors associated with premenopausal young (<40) vs. older (≥40) AA women's breast cancer in the African American Breast Cancer Epidemiology and Risk Consortium (2,008 cases and 5,144 controls). Unconditional logistic regression models assessed heterogeneity of tumor biology and risk factor associations by age, overall, and by estrogen receptor status.

Results: Premenopausal AA women <40 years had higher frequency of poorer-prognosis tumor characteristics compared with older women, including negative estrogen and progesterone receptor status, triple-negative subtype, higher grade, higher stage, and larger tumors. Adiposity (i.e., waist-to-hip ratio) and family history of breast cancer were more strongly associated with young-onset disease [case–control OR = 1.46, 95% confidence interval (CI) = 1.04–2.05; OR = 3.10, 95% CI = 2.08–4.63, respectively] compared with older-onset disease (OR = 1.11, 95% CI = 0.91–1.35; OR = 1.57, 95% CI = 1.26–1.94). Breastfeeding showed a slight inverse risk association among young women (OR = 0.70, 95% CI = 0.43–1.16). Oral contraceptive use was associated with increased risk regardless of age. Considering various cutoff points for young age (<40, <45, <50), age-related heterogeneity was greatest when <40 was used.

Conclusions: Among premenopausal AA women, diagnosis before age 40 is associated with more aggressive breast tumor biology and some etiologic differences.

Impact: Modifiable risk factors including breastfeeding, adiposity, and oral contraceptive use may be important targets for mitigating harms of young-onset breast cancer. *Cancer Epidemiol Biomarkers Prev; 26(12); 1722–9. ©2017 AACR.*

Introduction

African American (AA) women have a higher relative frequency of breast cancers with advanced stage, larger size, higher grade, hormone receptor negative, and basal-like subtype compared with white women with breast cancer (1–8). Similar tumor biology is also evident in young-onset (<40 years) breast cancers, which are more common among AA women (1, 9–11). Differences in risk factor profiles for young and older women may reflect distinct etiologies for breast cancers arising in young and AA women. Risk factors such as parity, age at first birth, oral contraceptive use, and obesity have been shown to differentially affect the risk of breast cancer according to age at diagnosis (12–19). These same risk factors are also differentially associated with hormone receptor–positive and –negative disease (16, 17, 20, 21), which may confound observed age-related patterns. However, population-based studies examining whether risk factor associations vary by age at diagnosis among AA women are rare and have been hampered by small sample sizes overall and by age (17, 22, 23). Furthermore, previous studies of young women's breast cancer have used inconsistent definitions of young age, defining young with varying age cutoff points or confounding age

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and menopausal status (17–19, 22–26), complicating comparisons across studies.

This study investigated risk factors for young AA women's breast cancer in the African American Breast Cancer Epidemiology and Risk (AMBER) Consortium, a large collaboration of breast cancer studies among AA women with extensive clinical, molecular, and epidemiologic data. We restricted our analysis to premenopausal women, as previous work has suggested that age and menopausal status may have independent roles in young women's breast cancer (12, 24). Our objectives were 2-fold: first, to characterize the biology of breast cancers diagnosed among young and older premenopausal AA women in the AMBER Consortium, and second, to identify epidemiologic risk factors associated with premenopausal young- versus older-onset breast cancers overall and by estrogen receptor (ER) status. We hypothesized that more aggressive breast tumor characteristics and distinct patterns of breast cancer risk factors would be associated with young-onset breast cancers (<40 years), and that ER status would modify observed risk factor associations by age at diagnosis.

