Research Article: Spotlight on Cancer Health Disparities

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Reproductive Factors and Risk of Luminal, HER2-Overexpressing, and Triple-Negative Breast Cancer Among Multiethnic Women

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Abstract

Background: Reproductive factors are among the most well-established risk factors for breast cancer. However, their associations with different breast cancer subtypes defined by joint estrogen receptor (ER)/progesterone receptor (PR)/HER2 status remain unclear.

Methods: We assessed relationships between reproductive factors and risks of luminal A ($ER^+/HER2^-$), luminal B ($ER^+/HER2^+$), triple-negative (TN; $ER^-/PR^-/HER2^-$), and HER2-overexpressing (H2E; $ER^-/HER2^+$) breast cancers in a population-based case–case study consisting of 2,710 women ages 20–69 years diagnosed between 2004 and 2012. ORs and 95% confidence intervals (CI) were estimated with luminal A cases serving as the reference group using polytomous logistic regression.

Results: Earlier age at first full-term pregnancy and age at menopause were positively associated with odds of TN breast cancer (P_{trend}: 0.003 and 0.024, respectively). Parity was associated with a 43% (95% CI, 1.08–1.89) elevated odds of H2E breast cancer, and women who had ≥3 full-term pregnancies had a 63% (95% CI, 1.16–2.29, $P_{trend} = 0.013$) increased odds of this subtype compared with nulliparous women. Breast feeding for ≥36 months was associated with a 49% (OR 0.51; 95% CI, 0.27–0.99) lower odds of TN breast cancer.

Conclusion: Our results suggest that reproductive factors contribute differently to risks of the major molecular subtypes of breast cancer.

Impact: African American and Hispanic women have higher incidence rates of the more aggressive TN and H2E breast cancers and their younger average age at first pregnancy, higher parity, and less frequent breast feeding could in part contribute to this disparity. *Cancer Epidemiol Biomarkers Prev; 25(9); 1297–304. ©2016 AACR.*

Introduction

Reproductive factors are among the most well-established risk factors for breast cancer. In meta-analyses evaluating breast cancer overall, there is a reduced risk of 4% to 9% per year delay in menarche, 7% for each additional birth, and 4% for every additional 12 months of breast feeding, but an increased risk of 3% to 5% per year increase in age at first birth (1, 2).

However, it is now recognized that the major molecular subtypes of breast cancer, defined by patterns of gene expression (3, 4) or joint tumor marker expression (5), have unique biologic features and also exhibit distinct clinical profiles and outcomes. The molecular subtypes based on marker expression include: triple-negative tumors (TN) which lack expression of the estrogen receptor (ER), progesterone receptor (PR) and HER2-neu (HER2) and widely overlap with the basal-like phenotype; HER2-overexpressing tumors (H2E) which are $ER^-/HER2^+$; luminal B tumors which are ER^+ or $PR^+/HER2^+$; and luminal A tumors which are ER^+ or $PR^+/HER2^-$. TN and H2E tumors are well known to have a poorer prognosis than the more common luminal A and luminal B subtypes (5–7). Reproductive factors are hypothesized to influence breast cancer risk primarily through hormonal pathways (8,9), as supported by increasing evidence that these risk factors, with the exception of breast feeding, seem to be most associated with luminal (i.e., ER^+) breast cancer subtypes (10–13).

Relatively few studies (12, 14–23) have assessed the role of reproductive factors on risk of different molecular subtypes of breast cancer. Many have been limited by the inclusion of small numbers of TN and H2E cases, resulting in limited power to detect variability in the associations and partly explaining some inconsistencies in findings. Although TN and H2E subtypes disproportionately affect African American and Hispanic women in addition to other medically disadvantaged populations (5, 24), prior studies have included mostly non-Hispanic women and only one prior study evaluated reproductive differences in relation to tumor subtypes exclusively among Hispanic women (25). Given pronounced differences in reproductive factors by race/ethnicity (e.g., fertility rates of 72.9 vs. 64.6 vs. 58.7 per 1000 women of child bearing age and mean ages at first birth of 24.0 vs. 23.9 vs. 26.8 years for Hispanic, African American, and non-Hispanic white women in the United States, respectively; ref. 26), variations in risks of different breast cancer subtypes associated with reproductive factors could to some extent account for the different frequencies of aggressive breast cancer subtypes observed across populations. Here we present results from a study focused on characterizing the associations between various reproductive factors and risk of different breast cancer subtypes among multiethnic women.

