Published in final edited form as:
Cancer Epidemiol Biomarkers Prev. 2014 June ; 23(6): 1115–1120. doi:10.1158/1055-9965.EPI-14-0110.

Associations between Estrogen Receptor Negative Breast Cancer and Timing of Reproductive Events Differ between African-American and European-American Women

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Abstract

The effects of reproductive factors on breast cancer risk appear to differ by estrogen receptor (ER) status. Menarche and first live birth (FLB) tend to occur at younger ages in African-Americans (AAs) than European-Americans (EAs), and could play a role in breast cancer disparities. In the Women's Circle of Health Study (WCHS), a case-control study of breast cancer in EA and AA women, in-person interviews were conducted to collect epidemiological data, including reproductive histories. Data on ER status, abstracted from pathology reports, were available for 814 AA and 538 EA breast cancer cases, and were analyzed with 1015 AA and 715 EA controls, to evaluate associations between subgroups and age at menarche, age at FLB and the interval between those ages. Among AA women, later age at menarche (≥14 yrs) was associated with reduced risk of both ER+ and ER-breast cancer, with odds ratios (ORs) strongest for ER- disease (OR =0.57; 95% CI, 0.37-0.88); associations were weaker and non-significant for EA women. There were no significant associations with age at FLB, but AA women with a FLB within 15 years of menarche had increased risk of ER- disease (OR=2.26; 95% CI, 1.29-3.95), with no significant associations among EAs.In our data, earlier age at menarche and shorter intervals until FLB are associated with ER- breast cancer in AA women; differential distributions by race of these and other reproductive risk factors could contribute to the higher prevalence of ER - breast cancer in AA women.

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The authors have no potential conflicts of interest to report

Keywords

breast cancer; estrogen receptor; African-American; menarche; reproductive risk factors

Introduction

Although white women of European ancestry (EA) have the highest incidence of breast cancer of all racial groups in the US, American women of African ancestry (AA) are more likely to be diagnosed at an earlier age and with more aggressive tumors (1). Tumors that are negative for the estrogen receptor (ER), most prevalent in AA women, lack therapeutic targets and are associated with poorer survival. Until recently, there have been few explanations for these differences in tumor biology between EA and AA women, but there is accumulating evidence suggesting that differences in parity and in breastfeeding could contribute to these disparities (2-4), with parity associated with reduced risk of ER+ breast cancer, but increased risk of ER- tumors (reviewed in (3). In several studies, younger age at first live birth (FLB) has also been associated with reduced risk of ER+, but increased risk of ER- breast cancer (5,6), although there are conflicting data, as recently reviewed by Martinez and colleagues (7).

Early age at menarche is an established risk factor for breast cancer and appears to be associated with larger, more advanced tumors (8,9). AAs have younger age at menarche than EAs (10,11), hypothesized to be a contributing factor to their higher risk of early onset breast cancer (12). Age at menarche has declined in the last two centuries, and has been consistently younger (by approximately 0.5 years) for AAs than for EAs (13), with the decline between 1973 and 1994 greater for AAs (0.8 years) than for EAs (0.2 years) (14).

There have been limited studies investigating potential associations between breast cancer subtypes and reproductive risk factors that may vary between AA and EA women, with mixed results (reviewed by Li (5)); few have included substantial numbers of both AA and EA women. Here we report on associations between breast cancer risk and reproductive factors according to ER status in a large study of breast cancer in AA and EA women.

Materials and Methods

Study population

The Women's Circle of Health Study (WCHS) was a case-control study designed to examine risk factors for ER-, early onset breast cancer among AA and EA women in metropolitan New York City (NYC) and in several counties in New Jersey (NJ). As previously described (15-17), eligible cases were English-speaking women diagnosed with incident invasive or *in situ* breast cancer, aged 20 to 75, who self-identified as AA or EA and had no previous history of cancer other than non-melanoma skin cancer. Cases were identified in NY Chospitals with large referral patterns for AAs, and through population-based rapid case ascertainment in seven counties in NJ through the NJ State Cancer Registry. Controls were identified using random digit dialing in both NYC and NJ, and were frequency matched to cases by self-reported race and 5-year age categories. Participation rates for cases were