Materials and Methods

Study population

The AMBER Consortium is a collaboration of four of the largest epidemiologic studies of breast cancer among AA women (27). Included are two case–control studies, the Carolina Breast Cancer Study (CBCS; refs. 17, 28) and Women's Circle of Health Study (WCHS; ref. 29), as well as two prospective cohort studies, the Black Women's Health Study (BWHS; ref. 30) and the Multiethnic Cohort Study (MEC; ref. 31). The AMBER Consortium and participating studies have been described in detail previously (27). Briefly, the CBCS recruited breast cancer cases and controls aged 20–74 years across 24–44 North Carolina counties in three phases [phase I: 1993–1996, phase II: 1996–2001, and phase III (cases only): 2008–2013]. The WCHS recruited cases and controls aged 20–75 years in New York (2002–2008) and New Jersey (2006–present). The BWHS enrolled participants ages 21–69 years from 17 continental states in 1995 with biennial follow-up to record changes to exposure history, incident disease, and mortality, and provided nested case–control data comprised of all incident breast cancer cases and up to four matched controls for each case to the Consortium (27). The MEC was not included in this analysis because participants were age 45 and older at enrollment.

This study included premenopausal AA cases diagnosed with invasive breast cancer and matched premenopausal controls from the CBCS (701 cases, 298 controls), WCHS (569 cases, 565 controls), and BWHS (738 cases, 4,281 controls), for a total study population of 2,008 cases and 5,144 controls. All postmenopausal women (defined on the basis of self-reported cessation of menstruation, bilateral oophorectomy, or ovary irradiation), and women with unknown menopausal status were excluded to estimate age effects independent of menopausal status. Each study and the AMBER Consortium collaboration were approved by Institutional Review Boards at participating institutions, and all participants gave written informed consent.

Data collection

The collection of tumor characteristic and risk factor exposure data in the AMBER Consortium has been described previously (27, 32). Briefly, each study contributed paraffin-embedded breast tumor tissue to two core research facilities [the Translational Pathology Lab (TPL) at the University of North Carolina at Chapel Hill (UNC) for the CBCS and the Roswell Park Cancer Institute for the WCHS and BWHS] where tissue microarrays (TMA) were constructed for all available tumor specimens. IHC assays were conducted on all TMAs at UNC's TPL to define expression of estrogen and progesterone receptors (ER/PR) and HER2 (32). Positive expression was defined as ≥1% staining for ER and PR, and ≥10% staining at the 3+ level for HER2 consistent with previous work (32). Breast cancer subtype was defined as four groups based on positivity of three IHC markers: luminal A (ER^+ or PR^+, $HER2^-$), luminal B (ER^+ or PR^+, $HER2^+$), $HER2^+$/ER^- (ER^-, PR^-, $HER2^+$), and triple-negative (ER^-, PR^-, $HER2^-$). For cases with missing IHC-based tumor characteristics, ER, PR, and HER2 data were defined from medical records (representing 60% of ER, 59% of PR, and 73% of HER2 expression data). Cases with both IHC-based and clinical hormone receptor data showed high agreement for the two measures (κ statistic range = 0.68–0.76, concordance range = 88–91%), and IHC-based measures were preferentially selected for inclusion in analyses when available. Tumor grade was centrally reviewed by a study pathologist for 56% of cases, with grade data obtained from medical records for remaining cases (κ statistic = 0.95, concordance = 96% for both grade measures). Other tumor characteristics [including stage (I–IV), lymph node status (positive vs. negative), and estimated tumor size (≤2, 2–4.9, ≥5 cm)] were acquired from medical records.

Risk factor exposure data for cases and controls were obtained via in-home interviews by study staff (CBCS and WCHS) or mailed questionnaire (BWHS), as described previously (27). Participants were asked questions regarding their medical and family histories as well as biologic, anthropometric, reproductive, and lifestyle exposures. For CBCS and WCHS, interviewers also measured body weight, height, and waist and hip circumferences during home interviews; for the BWHS, these measures were self-reported on questionnaires by study participants (33). Questionnaire and interview data from each study were then harmonized by the AMBER Biostatistics and Data Management core to create a central database with consistent exposure definitions across studies. Breast cancer risk factors were categorized as: age at menarche (<13, ≥13 years), parity (nulliparous, 1–2, ≥3 live births), age at first live birth (<25, ≥25 years), age at last live birth (<30, ≥30 years), time since last live birth (<10, ≥10 years), lifetime duration of breastfeeding (never, <3 months, ≥3 months), oral contraceptive use (never, ever), duration (never/<1 year, 1–4 years, ≥5 years) and recency (never, <10 years, ≥10 years), and first-degree family history of breast cancer (no, yes). Body mass index (BMI) was defined as body weight/height (kg/m^2) using categories from the National Heart, Lung, and Blood Institute (<25 normal/underweight, 25.0–29.9 overweight, and ≥30 obese; ref. 34). Waist-to-hip ratio (WHR) was calculated as the ratio of waist/hip circumference (cm) and categorized in tertiles as <0.77, 0.77–0.83, and ≥0.84, consistent with previous work (12).

