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Reproductive History and Risk of Three Breast Cancer Subtypes Defined by Three Biomarkers

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Abstract

Breast cancer subtypes defined by estrogen-receptor (ER), progesterone-receptor (PR), and HER2 expression are biologically distinct and, thus, may have distinct etiologies. In particular, it is plausible that risk factors operating through hormonal mechanisms are differentially related to risk of such tumor subtypes. Using data from the Breast Cancer Surveillance Consortium, we explored associations between reproductive history and three breast cancer subtypes. Data on parity and age at first birth were collected from 743,623 women, 10,896 of whom were subsequently diagnosed with breast cancer. Cases were classified into three subtypes based on tumor maker expression: 1) ER-positive (ER+, N=8,203), 2) ER-negative / PR-negative / HER2-positive (ER-/PR-/HER2+, N=288), or 3) ER, PR, and HER2-negative (triple-negative, N=645). Associations with reproductive history, evaluated using Cox regression, differed significantly across tumor subtypes. Nulliparity was most strongly associated with risk of ER+ breast cancer [hazard ratio (HR) = 1.31, 95% confidence interval (CI): 1.23–1.39]; late age at first birth was most strongly associated with risk of ER-/PR-/HER2+ disease (HR=1.83, 95% CI: 1.31–2.56). Neither parity nor age at first birth was associated with triple-negative breast cancer. In contrast to ER+ and ER-/PR-/HER2+ subtypes, reproductive history does not appear to be a risk factor for triple-negative breast cancer.

Keywords

breast cancer; parity; age at first birth; triple-negative

INTRODUCTION

Increasing evidence suggests that breast cancer subtypes defined by expression of the estrogen receptor (ER), progesterone receptor (PR), and HER2 represent distinct biological entities (1–4) with distinct clinical profiles (5–8). Breast cancers that are ER-positive (ER+) have been associated with over-expression of genes in the ER signaling pathway (3) and,

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clinically, are associated with the most favorable prognosis (5–8). By comparison, triple-negative breast cancers (i.e., ER-negative, PR-negative, HER2-negative) are most likely to exhibit a basal-like pattern of gene expression, characterized by over-expression of genes in the p21 and DNA replication pathways (3), and exhibit a more aggressive tumor pathology (5–7,9). Breast cancers that are ER-negative, PR-negative, and HER2-positive (ER-/PR-/HER2+) exhibit over-expression of genes in the HER2 signaling pathway and, like triple-negative breast cancers, are associated with a less favorable prognosis (5–8).

The distinct genotypes and phenotypes of ER+, triple-negative, and ER-/PR-/HER2+ tumors suggest that these disease subtypes likely also have distinct etiologies. Few studies, however, have assessed associations with traditional breast cancer risk factors separately for ER+, triple-negative, and ER-/PR-/HER2+ breast cancers. In particular, while much literature has been devoted to characterizing risk factor associations for ER+ breast cancer (10–13), few risk factors have been identified for the less common but poorer prognosis triple-negative and ER-/PR-/HER2+ subtypes. The few studies that have explored risk factor associations for triple-negative and ER-/PR-/HER2+ cancers have been inconsistent and limited by small numbers. One finding that has been reported by multiple studies, however, is an increased risk of triple-negative disease among parous women (14–16). Most recently, Ma et al. reported a 1.5-fold increased risk of triple-negative breast cancer in women aged 45–64 years with ≥ 4 full-term pregnancies relative to nulliparous women (16). Such an association is in contrast to the well-established inverse association between parity and risk of ER+ breast cancer (10–13). However, not all studies of triple-negative breast cancer have noted this association (17–19) and few studies have been adequately powered to assess the association between parity and risk of ER-/PR-/HER2+ disease (14,16,17,20). Thus, there remains a need to better characterize the relationship between reproductive history and risk of triple-negative and ER-/PR-/HER2+ breast cancers in contrast to ER+ disease. Here we examine the association between parity, age at first birth, and risk of these three breast cancer subtypes using data from the Breast Cancer Surveillance Consortium (BCSC).

