OXFORD

JNCI J Natl Cancer Inst (2015) 107(9): djv172

doi:10.1093/jnci/djv172
First published online June 17, 2015
Article

ARTICLE

Important Role of Menarche in Development of Estrogen Receptor–Negative Breast Cancer in African American Women

Christine B. Ambrosone, Gary Zirpoli, Chi-Chen Hong, Song Yao, Melissa A. Troester, Elisa V. Bandera, Pepper Schedin, Traci N. Bethea, Virginia Borges, Song-Yi Park, Dhyan Chandra, Lynn Rosenberg, Laurence N. Kolonel, Andrew F. Olshan, Julie R. Palmer

Affiliations of authors: Roswell Park Cancer Institute, Buffalo, NY (CBA, GZ, CCH, SY, DC); University of North Carolina Lineberger Cancer Center, Chapel Hill, NC (MAT, AFO); Rutgers Cancer Institute of New Jersey, New Brunswick, NJ (EVB); Oregon Health & Science University, Portland, OR (PS); Slone Epidemiology Center at Boston University, Boston, MA (TNB, LR, JRP); University of Colorado Denver School of Medicine, Denver, CO (VB); University of Hawaii Cancer Center, Honolulu, HI (SYP, LNK).

Correspondence to: Christine B. Ambrosone, PhD, Department of Cancer Prevention and Control, Roswell Park Cancer Institute, Elm and Carlton Sts, Buffalo, NY 14263 (e-mail: christine.ambrosone@roswellpark.org).

Abstract

Background: Menarche is a critical time point for diverging fates of mammary cells of origin. African American women have young age at menarche, which could be associated with their high rates of estrogen receptor–negative (ER-) breast cancer.

Methods: In the AMBER Consortium, using harmonized data from 4426 African American women with breast cancer and 17 474 controls, we used polytomous logistic regression to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for ages at menarche and first live birth (FLB), and the interval between, in relation to ER+ and ER- breast cancer. All statistical tests were two-sided.

Results: Risk of ER- breast cancer was reduced with later age at menarche among both parous and nulliparous women (≥15 vs <11 years OR = 0.62, 95% CI = 0.48 to 0.81 and OR = 0.56, 95% CI = 0.29 to 1.10, respectively), with no effect of age at FLB. For ER+ breast cancer, the inverse association was weaker among nulliparous women. While longer intervals between menarche and FLB were associated with increased risk of ER+ breast cancer in a dose-response fashion (OR for 20 year interval = 1.39, 95% CI = 1.08 to 1.79, P_{trend} = .003), ER- risk was only increased for intervals up to 14 years and not beyond (P_{trend} = .33).

Conclusions: While ER- breast cancer risk was markedly reduced in women with a late age at menarche, there was not a clear pattern of increased risk with longer interval between menarche and FLB, as was observed for ER+ breast cancer. These findings indicate that etiologic pathways involving adolescence and pregnancy may differ for ER- and ER+ breast cancer.

Burgeoning understanding of the heterogeneous nature of breast cancer, and the growing literature suggesting that etiologic pathways differ between specific breast cancer subtypes, has prompted examination of risk relationships separately by subtypes, characterized by estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor 2 (HER2). Because ER-negative (ER-) and triple-negative (ER-, PR-, HER2-) breast cancers are more common in African American women

Received: February 9, 2015; **Revised:** April 21, 2015; **Accepted:** May 22, 2015

than in other groups in the United States, we formed the AMBER Consortium (1) in order to have the critical statistical power to examine risk factors for breast cancer subtypes among African American women.

As summarized by Palmer and colleagues (2), we and others have found that associations between parity, breastfeeding, and breast cancer differ according to ER status, with parity associated with reduced risk of ER+ breast cancer but increased risk of ER- disease, a difference in etiology that appears to be ameliorated by breastfeeding. However, less is known regarding timing of menarche and first live birth (FLB) and if they differentially affect breast cancer risk according to ER status. In the few studies that have investigated potential associations by subgroups, the results have not been consistent, perhaps because of the low prevalence of ER- tumors, resulting in small numbers (reviewed in [3]). Because African American girls have earlier pubertal onset and menarche than Americans of European descent (4–6) and also tend to have children at a younger age (7), the relevance of these exposures to development of ER- and triple-negative breast cancer among African American women merits investigation. Here we examined associations between breast cancer subgroups and age at menarche, age at FLB, and the interval between those events, hypothesizing that these factors could play a role in the higher proportion of ER- breast cancer among African American women.