Statistical analysis

Case–case and case–control analyses were conducted to identify differences in the associations between tumor characteristics and epidemiologic risk factors and breast cancer by age at diagnosis (<40 vs. ≥40 years) among premenopausal AA women (age range 22–59 years). Case–case analyses of tumor characteristics associated with young- versus older-onset disease included all

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cases ($N = 2{,}008$), while case–control analyses of risk factors included all cases and controls except cases from phase III of the CBCS (total N cases = 1,592; N controls = 5,144), as no matched controls were available for phase III. Case–control analyses examined risk factor associations for breast cancer among young and older women overall and further stratified by ER status among young women, in which ER-positive and ER-negative cases were compared separately to all controls. Unconditional logistic regression models were used to estimate adjusted ORs and 95% confidence intervals (CIs) to assess differences in tumor characteristics and breast cancer risk factors associated with breast cancer by age at diagnosis for all analyses. In case–control analyses, effect measure modification by age was evaluated using likelihood ratio tests in which the estimated log-likelihood of the adjusted model was compared with that of the same model including a multiplicative interaction term for age and the corresponding risk factor. Statistically significant modification was assessed using an α-level of 0.1. Heterogeneity in risk factor associations by ER status among young women was assessed by comparing case–case ORs, with ER status defined as the outcome and each risk factor as the explanatory variable. These case–case ORs represent the ratio of case–control ORs for risk factors associated with ER-positive versus ER-negative disease, and statistical significance was defined using an α-level of 0.05. In addition, we conducted sensitivity analyses to examine whether patterns of tumor characteristics and risk factors associated with young- versus older-onset disease were impacted by the cutoff point used to define young age (40, 45, and 50 years). All models controlled for study, diagnosis year, geographic region, and education status to account for differences between studies. Case–control models additionally adjusted for other risk factors that were identified *a priori* via directed acyclic graphs as potential confounders of each risk factor association. Models for age at first live birth, time since last birth, and lifetime breastfeeding duration were restricted to parous women. Statistical significance was defined at an α-level of 0.05. All analyses were performed using SAS software, version 9.4 (SAS Institute, Inc.).

Table 1. Case-case ORs of tumor characteristics by age among premenopausal cases in the AMBER Consortium

Tumor characteristic	≥40 years (ref; $N = 1{,}475$) N (%)	<40 years ($N = 533$) N (%)	OR (95% CI)[a]
Mean age (±SD)	46.2 (±4.3)	34.7 (±3.8)	
Stage			
Stage I	450 (35.8)	116 (24.9)	1.0
Stage II	572 (45.5)	264 (56.8)	1.81 (1.34–2.45)
Stage III/IV	234 (18.6)	85 (18.3)	1.32 (0.90–1.94)
Missing	219	68	
Subtype			
Luminal A	492 (51.4)	157 (43.5)	1.0
Luminal B	150 (15.7)	49 (13.6)	1.37 (0.86–2.17)
$HER2^+/ER^-$	65 (6.8)	29 (8.3)	1.35 (0.77–2.37)
Triple-negative	250 (26.1)	126 (34.9)	1.56 (1.09–2.21)
Missing	518	172	
ER status			
Positive	768 (62.1)	227 (52.1)	1.0
Negative	469 (37.9)	209 (47.9)	1.35 (1.03–1.77)
Missing	238	97	
PR status			
Positive	699 (56.8)	199 (46.2)	1.0
Negative	531 (43.2)	232 (53.8)	1.57 (1.20–2.06)
Missing	245	102	
HER2 status			
Negative	752 (77.5)	286 (78.1)	1.0
Positive	218 (22.5)	80 (21.9)	1.15 (0.81–1.65)
Missing	505	167	
Grade			
Low	144 (12.7)	33 (8.4)	1.0
Moderate	373 (33.0)	117 (29.8)	2.00 (1.11–3.62)
High	613 (54.2)	243 (61.8)	2.17 (1.23–3.85)
Missing	345	140	
Node status			
Negative	486 (53.8)	175 (51.2)	1.0
Positive	418 (46.2)	167 (48.8)	1.13 (0.87–1.47)
Missing	571	191	
Tumor size			
≤2 cm	477 (40.2)	131 (30.6)	1.0
2–4.9 cm	487 (41.0)	206 (48.1)	1.70 (1.28–2.26)
≥5 cm	223 (18.8)	91 (21.3)	1.31 (0.83–2.07)
Missing	288	105	