MATERIALS AND METHODS

The BCSC is a collaborative effort between geographically dispersed mammography registries. Details regarding the BCSC have been provided elsewhere (21). The present analysis includes data from the five BCSC registries that collect data on HER2 expression status and reproductive history: Group Health (western Washington State), the New Hampshire Mammography Network, the New Mexico Mammography Project, the San Francisco Mammography Registry, and the Vermont Breast Cancer Surveillance System. These registries collect risk factor information through self-administered questionnaires completed by women at the time of screening mammography (22). Specifically, self-reported data on attained age, race, Hispanic ethnicity, prior history of breast procedures, family history of breast cancer in first-degree relatives, prior births, and age at first birth are collected at the time of mammography.

Each registry and the BCSC Statistical Coordinating Center have received institutional review board approval for either active or passive consenting processes or a waiver of consent to enroll participants, link data, and perform analytic studies. All procedures are Health Insurance Portability and Accountability Act compliant. All registries and the Statistical Coordinating Center have received a Federal Certificate of Confidentiality and other protection for the identities of women, physicians, and facilities who are subjects of this research.

Study Population

The study population included women ages of 40–84 years with no history of invasive or *in situ* breast cancer at the time of mammography screening. Women meeting these criteria who received at least one screening mammogram at a BCSC facility during the study period were included in the study population. Mammograms were considered to be for screening purposes based on a standard definition used by the BCSC (23). The timing and duration of the study period varied among BCSC registries, reflecting differences in the earliest breast cancer diagnosis date for which HER2 data had been submitted to the Statistical Coordinating Center, and the date up to which cancer ascertainment was complete. Registry-specific study period start dates ranged from January 1, 1999 to January 1, 2003; end dates ranged from May 31, 2007 to October 31, 2008.

After excluding women not meeting eligibility criteria, 743,623 women were eligible for inclusion in the present analysis. Among women not diagnosed with breast cancer during follow-up, the median duration of follow-up was 5.1 years. Over follow-up, 486,353 women (65%) in the study population received more than one mammogram and 212,217 (29%) received ≥ 4 mammograms.

Case Population

Information on invasive breast cancer diagnoses among women in the study population was obtained by each BCSC registry through linkage with cancer registries and/or pathology databases. Case eligibility was contingent on a diagnosis of invasive breast cancer at any time interval subsequent to an eligible screening mammogram that occurred within the study period. Among women in the study population who met case criteria (N=10,896), the median duration of follow-up after the first eligible screening mammogram and prior to breast cancer diagnosis was 2.2 years. The median time between diagnosis and a case's most recent prior screening mammogram was 56 days (range: 0 days to 8.3 years). Women diagnosed with invasive breast cancer on the same day as their first screening mammogram during the study period (N=346) were recoded such that they contributed one day of follow-up and, therefore, contributed to the analysis. Data on ER and PR status was available for 90% (N=9,797) of cases. HER2 status was known for 56% of cases (N=6,137), including 61% of ER-/PR- cases (N=933). Cases with HER2 results of 0, 1+, or 2+ from immunohistochemistry (IHC) testing and/or a negative (ratio<1.8) or borderline (1.8 ≤ ratio< 2.2) result on fluorescence *in situ* hybridization (FISH) testing were considered HER2-negative (HER2-); conversely, HER2 results of 3+ on IHC and/or a positive FISH result (ratio ≥ 2.2) were considered HER2-positive (HER2+). Among cases with sufficient tumor marker data, 8,203 (89%), 288 (3%), and 645 (7%) were classified as having tumors of the ER+, ER-/PR-/HER2+, and triple-negative subtype, respectively. An additional 1,630 cases could not be classified into a subtype due to insufficient tumor marker data (1,042 missing ER status, 588 ER-/PR- with missing HER2 status), and 130 were ER- and either PR+ or missing PR status.