Methods

Study Population

Investigators from the Black Women's Health Study (BWHS) (8), Multiethnic Cohort Study (MEC) (9), Carolina Breast Cancer Study (CBCS) (10), and Women's Circle of Health Study (WCHS) (11,12) formed the AMBER consortium (1) in 2011, with a goal to merge epidemiological data and information on hormone receptor status, as well as to collect tumor blocks, for later identification of breast cancer–intrinsic subtypes to identify risk factors for more aggressive disease. Both BWHS and MEC are prospective cohort studies with participants enrolled by mailed questionnaires and followed with biennial (BWHS) and five-year interval (MEC) follow-up questionnaires. BWHS enrolled participants across the United States, and the MEC includes women from Hawaii and Southern California. CBCS and WCHS are both case-control studies, with CBCS 1 and 2 conducted with population-based sampling and in-person interviews from 1993 to 2001 in 24 counties in North Carolina. WCHS, initiated in 2002 in metropolitan New York City and several counties in eastern New Jersey, is still ongoing. Controls were frequency-matched on age, race, and area of residence. For CBCS, controls younger than age 65 years were identified from Division of Motor Vehicles lists and Health Care Financing Administration (CMS) lists for older women. In WCHS, controls were identified using random digit dialing and also recruited from the community (12). Each study obtained informed consent from its participants and was approved by the relevant institutional review boards. For these analyses, we included women who self-reported as African American or were diagnosed with invasive cancer (n = 3747) or ductal carcinoma in situ (DCIS; n = 679), confirmed by pathology reports or registry records from which we also obtained data on ER, PR, and HER2. Of the 5858 potential cases, ER status was available for 4426 women (2962 ER+, 1464 ER-) at the time of analysis. In total, there were 17 474 controls; BWHS and MEC controls were frequency-matched to cases on year of birth and completion of follow-up questionnaire.

Statistical Analyses

With the establishment of the consortium, data were harmonized for key variables that were consistent across all studies. For this analysis, we included merged data on age at menarche and age at FLB, as well as variables for inclusion in multivariable models. BWHS, WCHS, and CBCS data on age at menarche and FLB were continuous; MEC data were categorical. Thus, data from all four studies were grouped according to MEC categories. Because the time between menarche and FLB, which leads to differentiation of ductal cells (13), may be the time of greatest susceptibility to DNA damage, we also calculated the length of this interval. MEC data were excluded when evaluating the computed variable combining both age at menarche and FLB, because the MEC data were categorical. In an effort to better understand how parity could affect associations between age at menarche and risk of breast cancer subtypes, we also evaluated associations between risk and age at menarche, stratifying by whether or not participants had experienced a live birth (parous, nulliparous). Polytomous logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for associations with ER+ and ER- breast cancer in comparison with all controls, and unconditional logistic regression for triple-negative breast cancer vs all controls. All AMBER analyses a priori control for age (five-year categories), study, geographic region (New Jersey, Northeast excluding New Jersey, South, Midwest, and West) and time period (1993–1998, 1999–2005, and 2006–2013). We considered potential confounders for inclusion in multivariable models based on change in effect estimates, conservatively set at 5%, which is associated with low risk of introducing bias into the exposure coefficient (14,15). To maximize precision in estimated exposure effects in our full models, we also included strong predictors of breast cancer risk (14). Variables included in final models were education, family history of breast cancer, number of children, body mass index at age 20 years, menopausal status, and, among postmenopausal women, age at menopause. Trend tests were conducted using the median value in each category, and saturated tests were used for nonlinear variables. All analyses were performed using SAS 9.4 statistical software (SAS Institute Inc., Cary, NC). A P value of less than .05 was considered statistically significant, and all statistical tests were two-sided.

Results

Tumor characteristics and variables relevant for these analyses are shown in Table 1 for AMBER overall and for each of the contributing studies. ER- breast cancer was more prevalent in CBCS, because of the intentional oversampling of younger cases. Conversely, MEC has an older population and higher prevalence of ER+ disease. Distributions of age at menarche were similar across studies, but there were more women with earlier age at FLB in CBCS. Overall distributions of key characteristics of the study population according to case-control status are shown in Supplementary Table 1 (available online). Data for ER, PR, and HER2 were not available for all AMBER participants; missing data by study and by region for invasive cancer as well as DCIS are shown in Table 1 and Supplementary Table 2 (available online). In AMBER, 24.5% were missing data on ER status and 28.4% were missing for PR. HER2 testing did not become routine until well after 2001, and 51.3% of the cases from AMBER do not have HER2 results. Therefore, data for triple-negative status were available for approximately half of AMBER (n = 2669) (Supplementary Table 3, available online).