Abbreviations: ER, estrogen receptor; PR, progesterone receptor.
[a]Adjusted for study site, index year, geographic region, and education status.

Results

Breast tumor biology varies by age at diagnosis among AA women (case–case analyses)

Among premenopausal AA women, young age (<40 years) at breast cancer diagnosis was associated with poorer-prognostic tumor characteristics compared with older age at diagnosis (≥40 years; Table 1). Young women were significantly more likely to have higher stage and triple-negative tumors. While not significant, both luminal B and $HER2^+/ER^-$ tumors were associated with younger age at diagnosis. Young-onset breast cancers were also significantly more likely to be ER and PR negative, with markedly higher grade and larger tumor size. No age associations were observed for lymph node positivity.

Age modifies breast cancer risk-factor associations among AA women (case–control analyses)

To examine whether breast cancers arising among young and older premenopausal AA women are etiologically distinct, we estimated case–control ORs for risk factor associations among premenopausal women stratified by age (Table 2). Age at diagnosis most strongly modified associations with first-degree family history of breast cancer, with a 3-fold increase in risk among young women that was attenuated among older women ($P_{interaction} = 0.005$). Likelihood ratio tests also showed significant age modification for associations with WHR ($P = 0.06$) and breastfeeding duration ($P = 0.1$). Higher WHR was more strongly associated with young- compared with older-onset breast cancer, while breastfeeding, regardless of duration, had a reduced though nonsignificant OR for young- but not older-onset disease. ORs for BMI were not significantly modified by age, though obese BMI (≥30 kg/m^2) was more strongly associated with a reduced association among young women. Associations with parity were not modified by age, though higher parity appeared to increase the odds of disease among young but not older women. Later age at first birth was associated with older-onset but not younger-onset breast cancer, while longer time since last birth appeared to reduce odds of breast cancer for older women. Oral contraceptive use showed similar patterns of association across age groups, with ever and more recent use as well as longer use duration associated with an increased OR among young and older women. Later age at menarche was not associated with young-onset breast cancer but showed a significantly reduced OR for older-onset breast cancer.

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In summary, we observed differences in risk factor patterns by age among premenopausal AA women, with the strongest differences for family history, WHR, and breastfeeding duration.

Given the difference in tumor characteristics observed between young and older-onset breast cancer in AA women, we examined whether breast cancer biology modified the etiologic patterns we

Table 2. Case–control ORs of breast cancer risk factors by age among premenopausal women in the AMBER Consortium