Statistical Analyses

We used Cox proportional hazards regression to assess the association between parity, age at first birth, and breast cancer risk by tumor subtype. Separate models were constructed for each outcome (i.e., invasive ER+, ER-/PR-/HER2+, and triple-negative breast cancer). Women diagnosed with breast cancer of a subtype other than the model-specific outcome were censored at diagnosis. Women diagnosed with *in situ* breast cancer were also censored at the time of diagnosis and, thus, did not contribute to any case group. We compared HR estimates across subtype-specific models using competing risks partial likelihood methods to evaluate equality (24). In each model, the time axis was defined as the time (in days) since a woman's first eligible screening mammogram during the study period. To account

for the fact that some women contributed risk factor information from repeated questionnaires during study follow-up, exposures and covariates other than age were modeled with time-varying variables, such that a woman's variable values were updated each time she completed a questionnaire. We evaluated proportional hazards assumptions for all models by testing for a non-zero slope of the scaled Schoenfeld residuals on ranked failure times and on the log of analysis time. All analyses were conducted using STATA MP Version 11.0 (College Station, Texas).

In two sets of analyses we examined the association between parity (nulliparous / parous), age at first birth (nulliparous / age <30 years / age ≥ 30 years or greater), and subtype-specific breast cancer risk. The selection of exposure categories for parity and age at first birth was based on the level of detail consistently available across BCSC registries. Analyses were adjusted for a limited set of confounders, including race (white / non-white), family history of breast cancer in first-degree female relatives (yes / no), and personal history of a benign breast procedure (yes / no); baseline hazards were stratified by age (five-year categories). Additional possible confounders were evaluated (education level, Hispanic ethnicity, body mass index), but were not included in the final multivariate model since they altered estimates by less than 10%.

Parity, age at first birth, and most covariates in the regression models were associated with some degree of missingness. Since these variables were unlikely to change with great frequency over follow-up, a filling process was used to resolve missing values: missing values of a variable were replaced with non-missing data provided by the same woman at a prior mammogram or, if no prior non-missing data were available, missing data were replaced with non-missing data provided at a subsequent mammogram from the same woman. Prior to filling, parity was unknown for 11.6% (N=232,169) of observations; age at first birth was unknown for 4.7% (N=66,937) of observations in women who reported being parous. Filling reduced missingness in these variables to 7.4% (N=147,672) and 2.5% (N=37,638), respectively. We used a complete-case approach in primary analyses, excluding observations with incomplete exposure and covariate data (after filling), and censoring case observations with insufficient tumor marker data to allow for case group allocation at the time of diagnosis. To explore the possible impact of missing data, we also performed multiple imputation (25), using an imputation model that included all exposures and covariates, a censoring indicator, a variable for the log of analysis time, and tumor marker characteristics. Results based on multiple imputation served as a sensitivity analysis for comparison to results from the primary analyses presented.

RESULTS

Distributions of demographic characteristics for the overall study population and for each case group, based on information provided at each woman's most recent mammogram during the study period and excluding observations from women with unknown parity, are presented in Table 1. Compared to the overall study population, a greater proportion of ER-/PR-/HER2+ cases reported Asian/Pacific Islander race/ethnicity (20% versus 12%) and a greater proportion of triple-negative cases were African-American (7% vs. 3%). With respect to tumor characteristics, women with ER+ breast cancer were more likely to be diagnosed at stage I (60% versus 40% and 45% of ER-/PR-/HER2+ and triple-negative cases, respectively) and were less likely to have high grade tumors (20% in grades 3 and 4 versus 71% and 76% of ER-/PR-/HER2+ and triple-negative cases, respectively).