Table 1. Characteristics of cases and controls by study in the AMBER Consortium*

	BWHS		CBCS		MEC		WCHS		AMBER	
Characteristic	Cases No. (%)	Controls No. (%)	Cases No. (%)	Controls No. (%)	Cases No. (%)	Controls No. (%)	Cases No. (%)	Controls No. (%)	Cases No. (%)	Controls No. (%)
Total	1638	10 801	806	788	955	4664	1027	1221	4426	17 474
HR status										
ER+	1113 (67.9)		405 (50.2)		705 (73.8)		739 (72.0)		2962 (66.9)	
ER-	525 (32.1)		401 (49.8)		250 (26.2)		288 (28.0)		1464 (33.1)	
Missing	758 (31.6)		88 (9.8)		207 (17.8)		379 (27.0)		1432 (24.5)	
ER-, PR-, HER2-	176 (21.9)		233 (38.0)		98 (20.7)		171 (22.0)		678 (25.4)	
All others	627 (78.1)		381 (62.0)		375 (79.3)		608 (78.0)		1991 (74.6)	
Missing	1593 (66.5)		280 (31.3)		689 (59.3)		627 (44.6)		3189 (54.4)	
Age at diagnosis, y										
<40	107 (6.5)		129 (16.0)		0		122 (11.9)		358 (8.1)	
40–49	466 (28.4)		264 (32.8)		11 (1.2)		275 (26.8)		1016 (23.0)	
50–59	557 (34.0)		190 (23.6)		126 (13.2)		358 (34.9)		1231 (27.8)	
≥60	508 (31.0)		223 (27.7)		818 (85.7)		272 (26.5)		1821 (41.1)	
Age at menarche, y										
<11	195 (11.9)	1197 (11.1)	81 (10.1)	66 (8.4)	78 (8.3)	341 (7.5)	128 (12.5)	140 (11.5)	482 (11.0)	1744 (10.1)
11–12	761 (46.6)	4674 (43.4)	337 (41.9)	311 (39.6)	398 (42.5)	1855 (40.7)	407 (39.6)	479 (39.3)	1903 (43.3)	7319 (42.2)
13–14	552 (33.8)	3805 (35.4)	280 (34.8)	294 (37.5)	361 (38.5)	1721 (37.7)	364 (35.4)	437 (35.8)	1557 (35.4)	6257 (36.1)
≥15	124 (7.6)	1083 (10.1)	106 (13.2)	114 (14.5)	100 (10.7)	644 (14.1)	128 (12.5)	164 (13.4)	458 (10.4)	2005 (11.6)
Age at first live birth, y										
<18	164 (12.9)	1213 (14.7)	193 (28.1)	178 (25.5)	139 (17.4)	774 (20.1)	164 (19.0)	206 (20.1)	660 (18.2)	2371 (17.2)
18–19	221 (17.3)	1414 (17.2)	147 (21.4)	170 (24.3)	259 (32.4)	1352 (35.1)	168 (19.5)	197 (19.2)	795 (21.9)	3133 (22.7)
20–24	400 (31.4)	2883 (35.0)	211 (30.7)	216 (30.9)	266 (33.3)	1132 (29.4)	258 (29.9)	302 (29.5)	1135 (31.3)	4533 (32.8)
25–29	300 (23.5)	1598 (19.4)	83 (12.1)	82 (11.7)	94 (11.8)	389 (10.1)	149 (17.3)	157 (15.3)	626 (17.3)	2226 (16.1)
≥30	189 (14.8)	1122 (13.6)	53 (7.7)	53 (7.6)	42 (5.3)	204 (5.3)	124 (14.4)	163 (15.9)	408 (11.3)	1542 (11.2)
Interval between menarche and FLB, y										
<5	128 (10.6)	1065 (13.6)	169 (26.2)	173 (25.9)			139 (17.1)	193 (20.2)	436 (16.3)	1431 (15.1)
5–9	452 (37.3)	2994 (38.3)	290 (45.0)	312 (46.7)			320 (39.5)	358 (37.4)	1062 (39.8)	3664 (38.8)
10–14	313 (25.8)	1970 (25.2)	106 (16.4)	101 (15.1)			174 (21.5)	186 (19.5)	593 (22.2)	2257 (23.9)
15–19	179 (14.8)	1092 (14.0)	52 (8.1)	46 (6.9)			102 (12.6)	112 (11.7)	333 (12.5)	1250 (13.2)
≥20	140 (11.6)	701 (9.0)	28 (4.3)	36 (5.4)			76 (9.4)	107 (11.2)	244 (9.1)	844 (8.9)

* BWHS = Black Women's Health Study; CBCS = Carolina Breast Cancer Study; ER = estrogen receptor; FLB = first live birth; HER2 = human epidermal growth factor receptor 2; MEC = Multiethnic Cohort Study; PR = progesterone receptor; WCHS = Women's Circle of Health Study.

Results from fully adjusted logistic regression analyses for reproductive variables are shown in Table 2. Compared with women with menarche before age 11, later age at menarche (15 years of age and older) was associated with reduced risk of both ER+ (OR = 0.74, 95% CI = 0.61 to 0.89, P_{trend} < .001) and ER- breast cancer (OR = 0.62, 95% CI = 0.49 to 0.80, P_{trend} < .001). Later age at menarche (≥15 years) was also associated with reduced risk of triple-negative breast cancer (OR = 0.70, 95% CI = 0.49 to 1.01, P_{trend} = .03).