	<40 years ($N = 1,775$)			≥40 years ($N = 4,961$)			
Risk factor	**Controls *N* (%)**	**Cases *N* (%)**	**OR (95% CI)[a]**	**Controls *N* (%)**	**Cases *N* (%)**	**OR (95% CI)[a]**	**$P_{heterogeneity}$[b]**
BMI (kg/m^2)							
<25.0	466 (35.0)	149 (35.1)	1.0	955 (25.4)	283 (24.6)	1.0	0.8
25–29.9	368 (27.7)	119 (28.1)	0.92 (0.66–1.28)	1,172 (31.2)	376 (32.7)	0.99 (0.81–1.21)	
≥30.0	497 (37.3)	156 (36.8)	0.71 (0.51–0.98)	1,628 (43.4)	491 (42.7)	0.91 (0.75–1.10)	
Trend test			$P = 0.0005$			$P = 0.2$	
Missing	16	4		42	14		
WHR							
<0.77	441 (37.5)	104 (26.3)	1.0	1,166 (34.3)	1,166 (34.3)	1.0	0.06
0.77–0.83	341 (29.0)	128 (32.4)	1.14 (0.81–1.59)	952 (28.0)	952 (28.0)	1.02 (0.83–1.25)	
≥0.84	394 (33.5)	163 (41.3)	1.46 (1.04–2.05)	1,285 (37.8)	1,285 (37.8)	1.11 (0.91–1.35)	
Trend test			$P = 0.003$			$P = 0.9$	
Missing	171	33		394	77		
Age at menarche							
<13 years	803 (59.8)	251 (58.6)	1.0	2,038 (53.9)	654 (56.4)	1.0	0.3
≥13 years	540 (40.2)	177 (41.4)	0.97 (0.76–1.24)	1,746 (46.1)	506 (43.6)	0.85 (0.74–0.98)	
Missing	4	0		13	4		
Parity							
Nulliparous	516 (38.3)	111 (26.9)	1.0	872 (23.0)	222 (19.1)	1.0	0.2
1–2 births	644 (47.8)	224 (52.3)	1.19 (0.85–1.66)	2,081 (54.8)	654 (56.2)	1.09 (0.90–1.34)	
≥3 births	187 (13.9)	93 (21.7)	1.26 (0.78–2.03)	844 (22.2)	288 (24.7)	0.97 (0.75–1.25)	
Age at first live birth[c]							
<25 years	481 (59.0)	202 (63.9)	1.0	1,633 (56.9)	547 (58.8)	1.0	0.3
≥25 years	334 (41.0)	114 (36.1)	1.03 (0.74–1.43)	1,238 (43.1)	383 (41.2)	1.18 (0.99–1.41)	
Missing	16			54	12		
Age at last live birth[c]							
<30 years	483 (59.6)	198 (62.9)	1.0	1,436 (50.5)	453 (48.9)	1.0	0.1
≥30 years	327 (40.4)	117 (37.1)	0.89 (0.63–1.25)	1,408 (49.5)	474 (51.1)	1.03 (0.86–1.23)	
Missing	21	2		81	15		
Time since last birth[c]							
<10 years	515 (63.6)	202 (64.1)	1.0	521 (18.3)	183 (19.7)	1.0	0.3
≥10 years	295 (36.4)	113 (35.9)	1.14 (0.82–1.57)	2,323 (81.7)	744 (80.3)	0.86 (0.69–1.07)	
Missing	21	2		81	15		
Breastfeeding duration[c]							
Parous, never	388 (47.7)	177 (56.2)	1.0	1,444 (50.3)	491 (52.7)	1.0	0.1
<3 months	114 (14.0)	30 (9.5)	0.70 (0.43–1.16)	315 (11.0)	96 (10.3)	1.08 (0.82–1.42)	
≥3 months	312 (38.3)	108 (34.3)	0.83 (0.58–1.17)	1,111 (38.7)	344 (37.0)	0.94 (0.78–1.13)	
Missing	17	2		55	11		
Oral contraceptive use							
Never	177 (13.2)	74 (17.3)	1.0	539 (14.2)	232 (20.0)	1.0	0.7
Ever	1,167 (86.8)	354 (82.7)	1.22 (0.86–1.72)	3,254 (85.8)	929 (80.0)	1.18 (0.97–1.44)	
Missing	3	0		4	3		
OC use duration							
Never/<1 year	413 (30.7)	124 (29.0)	1.0	1,296 (35.2)	410 (35.2)	1.0	1.0
1–4 years	473 (35.1)	135 (31.6)	1.13 (0.82–1.55)	1,165 (30.7)	332 (28.5)	1.02 (0.85–1.23)	
≥5 years	460 (34.2)	168 (39.3)	1.42 (1.04–1.93)	1,334 (35.2)	422 (36.3)	1.22 (1.03–1.46)	
Missing	1	1		2	0		
OC use recency							
Never	177 (13.2)	74 (17.3)	1.0	539 (14.2)	232 (20.0)	1.0	0.4
<10 years	840 (62.5)	254 (59.3)	1.16 (0.69–1.95)	1,065 (28.1)	329 (28.3)	1.48 (1.08–2.03)	
≥10 years	327 (24.3)	100 (23.4)	0.90 (0.56–1.47)	2,189 (57.7)	600 (51.7)	1.13 (0.87–1.45)	
Missing	3	0		4	3		
Family history of breast cancer							
No	1,276 (94.7)	363 (84.8)	1.0	3,472 (91.4)	996 (85.6)	1.0	0.005
Yes	71 (5.3)	65 (15.2)	3.10 (2.08–4.63)	325 (8.6)	168 (14.4)	1.57 (1.26–1.94)	