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Materials and Methods

We conducted a population-based case–case study of different breast cancer subtypes defined by joint ER/PR/HER2 expression. Potentially eligible cases were identified through the population-based Surveillance, Epidemiology and End Results (SEER) cancer registries serving the Seattle-Puget Sound region and the state of New Mexico. Our catchment area in Seattle-Puget Sound included King, Pierce, and Snohomish counties spanning the Seattle-Tacoma-Everett greater metropolitan area, and six Central New Mexico counties (Bernalillo, Sandoval, Santa Fe, Socorro, Torrance, and Valencia) that include the greater Albuquerque metropolitan area. The study was independently approved by Institutional Review Boards (IRB) at the Fred Hutchinson Cancer Research Center and the University of New Mexico.

Cases were women 20 to 69 years old first diagnosed with invasive breast cancer between June 1, 2004, and June 30, 2012. Case subtypes were defined by joint ER/PR/HER2 status, including TN (defined as $ER^-/PR^-/HER2^-$), H2E (defined as $ER^-/HER2^+$), luminal A (defined as $ER^+/HER2^-$), and luminal B (defined as $ER^+/HER2^+$) breast cancers. Cases with unknown tumor marker information or other ER/PR/HER2 combinations were excluded. All women with incident TN or H2E cancers were eligible for the study. Given the much higher frequency of ER^+ disease, for statistical efficiency and to contain study costs, only a frequency matched (on age of diagnosis, year of diagnosis, and study site to the distributions among the combined TN and H2E case groups) randomly selected sample of ER^+ (luminal A and B) cases, 75% of the size of the TN case group, was selected as eligible for this study. Data were collected via medical records abstraction only for cases at the New Mexico site and via both medical records review and telephone interview for Seattle cases. In New Mexico, the medical records of all 681 eligible breast cancer cases (response rate: 100%) were reviewed under an IRB approved waiver of consent. At the Seattle site, 1,568 of 2,363 (response rate: 66.4%) eligible women newly diagnosed with invasive breast cancer during the study period were enrolled in addition to 461 eligible cases identified from prior studies with overlapping eligibility criteria (the design and methods of these studies have been previously described; refs. 27, 28). Seattle cases were further approached for their consent to participate in a structured interviewer-administered questionnaire covering a variety of topics related to breast cancer risk factors. Among the 1,568 newly enrolled cases, interview and medical records data were both obtained for 1,050, medical record only data were available for 355, and interview only data were available for 163 women. All 461 eligible cases from prior studies were interviewed and 450 also had medical record data. To overcome the potential bias that would have resulted from only including participants who were alive at enrollment, eligible deceased cases were enrolled at both study sites through a waiver of consent. Data on deceased women were obtained only through the review of medical records. So across both study sites a total of 2,710 breast cancer cases were enrolled including 785 luminal A, 133 luminal B, 1299 TN, and 493 H2E cases.

Data collection

Detailed medical record abstractions collecting information on a wide range of demographic, epidemiologic, and clinical factors using the same protocol and instrument were conducted by trained study staff at both study sites. For quality control purposes, a random 10% sample of completed abstracts were exchanged between study sites for review and editing in order to insure consistency in abstracting approach, methodology, and coding. Medical records were sought from various sources including oncology and primary care practices to ascertain complete information on breast cancer tumor characteristics and established breast cancer risk factors, including reproductive history (e.g., parity, number of full-term pregnancy, and age at first full-term pregnancy), menopausal status at diagnosis, body mass index, first-degree family history of breast cancer, smoking status, use of menopausal hormone therapy (HT), and use of oral contraceptive (OC) use. At the Seattle site only, self-reported data through interviewer-administered structured telephone questionnaires were used to supplement medical record data. In addition to being queried on a number of breast cancer risk factors, women were specifically asked questions pertaining to age at menarche and their breast feeding history as these reproductive factors could not be consistently obtained from medical records.