Compared to parous women overall, nulliparous women had a 1.31-fold [95% confidence interval (CI): 1.23–1.39] increased risk of ER+ breast cancer. In contrast, there was no evidence of an increased risk of triple-negative [hazard ratio (HR) = 1.07, 95% CI: 0.87–

1.33] or ER-/PR-/HER2+ breast cancer (HR=1.15, 95% CI: 0.84–1.58) among nulliparous versus parous women. When compared more specifically to parous women who reported a first birth before age 30, nulliparous women had a greater risk of ER+ and ER-/PR-/HER2+ subtypes, but not triple-negative breast cancer. Risk of triple-negative breast cancer was modestly but not significantly increased among parous women who reported that their first birth occurred at age ≥ 30 relative to parous women with an earlier age at first birth. However, parous women with a later age at first birth faced a significantly increased risk of the other two disease subtypes; in particular, parous women whose first birth was at age ≥ 30 had a 1.83-fold (95% CI: 1.31–2.56) increased risk of ER-/PR-/HER2+ breast cancer relative to women with an earlier age at first birth. In analyses of parity overall and of parity combined with age at first birth, partial likelihood tests indicated a significant departure from equality of the subtype-specific HR estimates ($p<0.01$ for both analyses).

HR estimates for the ER+ subtype were changed by less than five percent in sensitivity analyses using multiple imputation to assess the impact of missing exposure, covariate, and tumor marker data. Estimates with respect to the ER-/PR-/HER2+ and triple-negative subtypes were affected to a greater extent, although conclusions were similar. Specifically, analyses based on multiply-imputed data indicated no increased risk of ER-/PR-/HER2+ breast cancer and a non-significant reduced risk of triple-negative breast cancer among nulliparous women relative to parous women with a first birth at age <30 years ($HR_{ER-/PR-/HER2+}$=1.09, 95% CI: 0.84 – 1.43; $HR_{triple-negative}$=0.89, 95% CI: 0.76–1.05, data not shown). Subtype-specific HR estimates for the association with late age at first birth were attenuated ($HR_{ER-/PR-/HER2+}$ =1.43, 95% CI: 1.08–1.90; $HR_{triple-negative}$=1.06, 95% CI: 0.87–1.29), although confidence intervals overlapped considerably with those from the primary analysis (Table 2).

DISCUSSION

In this large cohort of women undergoing screening mammography, we found differences in the magnitude and directionality of associations between reproductive history and risk of ER +, ER-/PR-/HER2+, and triple-negative breast cancer subtypes. Nulliparity was associated with a significantly increased risk of ER+ breast cancer but was not associated with risk of ER-/PR-/HER2+ or triple-negative breast cancer. Associations with age at first birth varied significantly in magnitude across subtypes: late age at first birth was most strongly associated with risk of ER-/PR-/HER2+ disease and was not associated with risk of the triple-negative breast cancer.

The limitations of this analysis should be considered in interpreting these findings. With respect to the study population, the BCSC is not a true prospective cohort with complete follow-up. Incomplete case-ascertainment could have resulted if women in the study population were diagnosed with breast cancer after moving outside the area covered by BCSC-affiliated cancer registries and pathology databases. We expect the impact of such bias to be small; in an exploratory analysis, we restricted follow-up to the 24-month interval following a screening mammogram (thereby reducing the opportunity for out-migration) and found almost no change in results. Also, because tumor marker data are taken from multiple laboratories across BCSC registries, and because the assays and practices for interpreting results of tumor marker testing can vary across institutions, particularly for HER2, some misclassification of case subtypes is possible. However, it is reasonable to assume that this misclassification is non-differential with respect to reproductive history. Lastly, the range of variables on reproductive history and the level of detail on these variables are limited; thus, we cannot report on subtype-specific associations with age at last birth or breastfeeding history, and we were unable to evaluate associations with increasing parity or finer categorizations of age at first birth. This latter limitation could influence the interpretation of

our results. In particular, previous studies of breast cancer overall have suggested that disease risk is lower in women with a first birth at age <20 than in women with a first birth between ages 20–29 (11); thus, grouping together all women with an age at first birth <30 could have reduced our ability to detect an increased risk in women with an age at first birth ≥ 30.