[a]Adjusted for age, study site, index year, geographic location, education level, and confounders, by model. BMI: WHR, parity; WHR: BMI, parity; parity: age at first live birth; age at last live birth: parity, age at first birth; time since last birth: parity, age at first live birth, age at last live birth; breastfeeding duration: BMI, parity, age at first live birth, age at last live birth; oral contraceptive use/duration/recency: parity, age at first live birth, age at last live birth (OC use duration and recency models also adjusted for the other).

[b]Likelihood ratio tests assessed age-related heterogeneity in risk factor associations by comparing the estimated log-likelihood of adjusted models to that of the adjusted model including a multiplicative interaction term for age and the corresponding risk factor (e.g., BMI*age). Statistically significant heterogeneity by age was defined with $\alpha = 0.1$.

[c]Among parous women.

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observed, specifically among young women (Supplementary Table S1). Increased odds of young-onset breast cancer associated with higher WHR was limited to ER-negative disease (OR = 1.64; 95% CI = 0.98–2.75), conversely, higher BMI had a stronger inverse association with ER-positive disease (OR = 0.61; 95% CI = 0.38, 0.98). In addition, family history of breast cancer was positively associated with young-onset disease regardless of ER status, though the association was stronger for ER-negative disease. However, no statistically significant differences by ER status were observed for these or any other risk factor associations that we examined, suggesting that etiologic associations for young-onset breast cancer are not strongly modified by disease subtype.

Age-dependent risk-factor associations are most pronounced with age 40 cutoff point

To examine whether our findings were sensitive to the cutoff point used to define young age, we repeated our analyses of tumor characteristics and risk factors associated with young-onset disease using older cutoff points of 45 and 50 years. We observed the strongest age-related heterogeneity when comparing the youngest women (<40) to women at least 40 years of age. Figure 1 shows ORs and 95% CI for risk of young-onset breast cancer defined as <40, <45, and <50 in our cohort for the three risk factors showing the strongest heterogeneity by age: breastfeeding history (ever/never), WHR (highest/lowest tertile), and family history of breast cancer (yes/no). For all three factors, the associations for young-onset breast cancer were attenuated when defining young women as <45 or <50 at diagnosis.

Discussion

Using data from one of the largest and most comprehensive study of breast cancer biology and epidemiology among AA women to date, the AMBER Consortium, we observed substantial differences in tumor characteristics and some evidence for etiologic heterogeneity of premenopausal young- and older-onset breast cancers. The etiologic associations that vary by age appear not to be driven by differences in ER status, as few associations among young women were modified by ER status. Furthermore, age-dependent heterogeneity of risk factor associations with breast cancer were greatest when comparing the youngest women (<40) to older (≥40) premenopausal women.

The age-related patterns of tumor characteristics we observed are consistent with previous findings (1–8, 10–12, 35), and our work supports the growing hypothesis that breast cancers diagnosed among young women <40 years are biologically distinct from those diagnosed in older women. It is well-established that AA women are more likely to be diagnosed with breast cancer under 40 years of age compared with white women (1, 9–11), highlighting the importance of identifying prevention strategies for young women's breast cancer, particularly for AA women.