Statistical analysis

Polytomous logistic regression was used to simultaneously estimate ORs and their associated 95% confidence intervals (CI) comparing a particular aspect of reproductive history across the four cases groups included. In all analyses, luminal A cases served as the reference comparison group because it is the most common breast cancer subtype. P_{trend} values were calculated by using continuous variables. All analyses were adjusted for age at diagnosis (in 5-year categories), year of diagnosis (as continuous), and study site as cases were frequency matched on these factors. None of the other potential confounders listed in Table 1 changed our risk estimates by more than 10% when individually assessed and so none was adjusted for in our final models. We also evaluated age, menopausal status, and ethnicity as potential effect modifiers of associations with parity, age at first birth, and breast feeding using log likelihood ratio tests. None of these interactions were statistically significant at $P < 0.05$. All analyses were conducted using Stata/SE version 11.2 (StataCorp LP).

In all analyses, data collected from medical records were prioritized over self-reported data. Of note though, the correlation between these two sources was quite high for parity (%agreement = 99.5%, $\kappa = 0.99$), number of full-term pregnancies (%agreement = 96.4%, $\kappa = 0.95$), age at first birth (categorized <20, 20–24, 25–29, and 30+, %agreement = 90.3%, $\kappa = 0.87$), menopausal status (%agreement = 96.3%, $\kappa = 0.93$), and age at menopause (categorized as <45, 45–54, and 55+, %agreement = 79.7%, $\kappa = 0.57$). We performed sensitivity analyses restricted to using only medical record data and demonstrated that study results did not change materially with this restriction (data not shown).

Results

Compared with other subtypes, women with luminal A cancers were somewhat more likely to be current users of estrogen + progestin HT and OCs (Table 1). Luminal B cases were somewhat younger, more frequently Hispanic, premenopausal and having a normal weight, and less likely to have private health insurance than women with other subtypes. TN cases were somewhat more frequently African American, obese, and ever users of menopausal HT and OCs. Women with H2E tumors were more likely to be never users of OCs than other case groups. Selected patient

Table 1. Distribution of demographic and risk factors by breast cancer subtype

Variables	Luminal A (*N* = 785) *n*, %	Luminal B (*N* = 133) *n*, %	Triple-negative (*N* = 1299) *n*, %	HER2-overexpressing (*N* = 493) *n*, %