When examining associations between age at FLB and breast cancer subtypes with FLB of 18 years of age or younger as the referent (Table 2), there was a suggestion of increased risk of ER+ disease with FLB at 25 to 29 years of age (OR = 1.21, 95% CI = 1.02 to 1.44), with no association observed for FLB of age 30 years or older (OR = 1.07, 95% CI = 0.88 to 1.30, P_{trend} = .03). Results were similar for ER- breast cancer (OR = 1.17, 95% CI = 0.93 to 1.47 for FLB at age 25–29 years) and no evidence of an association with later age at FLB.

We also evaluated the interval between menarche and FLB in relation to breast cancer subgroups (Table 2). Longer intervals were associated with increased risk of ER+ breast cancer, with an odds ratio of 1.39 (95% CI = 1.08 to 1.79, P_{trend} = .003) for 20 years or longer, compared with women with less than five years between menarche and FLB. For ER- breast cancer, there were no statistically significant trends of increased risk with increasing length of interval (P_{trend} = .33), although odds ratios were above 1.0 for every category, with the greatest risk at 10 to 14 years (OR = 1.40, 95% CI = 1.10 to 1.80). An increased risk of triple-negative disease was observed for intervals of five to 14 years, but not for longer intervals. Because breastfeeding has been shown to reduce risk associated with parity among women with ER- breast cancer, we further evaluated associations with longer intervals according to breastfeeding (ever/never). Stratification by breastfeeding showed higher risk of both ER+ and ER- breast cancer with longer intervals among women who never breastfed (Supplementary Table 4, available online). Increases in risk for women with ER+ breast cancer were attenuated and became statistically nonsignificant among women who breastfed, and odds ratios for ER- breast cancer among women who breastfed were lower than for those who did not.

Because of the overall importance of interval for ER+ but not ER- breast cancer, we next evaluated associations with age at menarche stratified by parity, because parity is strongly associated with reduced risk of ER+ cancers. As shown in Table 3, among women who had given birth, later menarche was associated with reduced risk of ER+ disease (P_{trend} ≤ .001), particularly for those with menarche at age 15 years or older (OR = 0.70, 95% CI = 0.56 to 0.86). However, among nulliparous women, there were weak, if any, associations between age at menarche and risk of ER+ breast cancer, with odds ratios for each age at menarche category close to unity. In contrast to findings for ER+ breast cancer of reduced risk with later age at menarche among parous but not nulliparous women, later age at menarche (≥15 years) was associated with reduced risk of ER- breast cancer among both parous (OR = 0.62, 95% CI = 0.48 to 0.81) and nulliparous (OR = 0.56, 95% CI = 0.29 to 1.10) women. Menarche at age 13 years or older was also associated with reduced risk of triple-negative breast cancer among parous women (OR = 0.81, 95% CI = 0.59 to 1.11 for 13- to 14-year-olds; OR = 0.74, 95% CI = 0.50 to 1.10 for ≥15-year-olds, P_{trend} = .03); there were few nulliparous women with triple-negative breast cancer, and estimates were unstable.

When we limited analyses to only women with invasive breast cancer, excluding those with DCIS, risk estimates were

Table 2. Ages at menarche and first live birth and the interval between, in relation to breast cancer subgroups in the AMBER Consortium