82.4% for AAs and 79.1% for EAs, and for controls, 52.5% (AAs) and 49.0% (EAs). With the assistance of community partners and advocates, we also recruited AA controls in NJ through churches and health fair events in the same counties in which cases were identified, to better represent the AA population at large than RDD alone (18). In-home interviews were conducted and data collected on a number of potential risk factors, including reproductive, medical and family histories, and lifestyle factors. Data on hormone receptors were abstracted from pathology reports. Although pathology data came from a number of hospitals in NY and NJ, central review of slides by one pathologist at RPCI (TK) confirmed that the majority of reports were accurate, particularly in dichotomous positive vs. negative. Due to lack of pathology information for some cases, we excluded 309 AA and 234 EA cases, with a total of 3082 participants. This study was approved by the Institutional Review Boards at Roswell Park Cancer Institute (RPCI), the Rutgers Cancer Institute of New Jersey (RCINJ), Icahn School of Medicine at Mount Sinai, and the participating hospitals in NYC.

Data collection and statistical analyses

In the interview, risk factor data were collected, including age at first menstrual period (age at menarche), how many pregnancies they had had, and what the outcome of each pregnancy was. For live births, participants were asked in what month and year the pregnancy ended. History of benign breast disease (BBD) was coded as positive if the diagnosis was confirmed by a physician. Women were defined as postmenopausal if they reported that they had ceased menstruation naturally at least one year prior to reference date, or if they had both ovaries removed. Family history of breast cancer was reported breast cancer in a first degree relative.

Distributions of age at FLB and the interval between menarche and FLB differed markedly by race, with 20% of AA women having FLB before age 18, but only 2% of EAs. Similarly, the interval between menarche and FLB was < 5 years for 15% to 20% of AA women, but only for 2% of EA women. Thus, we categorized FLB and the interval between menarche and FLB according to distributions among controls specific to each of those populations. For analysis, we compared categories across controls and cases according to ER status, using chi-square tests for categorical data, and also determined p values for case-case differences between women with ER+ and ER- tumors. Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were estimated using unconditional logistic regression to examine associations between age at menarche, age at FLB and the interval between those ages, and odds of ER+ and ER- breast tumors. Full models were adjusted for factors associated with the exposure or with risk of breast cancer in our data, and included age, study site, education, history of BBD, family history of breast cancer, menopausal status, body mass index (BMI) at age 20 (17), country of origin, and reference year. Associations were evaluated among all cases and also excluding women with DCIS from the analysis. All analyses were conducted using SAS 9.3.

Results

Table 1 shows characteristics of the study participants, separately for AAs and EAs. There were no significant case-control differences in the reproductive characteristics of interest in

either AAs or EAs. However, as noted above, AA women were more likely to have an early age at menarche (< 11 years of age) than EAs, younger age at FLB (< 18 years), and shorter intervals between menarche and FLB. As expected, the majority of breast cancers were invasive, rather than *in situ*, with a greater proportion of ER- tumors among AA women (28.6%) than among EAs (17.1%).

Table 2 shows associations between menstrual and reproductive risk factors by ER status among AA women only. Later age at menarche (≥ 14 yrs) was associated with reduced risk of ER+ breast cancer (OR=0.70 (95% CI, 0.51-0.95), but associations were strongest for ER- disease (OR=0.57, 95% CI, 0.37-0.88). Compared to ER+ breast cancer, later age at menarche was associated with reduced odds of ER- disease (OR=0.74, 95% CI, 0.46-1.21) in case-case analysis.

Among AA women, there were no significant increases in risk of either ER+ or ER- breast cancer with later age at FLB. ORs for ER+ breast cancer were increased for all intervals from menarche to FLB beyond < 5 years, although confidence intervals included unity, with the greatest risk for 15-19 years (OR=1.73, 95% CI, 1.07-2.78). For ER- tumors, the greatest ORs were for 5-9 years (OR=2.03, 95% CI, 1.23-3.36) and 10-14 years (OR=2.26, 95% CI, 1.29-3.95). In case-case analysis, there was increased odds of ER-, compared to ER+, breast cancer for intervals up to 15 years, with no differences observed with longer durations.

Among EA women (Table 3), there were no differences by ER status for age at menarche, with a suggestion of decreased risk of both ER+ and ER- breast cancer with menarche ≥ 14 years. FLB after age 25 was associated with increased risk of ER+ breast cancer (OR=1.58; 95% CI, 0.77-3.21), with no associations for ER- disease. Although none of the associations were significant for interval between menarche and age at FLB, there appeared to be increased risk for both ER+ and ER- breast cancer with more years (≥15) between menarche and first pregnancy. There were no differences in results when DCIS cases were excluded (data not shown).