Year at diagnosis				
2004–2006	277 (35.3)	47 (35.3)	436 (33.6)	158 (32.0)
2007–2008	209 (26.6)	28 (21.1)	347 (26.7)	127 (25.8)
2009–2010	159 (20.3)	32 (24.1)	295 (22.7)	113 (22.9)
2011–2012	140 (17.8)	26 (19.5)	221 (17.0)	95 (19.3)
Study site				
Seattle	596 (75.9)	92 (69.2)	992 (76.4)	349 (70.8)
New Mexico	189 (24.1)	41 (30.8)	307 (23.6)	144 (29.2)
Age at diagnosis (in years)				
<40	98 (12.5)	27 (20.3)	189 (14.5)	53 (10.8)
40–49	210 (26.8)	46 (34.6)	361 (27.8)	119 (24.1)
50–59	272 (34.6)	41 (30.8)	416 (32.0)	194 (39.4)
60–69	205 (26.1)	19 (14.3)	333 (25.6)	127 (25.8)
Race/ethnicity				
Non-Hispanic white	613 (79.2)	94 (72.3)	987 (76.5)	374 (76.6)
Hispanic white	77 (9.9)	23 (17.7)	126 (9.8)	57 (11.7)
African American	25 (3.2)	4 (3.1)	102 (7.9)	22 (4.5)
Asian/Pacific Islander	48 (6.2)	5 (3.8)	46 (3.6)	24 (4.9)
Native American	11 (1.4)	4 (3.1)	30 (2.3)	11 (2.3)
Missing	11	3	8	5
Health insurance status				
Any private	646 (84.2)	101 (78.3)	1,043 (82.4)	393 (82.2)
Any Medicaid	54 (7.0)	11 (8.5)	83 (6.6)	28 (5.9)
Medicare	42 (5.5)	11 (8.5)	99 (7.8)	35 (7.3)
No insurance	25 (3.3)	6 (4.7)	41 (3.2)	22 (4.6)
Missing	18	4	33	15
First-degree family history of breast cancer				
No	577 (76.7)	103 (80.5)	985 (77.7)	381 (80.2)
Yes	175 (23.3)	25 (19.5)	282 (22.3)	94 (19.8)
Missing	33	5	32	18
Menopausal status				
Premenopausal	302 (39.6)	69 (54.3)	473 (37.5)	154 (32.4)
Perimenopausal	66 (8.7)	8 (6.3)	105 (8.3)	47 (9.9)
Postmenopausal	395 (51.8)	50 (39.4)	683 (54.2)	275 (57.8)
Missing	22	6	38	17
Smoking status at breast cancer diagnosis				
Never	454 (59.0)	68 (53.1)	739 (57.7)	286 (59.0)
Current	107 (13.9)	17 (13.3)	196 (15.3)	73 (15.1)
Former	209 (27.1)	43 (33.6)	345 (27.0)	126 (26.0)
Missing	15	5	19	8
Body mass index at diagnosis (kg/m^2)				
<25.0	283 (36.7)	54 (41.9)	435 (34.1)	190 (39.3)
25.0–29.9	221 (28.6)	40 (31.0)	379 (29.7)	147 (30.4)
≥30.0	268 (34.7)	35 (27.1)	461 (36.2)	146 (30.2)
Missing	13	4	24	10
Recency of menopausal hormone use at diagnosis[a]				
Never user	619 (83.8)	113 (90.4)	1,005 (83.6)	382 (84.3)
Former user	42 (5.7)	7 (5.6)	90 (7.5)	38 (8.4)
Current estrogen alone user	34 (4.6)	5 (4.0)	81 (6.7)	24 (5.3)
Current estrogen + progestin user	44 (6.0)	0 (0.0)	26 (2.2)	9 (2.0)
Missing	46	8	97	40
Recency of hormonal oral contraceptive use at diagnosis[a]				
Never user	620 (82.8)	105 (85.4)	1005 (81.8)	409 (88.1)
Former user	38 (5.1)	8 (6.5)	87 (7.1)	20 (4.3)
Current user	61 (8.1)	6 (4.9)	76 (6.2)	24 (5.2)
Ever user with unknown end date	30 (4.0)	4 (3.3)	60 (4.9)	11 (2.4)
Missing	36	10	71	29