Characteristic	Controls No. (%)	ER+		ER-		ER-, PR-, HER2-	
		No. (%)	OR (95% CI)*	No. (%)	OR (95% CI)*	No. (%)	OR (95% CI)*
Age at menarche, y							
<11	1744 (10.1)	306 (10.4)	1.00 (Ref)	176 (12.1)	1.00 (Ref)	74 (11.0)	1.00 (Ref)
11–12	7319 (42.2)	1274 (43.3)	.99 (.86 to 1.15)	629 (43.1)	.84 (.70 to 1.02)	297 (44.0)	.95 (.72 to 1.26)
13–14	6257 (36.1)	1056 (35.9)	.88 (.76 to 1.03)	501 (34.3)	.75 (.62 to .91)	233 (34.5)	.82 (.61 to 1.10)
≥15	2005 (11.6)	305 (10.4)	.74 (.61 to .89)	153 (10.5)	.62 (.49 to .80)	71 (10.5)	.70 (.49 to 1.01)
P†			<.001		.001		.10
P_{trend}			<.001		<.001		.03
Age at FLB, y							
≤18	2371 (17.2)	427 (18.0)	1.00 (Ref)	233 (18.7)	1.00 (Ref)	114 (19.6)	1.00 (Ref)
18–19	3133 (22.7)	517 (21.7)	.97 (.83 to 1.13)	278 (22.3)	1.02 (.83 to 1.24)	134 (23.1)	1.01 (.76 to 1.35)
20–24	4533 (32.8)	722 (30.4)	.93 (.81 to 1.08)	413 (33.1)	1.08 (.89 to 1.31)	204 (35.1)	1.15 (.88 to 1.50)
25–29	2226 (16.1)	426 (17.9)	1.21 (1.02 to 1.44)	200 (16.1)	1.17 (.93 to 1.47)	82 (14.1)	1.06 (.76 to 1.49)
≥30	1542 (11.2)	286 (12.0)	1.07 (.88 to 1.30)	122 (9.8)	.96 (.73 to 1.26)	47 (8.1)	.78 (.52 to 1.17)
P†			.01		.44		.29
P_{trend}			.03		.60		.53
Interval between menarche and FLB, y							
<5	1431 (15.1)	278 (16.3)	1.00 (Ref)	158 (16.3)	1.00 (Ref)	87 (18.4)	1.00 (Ref)
5–9	3664 (38.8)	652 (38.3)	1.05 (.89 to 1.25)	410 (42.4)	1.23 (1.00 to 1.53)	211 (44.5)	1.22 (.91 to 1.62)
10–14	2257 (23.9)	370 (21.8)	1.14 (.94 to 1.39)	223 (23.1)	1.40 (1.10 to 1.80)	110 (23.2)	1.48 (1.06 to 2.08)
15–19	1250 (13.2)	223 (13.1)	1.26 (1.01 to 1.58)	110 (11.4)	1.28 (.95 to 1.72)	41 (8.6)	.97 (.62 to 1.51)
≥20	844 (8.9)	178 (10.5)	1.39 (1.08 to 1.79)	66 (6.8)	1.12 (.79 to 1.58)	25 (5.3)	.84 (.50 to 1.41)
P†			.05		.04		.03
P_{trend}			.003		.33		.61

* Odds ratio and 95% confidence interval adjusted for age, study, time period, geographic region, education, family history of breast cancer, parity, menopausal status/age at menopause, and body mass index at age 20 years. ER = estrogen receptor; FLB = first live birth; HER2 = human epidermal growth factor receptor 2; OR = odds ratio; PR = progesterone receptor.

† *P* values calculated using a two-sided Wald test.

ARTICLE

Table 3. Associations of age at menarche with breast cancer subgroups according to parity in the AMBER Consortium

Characteristic	Controls No. (%)	ER+		ER-		ER-, PR-, HER2-	
		No. (%)	OR (95% CI)*	No. (%)	OR (95% CI)*	No. (%)	OR (95% CI)*
Age at menarche among parous women†, y							
<11	1340 (9.6)	243 (10.1)	1.00 (Ref)	143 (11.4)	1.00 (Ref)	59 (10.1)	1.00 (Ref)
11–12	5835 (41.7)	1030 (42.9)	.97 (.82 to 1.14)	543 (43.4)	.85 (.69 to 1.04)	264 (45.1)	1.00 (.73 to 1.36)
13–14	5143 (36.8)	878 (36.6)	.86 (.73 to 1.02)	431 (34.5)	.73 (.59 to .90)	199 (34.0)	.81 (.59 to 1.11)
≥15	1674 (12.0)	250 (10.4)	.70 (.56 to .86)	133 (10.6)	.62 (.48 to .81)	64 (10.9)	.74 (.50 to 1.10)
P*			<.001		.002		.09
P_{trend}			<.001		<.001		.03
Age at menarche among nulliparous women, y							
<11	400 (12.3)	63 (11.9)	1.00 (ref)	31 (15.3)	1.00 (Ref)	14 (16.1)	1.00 (Ref)
11–12	1455 (44.7)	242 (45.7)	1.07 (.77 to 1.47)	86 (42.4)	.83 (.53 to 1.33)	33 (37.9)	.76 (.37 to 1.55)
13–14	1083 (33.2)	170 (32.1)	.92 (.65 to 1.29)	68 (33.5)	.87 (.54 to 1.41)	33 (37.9)	1.00 (.49 to 2.06)
≥15	320 (9.8)	55 (10.4)	.91 (.59 to 1.40)	18 (8.9)	.56 (.29 to 1.10)	7 (8.0)	.38 (.13 to 1.12)
Pǂ			.62		.37		.22
P_{trend}			.54		.29		.35

* Odds ratio and 95% confidence interval adjusted for age, study, time period, geographic region, education, family history of breast cancer, parity, menopausal status/age at menopause, and body mass index at age 20 years. ER = estrogen receptor; HER2 = human epidermal growth factor receptor 2; OR = odds ratio; PR = progesterone receptor.

† Additionally adjusted for number of children.

ǂ P values calculated using a two-sided Wald test.

essentially unchanged (data not shown). We also performed analyses stratified by menopausal status. For age at menarche, results for ER- breast cancer were similar in both premenopausal and postmenopausal breast cancer, with reduced risk with later age at menarche in both groups. For the other reproductive variables, some results were stronger or weaker in either premenopausal or postmenopausal women, but, for the most part, trends remained the same in both groups as they did in the overall population (data not shown).