Missingness in exposure, covariate, and tumor marker data presents a further limitation to the interpretation of study findings. Sensitivity analyses using multiple imputation to account for missing data suggest that this missingness did not impact findings with respect to the ER+ subtype. However, these analyses do suggest the association between age at first birth and risk of ER-/PR-/HER2+ breast cancer observed in the primary analysis could be overestimated.

Consistent with the results presented here, several epidemiologic studies stratifying breast cancer cases by ER status alone or by joint ER/PR status have indicated that the inverse association between parity and breast cancer risk, and the positive association with age at first birth, are largely restricted to hormone receptor-positive breast cancers (11–13). Evidence regarding the association between reproductive history and risk of triple-negative breast cancer is more inconsistent (14–20). Three studies have noted positive associations between parity and risk of triple-negative breast cancer (14,15,20), while two have noted no association (16,17), and two have noted a non-significant inverse association (18,19). The very few studies that have explored the association between reproductive history and risk of ER-/PR-/HER2+ breast cancer have also failed to produce any consistent findings (14,16,17,20); such inconsistencies may be the result of small sample sizes in prior studies (range N=39 to N=154), and may also reflect the considerable differences between existing studies with respect to the demographic composition of study populations.

Nulliparity and late age at first live birth are well-established risk factors for breast cancer overall (26), although the exact biological mechanisms underlying these associations are unknown. One hypothesis is that the inverse association between parity and breast cancer risk is in part attributable to the fact that parous women experience fewer lifetime ovulatory cycles than their nulliparous counterparts, resulting in a lower cumulative lifetime exposure to endogenous ovarian hormones (27). If such hormonal biological mechanisms predominate, then it is not surprising that our results suggest nulliparity and late age at first birth are associated with risk of ER+ but not triple-negative breast cancer. However, given that ER-/PR-/HER2+ breast cancers are thought to be hormonally insensitive, the fact that we observed a positive association between late age at first birth and risk of ER-/PR-/HER2+ breast cancer suggests that non-hormonal mechanisms for association may also be important. One such hypothesis is that differentiation in the breast tissue induced by pregnancy makes the breast less susceptible to carcinogenic insult, especially if that differentiation is induced earlier in life (28). If and how non-hormonal mechanisms could differentially contribute to risk of specific subtypes of breast cancer, however, remains unclear.

There is considerable evidence to suggest that ER+, ER-/PR-/HER2+, and triple-negative subtypes of breast cancer are biologically (1–4) and clinically (5–8) distinct forms of disease. A growing literature, including the present analysis, now supports the hypothesis that these tumor subtypes are also distinct in their epidemiology (14–20). While there remains a need to better characterize the epidemiology of ER-/PR-/HER2+ and triple-negative subtypes, the results of this analysis suggest that late age at first birth is associated with risk of ER-/PR-/HER2+ breast cancer, but that neither age at first birth nor parity are associated with risk of triple-negative breast cancer.

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Table 1

Study population and case group characteristics[a]