Discussion

In this analysis of data from 814 AA and 538 EA women with breast cancer and 1723 controls, we found differential relationships according to ER status, and results differed by ancestral background. Associations were strongest for age at menarche among AA women, with a 43% reduction in odds of ER- breast cancer with menarche at or after 14 years of age. Our findings of no differential associations by ER status and age at menarche among EA women are consistent with recent results from studies of primarily white premenopausal women (5), European women (6) and Mexican and Mexican-American women (7). However, our findings of strongly decreased risk of ER- breast cancer with later age at menarche among AA women are novel and need replication, as well as further examination of the driving forces behind these associations in AA women.

Although AA women have been observed to generally have children at a younger age, we found no differential associations with age at FLB by ER status among AA women. Among EA women, later age at FLB was associated with increased risk of ER+ breast cancer but no

association with ER- tumors. The majority of previous studies have found no differences in risk with FLB by ER status, and a few have shown increased risk of ER+ disease, as reviewed in (5), with recent studies having conflicting findings (5-7). A limited number of studies have evaluated the interval between menarche and FLB in relation to breast cancer subgroups. Our data showed that, in comparison to women for whom there was a short interval (up to 5 five years) between menarche and FLB, AA women with up to a 14 year interval, but not beyond, were at significantly increased risk of ER-, and modestly increased risk of ER+, breast cancer. The stronger association with ER- breast cancers was supported by case-case analysis. Previous studies that have investigated this interval in relation to ER status in EA and Asian populations have had conflicting findings (5-7, 19,20).

It is unclear why associations with hormonal and reproductive factors appear to play a more prominent role in ER – breast cancer in AAs than in EAs, including parity and breastfeeding as we have recently shown (2). AAs experience menarche at an earlier age than EAs, have more children at younger ages, and tend not to breastfeed, all factors associated with differential risk by ER status.

Thus, it is possible that these menstrual and reproductive patterns could be related to the higher prevalence of earlier onset, ER- breast cancer among AAs. Early menarche, early FLB, and short intervals between menarche and pregnancies could essentially down-shift a high hormonal milieu to younger ages, leading to more rapid development of aggressive tumors. This area of research clearly merits further attention, and warrants not only consortia with large numbers of AA women to clarify and refine associations, but also studies to understand the biologic mechanisms underlying these associations between hormonally-related risk factors and development of ER – tumors. Ideal prospective studies would include comprehensive data on circulating hormonal levels, bone mass and breast growth during puberty and information on subsequent childbearing patterns in a multi-racial/multi-ethnic population, to better understand the mechanisms for and the basis of disparities in the development of aggressive breast cancer.

Acknowledgments

Financial Support. This work was supported by grants from the US Army Medical Research and Material Command (DAMD-17-01-1-0334) (to D.H. Bovbjerg and C.B. Ambrosone), the National Cancer Institute (R01 CA100598 to C.B. Ambrosone; P01 CA151135 to C.B. Ambrosone, J.R. Palmer and A.F. Olshan; K22 CA138563 to E.V. Bandera; and CCSGs to Roswell Park Cancer Institute (P30 CA016056) and Rutgers Cancer Institute of NJ (P30 CA072720), the Breast Cancer Research Foundation (to C.B. Ambrosone) and a gift from the Philip L Hubbell family (to C.B. Ambrosone). The New Jersey State Cancer Registry (NJSCR) is a participant in the Centers for Disease Control and Prevention's National Program of Cancer Registries and is a National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) Expansion Registry. The NJSCR is supported by the Centers for Disease Control and Prevention under cooperative agreement 1US58DP003931-01 awarded to the New Jersey Department of Health. The collection of New Jersey cancer incidence data is also supported by the National Cancer Institute's SEER Program under contract N01PC-2010-00027 and the State of New Jersey.

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Cancer Epidemiol Biomarkers Prev. Author manuscript; available in PMC 2015 June 01.