Discussion

In this analysis in the AMBER consortium with more than 4000 African American women with breast cancer with available data on hormone receptors and more than 17 000 controls, we noted apparent differences by ER status in risk relationships with age at menarche, parity, and the time span between menarche and FLB. Although later age at menarche was associated with reduced risk of both ER+ and ER- breast cancer, for ER- cancer the association was observed in both parous and nulliparous women. Relationships were weaker in nulliparous women for ER+ cancer. In addition, length of interval between menarche and first birth was more strongly associated with reduced risk of ER+ than ER- breast cancer.

There are few reports in the literature of breast cancer in African American women with adequate sample size to be able to assess associations between risk factors according to ER status. The Nashville Breast Health Study recently reported that there were no associations with age at menarche for either ER+ or ER- breast cancer among African Americans (16), but to date there are only 386 African American cases in that study, 125 with ER- breast cancer. In our earlier analysis of data from the larger WCHS (3), which included both European American and African American women, later age at menarche was more strongly associated with reduced risk of ER- breast cancer than ER+ disease among African American women (3). However, there were no clear differences in associations between age at menarche and breast cancer among European American women by ER status, consistent with some other studies in non-African American populations (see review by Anderson et al. [17]). Thus, it is unclear if findings from this study can be generalized to non-African American women.

Although there were no clear trends with risk associated with age at FLB for ER+ or ER- breast cancer in our data, there were marked differences when we evaluated the time spans between menarche and FLB. There appears to be a clear dose-response association with time interval for ER+ breast cancer, but not for ER- disease. The observed increases in risk of ER+ breast cancer with increasing intervals of time are consistent with the breast tissue age model proposed by Pike et al. (18), which posits that the aging of breast tissue begins at menarche and continues at a constant rate until the first childbirth. It has been hypothesized that the terminal end buds of the breast ducts are not fully differentiated until a full-term pregnancy occurs, and experimental rodent data show that undifferentiated ductal cells are highly susceptible to the effects of carcinogens and DNA damage (13). This model of carcinogenesis could explain the associations observed with longer intervals between menarche and FLB and ER+ breast cancer. This may also be relevant for our observation that later age at menarche was associated with reduced risk of ER+ breast cancer only among parous women; later age at menarche had no effect on risk without a full-term pregnancy, supporting the mechanism of the importance of a live birth upon cell differentiation and risk of breast cancer.

Results for associations between ER- breast cancer and the length of time from menarche to FLB did not show similar patterns of dose response as those for ER+ disease, which led us to question if there were differential associations between menarche and parity according to ER status. When examining associations between age at menarche and risk of ER- breast cancer stratified by parity, there were no differences in the protective effects of later age at menarche according to whether or not a woman had given birth, again supporting the notion that age at menarche is a critical event in the development of ER- breast cancer, regardless of parity. This is in contrast to the observation that ER+ tumors are more influenced by the duration between menarche and FLB, with weaker evidence of an association among nulliparous women, suggesting that the origins of ER- vs ER+ breast cancer at the cellular and molecular level may be different.

In a recent provocative commentary, Anderson and colleagues (19) draw attention to a distinction between classifications of breast cancer into subtypes for etiology, eg, with a common set of causes, rather than for clinical prognosis, and propose that there are basically two etiologic subtypes to consider, with bimodal peak frequencies at age 50 and 70 years, similar to Pike's model (18). This coincides with the previous recognition that earlier (premenopausal) and later (postmenopausal) breast cancer could have differing etiologies, with premenopausal cancers more likely to be ER- and postmenopausal tumors ER+ (20,21). Anderson and colleagues propose that there are two distinct etiologic classes that arise from two main cell types of origin, luminal and basal/myoepithelial, with the latter occurring at an earlier age. However, it is not clear if ER+ and ER- tumors do derive from distinct classes of cells, as there is some evidence that both may derive from a common luminal progenitor cell population origin, with subsequent differentiation to ER+ or ER- cells, perhaps influenced by different hormonal environments during key windows of susceptibility (22,23).

Our findings support both of these paradigms of etiologic heterogeneity, with indications that menarche alone may be a critical event for the development of ER- breast cancer, vs the importance of time between menarche and reproduction to ER+ disease. These epidemiologic findings, viewed in the context of tumor heterogeneity as a reflection of differing cells of origin (24), could suggest that ER- breast cancer arises from a cell population that is exquisitely sensitive during puberty. It is clear from data from survivors of atomic bombings in Japan in World War II that exposure to ionizing radiation during adolescence, not adulthood, led to subsequent breast cancer, similar to breast cancer following radiation to the chest for Hodgkin's disease in young adults (25,26). Importantly, breast cancers arising from childhood treatment with radiation tend to be ER- and/or triple-negative and also to have more aggressive characteristics (27). Investigating mechanisms behind this phenomenon, Barcellos-Hoff's group showed with computational modeling and mouse studies that irradiation during puberty increases stem cell self-renewal and increases susceptibility to developing ER- breast cancer (28). Exposures other than ionizing radiation may similarly affect stem cells during puberty, thus underlying the importance of age at menarche in the etiology of ER- breast cancer in African American women.