	OVERALL STUDY POPULATION N (%)	CASES		
		ER+ N (%)	ER-/PR-/HER2+ N (%)	Triple-Negative N (%)
Age at mammogram				
40–44	148,013 (22)	789 (10)	31 (12)	77 (13)
45–49	112,680 (17)	976 (13)	44 (17)	98 (16)
50–54	117,825 (18)	1,172 (15)	60 (23)	82 (13)
55–59	88,363 (13)	1,185 (16)	40 (15)	98 (16)
60–64	63,954 (10)	992 (13)	31 (12)	86 (14)
65–69	50,435 (8)	824 (11)	25 (9)	54 (9)
70–74	40,228 (6)	791 (10)	16 (6)	47 (8)
75–79	30,600 (5)	595 (8)	12 (5)	50 (8)
80–84	16,870 (3)	321 (4)	6 (2)	19 (3)
Race / ethnicity				
White non-Hispanic	468,317 (74)	5,895 (80)	174 (70)	432 (75)
Hispanic white	43,715 (7)	281 (4)	2 (1)	4 (1)
African-American	19,251 (3)	207 (3)	10 (4)	41 (7)
Asian / Pacific Islander	75,142 (12)	734 (10)	51 (20)	69 (12)
Other	27,880 (4)	251 (3)	12 (5)	29 (5)
Missing	34,663	277	16	36
Prior breast biopsy or surgery				
No	530,624 (80)	5,333 (72)	185 (72)	448 (75)
Yes	133,429 (20)	2,114 (28)	73 (28)	148 (25)
Missing	4,915	198	7	15
Family history of breast cancer				
No	541,972 (85)	5,420 (77)	195 (80)	447 (77)
Yes	98,139 (15)	1,658 (23)	49 (20)	132 (23)
Missing	28,857	567	21	32
Education level				
Less than high school	175,120 (31)	2,071 (29)	67 (26)	162 (27)
High school or greater	396,370 (69)	5,075 (71)	194 (74)	441 (73)
Missing	97,478	499	4	8
Stage at diagnosis				
I	N/A	4,524 (60)	104 (40)	272 (45)
II		2,392 (32)	103 (39)	254 (42)
III / IV		607 (8)	56 (21)	80 (13)
Missing		122	2	5
Grade at diagnosis				
1	N/A	2,182 (30)	10 (4)	26 (5)
2		3,537 (49)	61 (25)	108 (19)
3		1,378 (19)	164 (68)	432 (74)

	OVERALL STUDY POPULATION N (%)	CASES		
		ER+ N (%)	ER-/PR-/HER2+ N (%)	Triple-Negative N (%)
4		63 (1)	7 (3)	14 (2)
Missing		485	23	31

[a]Counts reflect exposure status for members of the study cohort at the time of the last mammogram during the study period. Excludes women with unknown parity (N=74,869 total, 558 ER+ cases, 23 ER-/PR-/HER2+ cases, and 34 triple-negative cases).

Table 2

Reproductive history and subtype-specific breast cancer risk

	TOTAL		ER+ Cases		ER-/PR-/HER2+ Cases		Triple-Negative Cases	
	N[a] (%)	Person-Years (%)	N[a] (%)	HR (95% CI)[b]	N[a] (%)	HR (95% CI)[b]	N[a] (%)	HR (95% CI)[b]
Parity								
Nulliparous	126,062 (19)	651,619 (20)	1,676 (22)	1.31 (1.23–1.39)[c]	58 (22)	1.15 (0.84–1.58)	116 (19)	1.07 (0.87–1.33)
Parous	542,906 (81)	2,687,133 (80)	5,969 (78)	1.0 (ref)	207 (78)	1.0 (ref)	495 (81)	1.0 (ref)
Age at 1st birth								
Nulliparous	126,062 (20)	651,619 (20)	1,676 (22)	1.39 (1.31–1.48)[c]	58 (22)	1.34 (0.96–1.88)	116 (19)	1.09 (0.87–1.35)
Parous:								
Age <30	422,595 (65)	2,115,385 (65)	4,629 (62)	1.0 (ref)	147 (57)	1.0 (ref)	397 (66)	1.0 (ref)
Age 30+	97,972 (15)	489,309 (15)	1,177 (16)	1.37 (1.28–1.47)[c]	54 (21)	1.83 (1.31–2.56)[c]	93 (15)	1.18 (0.93–1.51)
Age unknown	22,339	82,440	163		6		5	

[a] Counts reflect exposure status for members of the study cohort at the time of the last mammogram during the study period. Excludes women with unknown parity (N=74,869 total, 558 ER+ cases, 23 ER-/PR-/HER2+ cases, 34 triple-negative cases).

[b] Adjusted for age at start of follow-up interval (5-year categories), white race, family history, and prior breast procedure.

[c] p<0.05