[a]Based on use information within 5 years prior to diagnosis date.

characteristics and frequencies of reproductive factors were examined by race/ethnicity (Table 2). Hispanic white women were mostly from the New Mexico site, and somewhat more likely to be uninsured, to be parous, and to have ever breast-fed a child than women of other races/ethnicities. African American women were more likely to have had three or more full-term pregnancies, to have first pregnancy at age 20 years or younger, to have menopause at <45 years of age, and to have never breast fed. Asian Pacific/Islander women were somewhat more likely to have first birth at age 30 years or older, and to have menopause at age ≥55 years. Native American/Alaska Native women were more likely to be insured through Medicaid or Medicare then other groups. In

Table 2. Distribution of selected characteristics and risk factors by race/ethnicity[a]

Variable	Non-Hispanic white ($N = 2068$) *n*, %	Hispanic white ($N = 283$) *n*, %	African American ($N = 153$) *n*, %	Asian/Pacific Islander ($N = 123$) *n*, %	Native American/ Alaska native ($N = 56$) *n*, %
Study site					
Seattle	1,668 (80.7)	36 (12.7)	139 (90.8)	119 (96.7)	40 (71.4)
New Mexico	400 (19.3)	247 (87.3)	14 (9.2)	4 (3.3)	16 (28.6)
Age at diagnosis					
<40	246 (11.9)	56 (19.8)	25 (16.3)	30 (24.4)	7 (12.5)
40–49	537 (26.0)	89 (31.4)	50 (32.7)	41 (33.3)	16 (28.6)
50–59	731 (35.3)	79 (27.9)	49 (32.0)	31 (25.2)	18 (32.1)
60–69	554 (26.8)	59 (20.8)	29 (19.0)	21 (17.1)	15 (26.8)
Health insurance status					
Any private	1,751 (86.4)	194 (69.0)	100 (67.6)	100 (82.0)	31 (57.4)
Any Medicaid	88 (4.3)	50 (17.8)	20 (13.5)	10 (8.2)	8 (14.8)
Medicare	127 (6.3)	17 (6.0)	21 (14.2)	8 (6.6)	13 (24.1)
No insurance	61 (3.0)	20 (7.1)	7 (4.7)	4 (3.3)	2 (3.7)
Missing	41	2	5	1	2
Parity					
Nulliparous	524 (25.5)	36 (12.8)	23 (15.1)	19 (15.7)	11 (19.6)
Parous	1,529 (74.5)	246 (87.2)	129 (84.9)	102 (84.3)	45 (80.4)
Missing	15	1	1	2	0
Number of full-term pregnancies					
Nulliparous	524 (25.5)	36 (12.8)	23 (15.1)	19 (15.7)	11 (19.6)
1	352 (17.1)	43 (15.2)	31 (20.4)	28 (23.1)	11 (19.6)
2	743 (36.2)	93 (33.0)	37 (24.3)	45 (37.2)	15 (26.8)
≥3	434 (21.1)	110 (39.0)	61 (40.1)	29 (24.0)	19 (33.9)
Missing	15	1	1	2	0
Age at first full-term pregnancy (in years)[b]					
<20	212 (14.9)	55 (28.5)	43 (35.5)	8 (8.1)	13 (31.0)
20–24	442 (31.0)	85 (44.0)	44 (36.4)	25 (25.3)	14 (33.3)
25–29	405 (28.4)	35 (18.1)	14 (11.6)	31 (31.3)	8 (19.0)
≥30	365 (25.6)	18 (9.3)	20 (16.5)	35 (35.4)	7 (16.7)
Missing	105	53	8	3	3
Age at menopause (in years)[c]					
<45	172 (17.7)	28 (23.3)	16 (29.1)	4 (12.1)	2 (8.7)
45–54	703 (72.2)	88 (73.3)	33 (60.0)	24 (72.7)	18 (78.3)
≥55	99 (10.2)	4 (3.3)	6 (10.9)	5 (15.2)	3 (13.0)
Missing	152	13	15	6	6
Age at menarche (in years)[d]					
<12	281 (20.0)	6 (21.4)	31 (32.6)	27 (27.0)	10 (29.4)
12–13	831 (59.1)	15 (53.6)	48 (50.5)	47 (47.0)	16 (47.1)
≥14	295 (21.0)	7 (25.0)	16 (16.8)	26 (26.0)	8 (23.5)
Missing	261	8	44	19	6
Ever breast feeding[b,d]					
No	244 (21.3)	3 (12.5)	25 (30.1)	14 (15.7)	9 (27.3)
Yes	814 (71.0)	19 (79.2)	51 (61.4)	69 (77.5)	22 (66.7)
Duration of breast feeding (in months)[b,d]					
Never	244 (23.1)	3 (13.6)	25 (32.9)	14 (16.9)	9 (29.0)
<6	300 (28.4)	7 (31.8)	20 (26.3)	25 (30.1)	11 (35.5)
6–11	195 (18.4)	3 (13.6)	14 (18.4)	17 (20.5)	4 (12.9)
12–23	169 (16.0)	5 (22.7)	9 (11.8)	15 (18.1)	2 (6.5)
24–35	88 (8.3)	3 (13.6)	3 (3.9)	9 (10.8)	3 (9.7)
≥36	62 (5.9)	1 (4.5)	5 (6.6)	3 (3.6)	2 (6.5)

[a]Twenty-seven women with unknown race/ethnicity were dropped from this table.
[b]Among parous women only.
[c]Among postmenopausal women only.
[d]Among Seattle cases only.

comparison, non-Hispanic women were somewhat more frequently postmenopausal, privately insured, and nulliparous than women in the other groups.

Compared to luminal A cases, parous women had a 43% increased odds of H2E breast cancer relative to nulliparous women (Table 3). However, the trends with increasing number of full-term pregnancies were not statistically significant among parous women. Parity was not associated with odds of the other breast cancer subtypes. Age at first birth and age at menopause were only differentially associated with odds of TN breast cancer with odds decreasing as age at first birth and age at menopause increased ($P_{trend} = 0.003$ and 0.024, respectively).