Some risk factors for young-onset breast tumors are potentially modifiable. In our study, breastfeeding had a slightly reduced OR for breast cancer in young women, while higher WHR was associated with increased odds of young-onset disease. Both risk factors showed the strongest associations among ER-negative tumors. In contrast, higher BMI showed an inverse association with young-onset disease that was strongest among ER-positive cancers, consistent with previous work (14–17, 33, 36). The observed differences between BMI and WHR underscore these factors as distinct measures of body fatness and suggest that abdominal adiposity, as represented by WHR, is an important factor contributing to young-onset disease (37, 38). Few studies have examined etiologic differences according to age and breast cancer subtype in populations of AA women. Millikan and colleagues (17) and Bertrand and colleagues (25) reported that a lack of breastfeeding and higher WHR were significantly positively associated with young-onset and basal-like (or ER-negative) breast cancers among AA women in the CBCS and BWHS, respectively. Other studies in predominately white populations have observed similar associations (12, 24, 26), suggesting that interventions to improve breastfeeding rates and reduce abdominal adiposity may benefit young women of all races. Given that AA women tend to breastfeed at lower rates and for shorter durations than white women (39) and are more likely to have ER-negative disease, breastfeeding-related interventions may be particularly relevant for reducing risk of young-onset disease among AA women. In addition, oral contraceptive use ≥5 years was

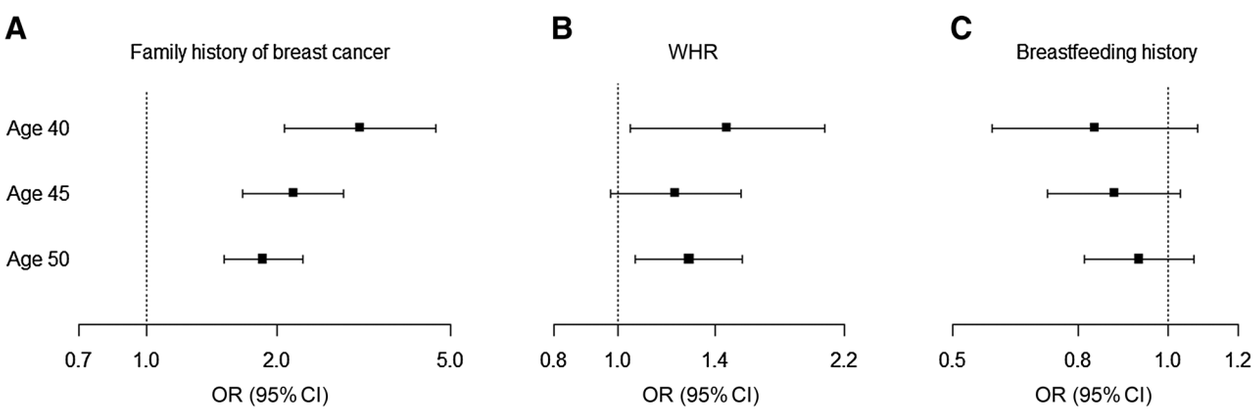

Figure 1.

Impact of age cutpoints on risk factor analyses. Case–control ORs for associations between family history of breast cancer (yes/no; **A**), WHR (highest/lowest tertile; **B**), and breastfeeding history (ever/never; **C**) and premenopausal young-onset breast cancer. Cutoff points defining "young" varied at <40, <45, or <50 years of age. Error bars, 95% CIs.

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associated with significantly increased ORs regardless of age, with a stronger association among young women that did not vary according to ER status. Others have shown similarly increased risk with longer and more recent oral contraceptive use for young and AA women (18, 23, 40–42), highlighting that reduced oral contraceptive use may mitigate breast cancer risk within this demographic.