These analyses are from the largest study of breast cancer in African American women, with rich epidemiological data and information on breast cancer subgroups, and including women from across the United States. Women in the cohort studies, for the most part, have higher education and higher socioeconomic status, whereas the case-control studies include women who have lower education levels and are from both the South (largely rural) and the northeast (primarily urban). Thus, we believe that findings from AMBER are generalizable to most African American women in the United States. It is unclear if results can be generalizable to non-African American women in the United States. Results may be more pronounced in African American women because they do tend to have earlier menarche and because ER- breast cancer is more common.

One limitation, however, is that there is incomplete data on receptor status. CBCS has the least amount of missing data because of collection of tumor blocks and immunohistochemistry performed in their laboratories. Because new cases are ascertained in MEC and BWHS and WCHS is still in the field, there is also a lag in receipt of pathology reports and tumor blocks for existing cases. Furthermore, the numbers of women with triple-negative breast cancer are relatively small, because of the fact that HER2 testing was not standard until well into the last decade. Thus, results for triple-negative breast cancer remain inconclusive. However, we do not believe that there would be any major systematic bias in missing ER status on approximately 25% of the cases, as it is across studies (reflected by regions) and across hospitals. Furthermore, findings were similar when DCIS cases, who are most likely to have missing data on receptors, were excluded.

Our findings add further evidence to the growing knowledge that there are distinct etiologic pathways for ER- and ER+ breast cancer and underscore that these differences likely begin at a very early age. There is growing understanding of factors that affect ages at puberty and menarche, such as early life obesity, which may be modifiable. Moreover, these results lend insight into mechanisms of diverging pathways of carcinogenesis, and, coupled with basic science findings from research investigating cells of origin in breast cancer development, could help to unravel the underlying complexities leading to ER- breast cancer. African American women are more likely to experience earlier menarche than European American women, and age at menarche has been declining in the United States in recent times, with the greatest declines observed among African American girls (29,30). Our findings from this study with more than 1450 African American women with ER- breast cancer provide a link between the early age at menarche in African American girls and the higher prevalence of ER- breast cancer in African American women. Translational studies merging findings from the laboratory and population sciences are needed to continue to understand the etiology of ER- breast cancer, particularly among African American women.

Funding

This research was funded by National Institutes of Health: P01 CA151135 (to CBA, JRP, and AFO), R01 CA058420 (to JRP and LR), UM1 CA164974 (to JRP and LR), R01 CA100598 (to CBA), UM1 CA164973 (to LNK), R01 CA54281 (to LNK), P50 CA58223, U01 ESO19472 (to MAT); the Breast Cancer Research Foundation (to CBA); and the University Cancer Research Fund of North Carolina.

Notes

The funding agencies had no role in the design and conduct of the study, the collection, management, analysis, or interpretation of the data, the preparation, review, or approval of the manuscript, nor the decision to submit the manuscript for publication.

Acknowledgements: We thank participants and staff of the contributing studies. We wish also to acknowledge the late Robert Millikan, DVM, MPH, PhD, who was instrumental in the creation of this consortium. Pathology data were obtained from numerous state cancer registries (Arizona, California, Colorado, Connecticut, Delaware, District of Columbia, Florida, Georgia, Hawaii, Illinois, Indiana, Kentucky, Louisiana, Maryland, Massachusetts, Michigan, New Jersey, New York, North Carolina, Oklahoma, Pennsylvania, South Carolina, Tennessee, Texas, Virginia).

References

1. Palmer JR, Ambrosone CB, Olshan AF. A collaborative study of the etiology of breast cancer subtypes in African American women: the AMBER consortium. *Cancer Causes Control*. 2014;25(3):309–319.