Among Seattle-Puget Sound cases with interview data, we examined additional reproductive factors including age at menarche and breast feeding history (Table 4). Although no differences across breast cancer subtypes were observed with

Table 3. Relationship between reproductive factors and risk of breast cancer subtypes[a]

	Luminal A	Luminal B		Triple-negative		HER2-overexpressing	
	n (%)	*n* (%)	OR (95% CI)	*n* (%)	OR (95% CI)	*n* (%)	OR (95% CI)
Number of full-term pregnancies							
Nulliparous	191 (24.7)	39 (30.0)	1.00 (ref)	291 (22.6)	1.00 (ref)	92 (19.0)	1.00 (ref)
Parous	583 (75.3)	91 (70.0)	0.82 (0.54–1.24)	994 (77.4)	1.13 (0.91–1.39)	392 (81.0)	1.43 (1.08–1.89)[b]
1	124 (16.0)	26 (20.0)	1.05 (0.61–1.82)	234 (18.2)	1.24 (0.93–1.65)	83 (17.1)	1.43 (0.98–2.08)
2	287 (37.1)	40 (30.8)	0.73 (0.45–1.18)	432 (33.6)	1.00 (0.79–1.27)	178 (36.8)	1.31 (0.96–1.79)
≥3	172 (22.2)	25 (19.2)	0.79 (0.46–1.37)	328 (25.5)	1.27 (0.98–1.66)	131 (27.1)	1.63 (1.16–2.29)[b]
P_{trend} (among parous women only)			0.416		0.729		0.431
Age at first full-term pregnancy[c]							
<20	76 (14.0)	14 (16.9)	1.00 (ref)	183 (20.1)	1.00 (ref)	61 (17.4)	1.00 (ref)
20–24	176 (32.4)	19 (22.9)	0.56 (0.27–1.19)	301 (33.1)	0.70 (0.51–0.97)[b]	115 (32.8)	0.83 (0.55–1.25)
25–29	153 (28.1)	25 (30.1)	0.82 (0.40–1.69)	230 (25.3)	0.61 (0.43–0.86)[b]	86 (24.5)	0.70 (0.46–1.08)
30+	139 (25.6)	25 (30.1)	0.84 (0.40–1.73)	196 (21.5)	0.56 (0.40–0.80)[b]	89 (25.4)	0.81 (0.52–1.25)
Continuous (1-year)			1.01 (0.97–1.05)		0.97 (0.95–0.99)[b]		0.99 (0.97–1.01)
P_{trend}			0.574		0.003		0.557
Age at menopause[d]							
<45	35 (10.0)	9 (21.4)	1.00 (ref)	136 (23.3)	1.00 (ref)	43 (18.4)	1.00 (ref)
45–54	277 (78.9)	29 (69.0)	0.41 (0.17–0.97)[b]	396 (67.8)	0.41 (0.27–0.63)[b]	166 (70.9)	0.50 (0.30–0.83)[b]
55+	39 (11.1)	4 (9.5)	0.51 (0.14–1.89)	52 (8.9)	0.39 (0.22–0.70)[b]	25 (10.7)	0.66 (0.33–1.34)
Continuous (1-year)			0.97 (0.91–1.04)		0.97 (0.94–1.00)[b]		0.99 (0.96–1.03)
P_{trend}			0. 397		0.024		0.759

[a]Number in columns may not add up to the total number of cases due to missingness in these variables. ORs were adjusted for reference year, age at reference date, and study site.
[b]Statistically significant at $P < 0.05$.
[c]Restricted to women who ever had a full-term pregnancy.
[d]Restricted to postmenopausal women with known age at menopause.

age at menarche, women who breast fed for 3 years or longer had an increased odds of luminal B cancer (OR 3.47; 95% CI, 1.17–10.33), but a decreased odds of TN (OR 0.51; 95% CI, 0.27–0.99) compared to parous women who never breast fed.

Discussion

We observed notable differences in the associations between several reproductive factors and different breast cancer subtypes. Despite the consensus that increasing parity is associated with reduced risk of breast cancer overall (1), results from prior studies have been inconsistent with regard to the relationship between parity and the less common subtypes of breast cancer. A higher risk of TN cancers for parous women relative to nulliparous women was observed in some studies (15, 20, 22), whereas others found no association between TN cancers and parity (12, 16–18, 21). However, two out of the five studies with null findings failed to observe an association for parity with any breast cancer subtype including luminal A tumors (12, 18), suggesting the possibility of

Table 4. Relationship between age at menarche, breast feeding history, and risk of breast cancer subtypes[a]