Several exposures associated with young women's breast cancer are not targetable for prevention. Family history of breast cancer showed the greatest heterogeneity according to age in our study, with a markedly higher OR among young women and a moderately elevated OR for older women. Family history often serves as a surrogate for genetic susceptibility for breast cancer, and other work has shown that women diagnosed with breast cancer at an early age have a greater frequency of genetic mutations related to tumorigenesis (43, 44). However, an individual's family history is variable over time and changes with age; older women are more likely to have a positive family history than young women given that breast cancer risk increases with age. Thus, the attenuated risk associations that we observed among older women may be explained by a stronger contribution of environment (relative to germline genetics) in family history of older women. This also underscores that a positive family history in a young woman is a strong marker of familial/genetic risk.

Reproductive exposures have most consistently shown differential patterns with breast cancer risk by age, as young women are more proximal to reproductive years than older women. In contrast to other studies, we did not observe the expected dual risk associations for parity, in which higher parity is associated with increased risk among young women but reduced risk for older women (13, 45, 46). We observed suggestions of this relationship in that parity was associated with increased risk of breast cancer among young women, though no associations with parity were statistically significant. However, other associations between reproductive factors and breast cancer were consistent with previous work, showing younger age at first live birth and longer time since last birth as protective for older-onset but not young-onset breast cancer (12, 17, 21, 24).

Prior epidemiologic studies of young women's breast cancer have used inconsistent cutoff points to classify young women, ranging from 35 to 50 years of age (12, 17–19, 22–26). Many studies have also included limited representation of young women, as women <40 years of age represent less than 7% of all breast cancers diagnosed in the United States (47). As such, conclusions regarding whether young- and older-onset breast cancers have distinct etiologies have been mixed, and different studies have yielded varied directions and magnitudes of associations for many risk factors. However, reproductive (particularly parity, breastfeeding history, and age at first birth) and body size exposures have consistently shown the strongest differences in patterns of association for young and older women. We identified that varying the age cutoff point in our study population from 40 to 50 years resulted in attenuated effect estimates with increased age for many risk factor associations. In addition, dichotomizing our cohort at age 40 enabled a comparison of younger and older premenopausal women, as we previously showed that age and menopausal status are best considered as separate factors in studies of young women's breast cancer (12). Taken together, our findings suggest that age-dependent heterogeneity in risk factor associations are most pronounced when classifying young women as <40 years.

Our results should be interpreted in light of some limitations. In our study, we did not evaluate underlying genetic or epigenetic factors that may differ according to age, and these factors may have contributed to our observed differences in breast tumor biology and risk associations with family history among young and older women. In addition, differences in breast cancer screening rates and/or adherence between young and older AA women may have influenced some tumor characteristics among young women, although screening data were unavailable in the Consortium. Breast cancers detected via screening tend to have more favorable tumor characteristics than self- or clinically detected tumors (48, 49). However, interval cancers, or those diagnosed between regular screening intervals, are more likely to be aggressive and may be present regardless of screening (50). While screening differences may contribute to differences in observed tumor characteristics, screening is unlikely to have influenced the etiologic associations we described by age and ER status.

In summary, we found strong evidence that breast cancers diagnosed among young AA women have tumor characteristics suggestive of poorer prognosis, underscoring the need for greater understanding of the etiology of young-onset disease. In one of the largest epidemiologic studies of young AA women's breast cancer to date, our findings suggest that potentially modifiable risk factors, such as breastfeeding and adiposity, are associated with young-onset breast cancer, in addition to other nonmodifiable factors such as family and reproductive history.

Disclosure of Potential Conflicts of Interest

C.K. Anders reports receiving commercial research grants from Novartis, Sanofi, Cascadian, Nektar, Tesaro, toBBB, GERON, Angiochem, Merrimack, PUMA, Lily, Merck, and Oncothyreon and is a consultant/advisory board member for Novartis, Sanofi, toBBB, GERON, Angiochem, Merrimack, Lily, Genentech, Nektar, and Kadmon. No potential conflicts of interest were disclosed by the other authors.

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Other (helped with interpretation of data, but did not perform the statistical analysis): C.K. Anders

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Biology and Etiology of Young-Onset Breast Cancers among Premenopausal African American Women: Results from the AMBER Consortium

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