2. Palmer JR, Viscidi E, Troester MA, et al. Parity, lactation, and breast cancer subtypes in African American women: results from the AMBER Consortium. *J Natl Cancer Inst*. 2014;106(10):dju237 doi:10.1093/jnci/dju237.
3. Ambrosone CB, Zirpoli GR, Bovbjerg DH, et al. Associations between estrogen receptor-negative breast cancer and timing of reproductive events differ between African American and European American women. *Cancer Epidemiol Biomarkers Prev*. 2014;23(6):1115–1120.
4. Herman-Giddens ME, Slora EJ, Wasserman RC, et al. Secondary sexual characteristics and menses in young girls seen in office practice: a study from the Pediatric Research in Office Settings network. *Pediatrics*. 1997;99(4):505–512.
5. Chumlea WC, Schubert CM, Roche AF, et al. Age at menarche and racial comparisons in US girls. *Pediatrics*. 2003;111(1):110–113.
6. Biro FM, Greenspan LC, Galvez MP, et al. Onset of breast development in a longitudinal cohort. *Pediatrics*. 2013; 132(6):1019–1027..
7. Martin JA, Hamilton BE, Osterman MJ, et al. Births: final data for 2013. *Natl Vital Stat Rep*. 2015;64(1):1–65.
8. Rosenberg L, Adams-Campbell L, Palmer JR. The Black Women's Health Study: a follow-up study for causes and preventions of illness. *J Am Med Womens Assoc*. 1995;50(2):56–58.
9. Kolonel LN, Henderson BE, Hankin JH, et al. A multiethnic cohort in Hawaii and Los Angeles: baseline characteristics. *Am J Epidemiol*. 2000;151(4):346–357.
10. Newman B, Moorman PG, Millikan R, et al. The Carolina Breast Cancer Study: integrating population-based epidemiology and molecular biology. *Breast Cancer Res Treat*. 1995;35(1):51–60.
11. Ambrosone CB, Ciupak GL, Bandera EV, et al. Conducting molecular epidemiological research in the age of HIPAA: a multi-institutional case-control study of breast cancer in African-American and European-American women. *J Oncol*. 2009;2009:871250.
12. Bandera EV, Chandran U, Zirpoli G, et al. Rethinking sources of representative controls for the conduct of case-control studies in minority populations. *BMC Med Res Methodol*. 2013;13:71.
13. Russo J, Tay LK, Russo IH. Differentiation of the mammary gland and susceptibility to carcinogenesis. *Breast Cancer Res Treat*. 1982;2(1):5–73.
14. Budtz-Jorgensen E, Keiding N, Grandjean P, et al. Confounder selection in environmental epidemiology: assessment of health effects of prenatal mercury exposure. *Ann Epidemiol*. 2007;17(1):27–35.
15. Lee PH. Should we adjust for a confounder if empirical and theoretical criteria yield contradictory results? A simulation study. *Sci Rep*. 2014;4:6085.
16. Cui Y, Deming-Halverson SL, Shrubsole MJ, et al. Associations of hormone-related factors with breast cancer risk according to hormone receptor status among white and African American women. *Clin Breast Cancer*. 2014;14(6):417–425.
17. Anderson KN, Schwab RB, Martinez ME. Reproductive risk factors and breast cancer subtypes: a review of the literature. *Breast Cancer Res Treat*. 2014;144(1):1–10.
18. Pike MC, Krailo MD, Henderson BE, et al. 'Hormonal' risk factors, 'breast tissue age' and the age-incidence of breast cancer. *Nature*. 1983;303(5920):767–770.
19. Anderson WF, Rosenberg PS, Prat A, et al. How many etiological subtypes of breast cancer: two, three, four, or more? *J Natl Cancer Inst*. 2014;106(8):dju165 doi:10.1093/jnci/dju165.
20. de Waard F. Premenopausal and postmenopausal breast cancer: one disease or two? *J Natl Cancer Inst*. 1979;63(3):549–552.
21. Yasui Y, Potter JD. The shape of age-incidence curves of female breast cancer by hormone-receptor status. *Cancer Causes Control*. 1999;10(5):431–437.
22. Visvader JE, Stingl J. Mammary stem cells and the differentiation hierarchy: current status and perspectives. *Genes Dev*. 2014;28(11):1143–1158.
23. Keller PJ, Arendt LM, Skibinski A, et al. Defining the cellular precursors to human breast cancer. *Proc Natl Acad Sci U S A*. 2012;109(8):2772–2777.
24. Visvader JE. Cells of origin in cancer. *Nature*. 2011;469(7330):314–322.
25. Preston DL, Mattsson A, Holmberg E, et al. Radiation effects on breast cancer risk: a pooled analysis of eight cohorts. *Radiat Res*. 2002;158(2):220–235.
26. Mertens AC, Liu Q, Neglia JP, et al. Cause-specific late mortality among 5-year survivors of childhood cancer: the Childhood Cancer Survivor Study. *J Natl Cancer Inst*. 2008;100(19):1368–1379.
27. Castiglioni F, Terenziani M, Carcangiu ML, et al. Radiation effects on development of HER2-positive breast carcinomas. *Clin Cancer Res*. 2007;13(1):46–51.
28. Tang J, Fernandez-Garcia I, Vijayakumar S, et al. Irradiation of juvenile, but not adult, mammary gland increases stem cell self-renewal and estrogen receptor negative tumors. *Stem Cells*. 2014;32(3):649–661.
29. Eveleth PB, Tanner JM. *Worldwide variation in human growth*. New York: Cambridge University Press; 1990.
30. Freedman DS, Khan LK, Serdula MK, et al. Relation of age at menarche to race, time period, and anthropometric dimensions: the Bogalusa Heart Study. *Pediatrics*. 2002;110(4):e43.