	Luminal A	Luminal B		Triple-negative		HER2-overexpressing	
	n (%)	*n* (%)	OR (95% CI)	*n* (%)	OR (95% CI)	*n* (%)	OR (95% CI)
Age at menarche							
<12	105 (19.8)	17 (21.5)	1.00 (ref)	169 (22.1)	1.00 (ref)	64 (21.6)	1.00 (ref)
12–13	308 (58.0)	49 (62.0)	0.95 (0.52–1.73)	439 (57.4)	0.90 (0.67–1.19)	167 (56.4)	0.88 (0.61–1.26)
≥14	118 (22.2)	13 (16.5)	0.64 (0.30–1.39)	157 (20.5)	0.83 (0.59–1.16)	65 (22.0)	0.88 (0.57–1.36)
Every 2-year			0.89 (0.65–1.22)		0.92 (0.79–1.06)		0.98 (0.81–1.18)
P_{trend}			0. 474		0.246		0.828
Ever breast fed a child[b]							
No	85 (21.3)	8 (14.0)	1.00 (ref)	144 (25.0)	1.00 (ref)	58 (23.7)	1.00 (ref)
Yes	314 (78.7)	49 (86.0)	1.30 (0.57–2.94)	432 (75.0)	0.77 (0.56–1.06)	187 (76.3)	0.80 (0.54–1.19)
Breast feeding duration (in months)[b]							
Never	85 (21.3)	8 (14.0)	1.00 (ref)	144 (25.0)	1.00 (ref)	58 (23.7)	1.00 (ref)
< 6	124 (31.1)	13 (22.8)	0.90 (0.35–2.33)	165 (28.6)	0.75 (0.52–1.07)	63 (25.7)	0.69 (0.44–1.10)
6–11	71 (17.8)	9 (15.8)	1.08 (0.38–3.01)	105 (18.2)	0.83 (0.55–1.25)	50 (20.4)	0.95 (0.57–1.57)
12–23	64 (16.0)	11 (19.3)	1.37 (0.50–3.72)	94 (16.3)	0.82 (0.53–1.26)	34 (13.9)	0.71 (0.41–1.22)
24–35	32 (8.0)	7 (12.3)	1.79 (0.58–5.53)	47 (8.2)	0.82 (0.48–1.40)	20 (8.2)	0.83 (0.43–1.62)
36+	23 (5.8)	9 (15.8)	3.47 (1.17–10.33)[c]	21 (3.6)	0.51 (0.27–0.99)[c]	20 (8.2)	1.18 (0.59–2.37)
Every 6 months			1.13 (1.03–1.23)[c]		0.96 (0.91–1.02)		1.01 (0.95–1.08)
P_{trend}			0.008		0.151		0.716

[a]Analyses were restricted to Seattle cases who completed the interview. ORs were adjusted for age at diagnosis and year of diagnosis.
[b]Restricted to parous women.
[c]Statistically significant at $P < 0.05$.

lack of power. Among seven studies (15–20, 25, 29) that performed case–case comparisons including the only study focusing on Hispanic women (25), three observed differences in risks between TN and luminal A tumors (15, 18, 29), but none have observed differences across H2E or luminal B subtypes. Here we found that parity appeared to be differentially associated only with risk of H2E breast cancer, a result which has not been previously observed. Of note, our sample size of H2E cases is substantially larger than any of these prior studies ($N = 493$ vs. 33–265), but this finding requires confirmation in other studies.

With respect to age at first birth, earlier case–control or cohort studies either did not find it to be associated with risk across breast cancer subtypes (11, 12, 17, 18, 30) or only positively associated with risk of luminal A cancers (13, 16, 18, 20, 31). We confirmed two recent studies with case–case comparisons which found that later age at first birth is associated with a lower risk of TN cancers relative to luminal A cancers (19,25), although four other case–case studies (TN case number ranging from 143 to 307) did not find differential risk for TN associated with age at first birth compared with luminal A subtype (16–18,20). Similarly, age at menopause was reported to be only positively associated with luminal cancers relative to cancer-free controls (12, 17, 18, 20) with no differences in risks seen across case subtypes (17, 18, 20). Again, of note our sample size of TN cases is substantially larger than any of the prior studies ($N = 1{,}294$ vs. 77–611). The potential biologic mechanisms underlying these associations are unknown and require further investigation.