Table 1

Characteristics of AA and EA participants in the WCHS

	AA			EA		
Characteristic	**Cases n (%)**	**Controls n (%)**	**p**	**Cases n (%)**	**Controls n (%)**	**p**
Age			0.0174			0.0003
< 40	102 (12.5)	152 (15.0)		60 (11.2)	107 (15)	
40-49	222 (27.3)	282 (27.8)		165 (30.7)	216 (30.2)	
50-59	285 (35.0)	385 (37.9)		185 (34.4)	286 (40.0)	
≥ 60	205 (25.2)	196 (19.3)		128 (23.8)	106 (14.8)	
Education			0.0019			<.0001
≤High School	371 (45.6)	374 (36.8)		114 (21.2)	80 (11.2)	
<College Graduate	217 (26.7)	301 (29.7)		113 (21.0)	134 (18.7)	
College graduate	145 (17.8)	212 (20.9)		167 (31.0)	231 (32.3)	
Post graduate	81 (10.0)	128 (12.6)		144 (26.8)	270 (37.8)	
Family history of breast cancer			0.0014			0.0045
No	678 (83.3)	898 (88.5)		414 (77.0)	596 (83.4)	
Yes	136 (16.7)	117 (11.5)		124 (23.0)	119 (16.6)	
Benign breast disease			<.0001			0.0026
No	551 (67.8)	778 (76.7)		312 (58.5)	476 (66.9)	
Yes	262 (32.2)	236 (23.3)		221 (41.5)	236 (33.1)	
Body mass index			0.9248			0.8753
<25	143 (17.6)	180 (19.8)		242 (44.9)	328 (45.9)	
25-<30	237 (29.1)	180 (19.8)		142 (26.4)	191 (26.8)	
≥30	434 (53.3)	548 (60.3)		154 (28.7)	195 (27.3)	
Body mass index at age 20			0.0071			0.0023
< 18.5	134 (17.5)	134 (13.7)		86 (16.4)	103 (14.6)	
18.5-<25	495 (64.6)	621 (63.8)		406 (77.3)	522 (74.0)	
≥25	137 (17.9)	219 (22.5)		33(6.3)	80 (11.4)	
Country of origin			0.0027			0.0001
United States	606 (74.4)	823 (81.1)		454 (84.4)	629 (88.0)	

	AA			EA		
Characteristic	**Cases n (%)**	**Controls n (%)**	**p**	**Cases n (%)**	**Controls n (%)**	**p**
Caribbean countries	152 (18.7)	137 (13.5)		18 (3.3)	2 (0.3)	
Other	56 (6.9)	55 (5.4)		66 (12.3)	84 (11.7)	
State			0.0010			<.0001
New York	223 (27.4)	351 (34.6)		179 (33.3)	334 (46.7)	
New Jersey	591 (72.6)	664 (65.4)		359 (66.7)	381 (53.3)	
Age at menarche (years)			0.2838			0.3383
< 11	107 (13.1)	109 (10.7)		52 (9.8)	58 (8.2)	
11-12	321 (39.4)	415 (40.9)		234 (43.9)	295 (41.6)	
≥ 13	386 (47.4)	490 (48.3)		247 (46.3)	356 (50.2)	
Age at first live birth (years)			0.4462			0.3087
< 18	135 (19.7)	176 (20.8)		7 (1.9)	10 (2.0)	
18-24	347 (50.6)	408 (48.2)		113 (30.3)	135 (26.5)	
25-29	113 (16.5)	126 (14.9)		117 (31.4)	143 (28.1)	
30-34	57 (8.3)	91 (10.8)		85 (22.8)	145 (28.5)	
≥ 35	34 (5.0)	45 (5.3)		51 (13.7)	76 (14.9)	
Interval between menarche and 1st birth			0.4329			0.6357
< 5	116 (16.9)	167 (19.8)		11 (3.0)	12 (2.4)	
5-9	275 (40.1)	313 (37.0)		60 (16.2)	68 (13.5)	
10-14	154 (22.4)	182 (21.5)		109 (29.5)	148 (29.4)	
15-19	79 (11.5)	93 (11.0)		104 (28.1)	140 (27.8)	
≥ 20	62 (9.0)	90 (10.7)		86 (23.2)	136 (27.0)	
Invasiveness						
In situ	133 (16.6)			103 (19.4)		
Invasive	666 (83.4)			427 (80.6)		
Estrogen receptor						
Negative	233 (28.6)			92 (17.1)		
Positive	581 (71.4)			446 (82.9)		

Table 2

Odds ratios (ORs) and 95% confidence intervals (CIs) associated with hormonal and reproductive characteristics in relation to ER status among African-American women in the WCHS