Several prior studies have observed that breast feeding is associated with a reduced risk of TN breast cancer compared to cancer-free controls (12, 16, 18, 19). Results from our study and two (16, 19) out of seven (15, 16, 18–20, 25, 29) previous studies with case–case comparisons suggest that the potential protection against TN cancers conferred by breast feeding may be even bigger than that for luminal cancers. So our finding adds to the growing evidence that breast feeding is the most consistently identified potentially modifiable risk factor for TN disease. However, ours is the only study to observe an elevated risk of luminal B cancer associated with breast feeding. Larger prior studies (case number ranging from 72 to 321) that assessed the relationship between breast feeding and luminal B breast cancer were generally null (15,16,18) and a smaller study with 36 luminal cases reported a reduced risk (29). Our finding thus should be interpreted with caution given it was based on 57 luminal cases.

Reproductive factors are thought to influence risk of breast cancer through their downstream effect on women's endogenous hormone levels (8, 9). Many aspects of reproductive and menstrual history, including age at menarche, age at first birth, age at menopause, parity, and duration of breast feeding, have a strong impact on the number of women's lifetime menstrual cycles and hence the cumulative exposure to endogenous ovarian hormones. As ovaries produce almost all endogenous estrogens in premenopausal women, it is plausible that low parity and later age at first birth may be associated with increased risk of luminal cancers but not TN or H2E cancers. However, it is unclear why the differential associations with luminal A versus TN or H2E subtypes were not seen for other aspects of reproductive factors such as age at menarche. Reproductive factors may also influence breast cancer risk through nonhormonal mechanisms. Breast tissues of parous women experience structural change and differentiation that would never occur among nulliparous women and breast tissues are further differentiated after breast feeding. It is unclear why the specific changes induced by breast feeding may be even more protective for TN breast cancer, but the additional confirmation of this relationship observed here should motivate future work as understanding the mechanisms involved could inform both prevention and treatment strategies specific to TN breast cancer.

The primary limitation of this study relates to its case–case design, where we compared less common breast cancer subtypes to luminal A cancers. With this approach we cannot directly estimate the true risks these factors bear relative to a cancer-free population. However, the associations between reproductive factors and breast cancer overall have been extensively studied and large pooled and meta-analyses (1, 2, 32, 33) have been conducted providing us with highly reliable estimates of the impact of these factors on overall risk. So a case–case design enables efficient evaluation of etiologic heterogeneity across breast cancer subtypes. We relied primarily on data from medical records, and the high agreement between data from two sources and the fact that results remained unchanged when restricting to medical records data only provides some reassurance that this bias likely had limited impact on our findings. Although data on breast feeding and age at menarche were exclusively from interviews, it is unlikely women would differentially recall these factors according to their breast cancer subtype. There is also some potential misclassification of our case groups given that ER, PR, and HER2 data were ascertained from the various laboratories and clinics that serve our catchment areas and so some variation in laboratory protocols and assays are expected. However, it is unlikely that this misclassification would be differential according to the reproductive factors assessed. Although this study included more Hispanic women than most previous studies on this topic, the numbers of cases with specific subtypes were still too small for analyses stratified by race/ethnicity.

The poorer prognosis of TN and H2E breast cancers and their disproportionately burden on Hispanic women and other medically disadvantaged groups makes it critical to identify factors that differentially influence the development of these two subtypes. Modifiable risk factors such as breast feeding, if its etiologic role on TN cancers is confirmed, are of great public health significance which may inform prevention strategies to help close the gap in breast cancer survival across racial/ethnic groups due to differential occurrence of breast cancer subtypes.

The potential detrimental effects of increasing parity, early age at first birth, and age at menopause, and never breast feeding in relation to H2E and TN breast cancers may partly explain the racial/ethnic differences in the occurrence of different breast cancer subtypes. Studies have consistently observed that the incidence rates of both TN and H2E breast cancer are higher in African American and Hispanic women (24, 34). Although we were limited by the sample sizes of African American and Hispanic women to detect variations in these relationships across race/ethnicity, it is well documented (26) and also observed in our study that African American and Hispanic women tend to have more births and have a first birth at a younger age and that African American women are less likely to breast feed for long durations (with one study showing that 12.5% of African Americans breast fed for 12 months or longer compared to 24.3% of whites; ref. 35). Thus, the different distributions of these reproductive factors, in addition to potential differences in biologic or genetic susceptibility, may to some extent account for the disproportionate burden of these aggressive breast cancer subtypes observed among African American and Hispanic women.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

The NCI had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

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