	Controls	ER+		ER-		ER- vs. ER+
	N (%)	N (%)	OR (95% CI)[1]	N (%)	OR (95% CI)[1]	OR (95% CI)[1]
Age at menarche						
< 12	278 (27.4)	174 (29.9)	1.0 (ref)	66 (28.3)	1.0 (ref)	1.0 (ref)
12-13	471 (46.4)	264 (45.4)	0.83 (0.64-1.08)	113 (48.5)	0.92 (0.64-1.31)	1.13 (0.78-1.65)
≥ 14	265 (26.1)	143 (24.6)	0.70 (0.51-0.95)	54 (23.2)	0.57 (0.37-0.88)	0.82 (0.51-1.29)
Age at first live birth (years)						
< 18	176 (20.8)	97 (20.1)	1.0 (ref)	38 (18.7)	1.0 (ref)	1.0 (ref)
18-24	408 (48.2)	234 (48.4)	1.03 (0.74-1.43)	113 (55.7)	1.33 (0.86-2.07)	1.35 (0.84-2.18)
25-29	126 (14.9)	82 (17.0)	1.37 (0.90-2.09)	31 (15.3)	1.46 (0.82-2.61)	1.12 (0.60-2.07)
≥ 30	136 (16.1)	70 (14.5)	1.02 (0.66-1.58)	21 (10.3)	0.91 (0.48-1.74)	0.93 (0.46-1.88)
Interval between menarche and 1st birth (years)						
< 5	167 (19.8)	85 (17.6)	1.0 (ref)	31 (15.3)	1.0 (ref)	1.0 (ref)
5-9	313 (37.0)	185 (38.3)	1.29 (0.90-1.83)	90 (44.3)	2.03 (1.23-3.36)	1.58 (0.92-2.71)
10-14	182 (21.5)	104 (21.5)	1.36 (0.91-2.03)	50 (24.6)	2.26 (1.29-3.95)	1.68 (0.93-3.04)
15-19	93 (11.0)	61 (12.6)	1.73 (1.07-2.78)	18 (8.9)	1.73 (0.86-3.50)	1.04 (0.49-2.20)
≥ 20	90 (10.7)	48 (9.9)	1.35 (0.82-2.24)	14 (6.9)	1.42 (0.66-3.08)	1.02 (0.44-2.36)

[1] Adjusted for age, country of origin, reference year, state, education, family history of breast cancer, history of benign breast disease, menopausal status/age at menopause, and body mass index at age 20

Table 3

Odds ratios (ORs) and 95% confidence intervals (CIs) associated with hormonal and reproductive characteristics in relation to ER status among European-American women in the WCHS

	Controls	ER+		ER-		ER- vs. ER+
	N (%)	N (%)	OR (95% CI)[1]	N (%)	OR (95% CI)[1]	OR (95% CI)[1]
Age at menarche (years)						
< 12	160 (22.6)	112 (25.3)	1.0 (ref)	21 (23.1)	1.0 (ref)	1.0 (ref)
12-13	383 (54.0)	237 (53.6)	0.85 (0.62-1.17)	54 (59.3)	1.07 (0.60-1.90)	1.30 (0.71-2.41)
≥ 14	166 (23.4)	93 (21.0)	0.82 (0.56-1.20)	16 (17.6)	0.78 (0.38-1.61)	0.95 (0.45-2.02)
Age at first live birth (years)						
< 20	32 (6.3)	20 (6.3)	1.0 (ref)	7 (12.3)	1.0 (ref)	1.0 (ref)
20-24	113 (22.2)	79 (25.0)	1.07 (0.54-2.13)	14 (24.6)	0.66 (0.23-1.88)	0.62 (0.20-1.95)
25-29	143 (28.1)	100 (31.6)	1.51 (0.76-3.03)	17 (29.8)	0.97 (0.34-2.78)	0.60 (0.19-1.89)
≥ 30	221 (43.4)	117 (37.0)	1.58 (0.77-3.21)	19 (33.3)	1.00 (0.33-3.00)	0.66 (0.20-2.22)
Interval between menarche and 1st birth (years)						
< 10	80 (15.9)	58 (18.5)	1.0 (ref)	13 (23.2)	1.0 (ref)	1.0 (ref)
10-14	148 (29.4)	93 (29.6)	0.95 (0.59-1.54)	16 (28.6)	0.85 (0.37-1.99)	0.95 (0.39-2.34)
15-19	140 (27.8)	91 (29.0)	1.42 (0.85-2.38)	13 (23.2)	1.30 (0.52-3.28)	0.95 (0.36-2.49)
≥ 20	136 (27.0)	72 (22.9)	1.31 (0.75-2.28)	14 (25.0)	1.56 (0.59-4.15)	1.21 (0.42-3.45)

[1] Adjusted for age, country of origin, reference year, state, education, family history of breast cancer, history of benign breast disease, menopausal status/age at menopause, and body mass index at age 20