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EPIDEMIOLOGY

Reproductive factors and risk of estrogen receptor positive, triple-negative, and HER2-neu overexpressing breast cancer among women 20–44 years of age

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Abstract Aspects of reproductive history are among the most well-established breast cancer risk factors. However, relatively little is known about how they influence risk of different molecular subtypes of breast cancer, particularly among younger women. Using data from a population-based case–control study of women 20–44 years of age, we assessed the relationships between various reproductive factors and risk of estrogen receptor positive (ER+), triple-negative, and HER2-overexpressing breast cancers. Detailed reproductive histories were obtained through structured interviewer administered in-person questionnaires. Reproductive histories among control women ($n = 941$) were compared to those of ER+ cases ($n = 781$), triple-negative cases ($n = 180$), and HER2-overexpressing cases ($n = 60$) using polytomous logistic regression. Age at menarche, parity, and number of full-term pregnancies were similarly associated with risk of all three breast cancer subtypes. In contrast, age at first live birth, the interval between age at menarche and age at first birth, and breastfeeding were inversely associated with risk of triple-negative breast cancer (P values for trend 0.002, 0.006 and 0.018, respectively), but were not associated with risk of ER+ or HER2-overexpressing cancers. A strong inverse association between breastfeeding and risk of triple-negative breast cancer has now been consistently observed across numerous studies, and at present it is the most well-established protective factor for this aggressive and lethal form of breast cancer. Further studies clarifying the biological mechanisms underlying this relationship and confirming our results with respect to age at first birth and the interval between age at menarche and age at first birth are needed.

Keywords Breast cancer · Triple-negative · Estrogen receptor · Reproductive factors

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Introduction

Reproductive factors are among the earliest and most well-established breast cancer risk factors. With respect to premenopausal breast cancer in particular, there is compelling evidence from pooled analyses that the risk of premenopausal breast cancer is reduced 9 % for each year of age menarche is postponed, is increased by 5 % for each additional year age at first birth is delayed [1], and is reduced by 4 % with each additional 12 months of breastfeeding [2]. However, almost all studies evaluating relationships between reproductive factors and premenopausal breast cancer risk have grouped all breast cancers together with few stratifying results according to tumor subtypes. The identification and validation of distinct molecular subtypes of breast cancer based on patterns of gene expression have shifted that how we approach this complex disease [3, 4]. The most common subtypes are estrogen receptor-positive (comprising the luminal A and luminal B subtypes), while two of the more aggressive subtypes, which carry comparatively poorer prognoses, are triple-negative tumors [they lack estrogen receptor (ER), progesterone receptor (PR), and HER2-neu (HER2) expression and the majority of them have the so-called basal-like phenotype] and HER2-

overexpressing tumors (ER−/HER2+) [5, 6]. The unique molecular characteristics of the different subtypes along with the considerable variability in their prognoses suggest that they likely have unique etiologies.

Only a handful of published studies have evaluated how reproductive factors may be differentially associated with risk of different molecular subtypes of breast cancer. Only one has presented results specifically focused on young women (35–44 years of age) [7], and the remainder either did not stratify results by age or menopausal status [8–10], or they only included postmenopausal women [11, 12]. Studies focused on young women are of particular relevance because triple-negative and HER2-overexpressing tumors both account for higher proportions of cases among premenopausal women than they do among postmenopausal women [9], and it is well established that the strength and direction of associations between reproductive factors and premenopausal versus postmenopausal breast cancer vary [1, 13]. Here, we present results from a study focused on quantifying the relationships between reproductive factors and risk of different molecular subtypes of breast cancer among young women 20–44 years of age.

Methods

The design and overall methods employed in this study have been previously published [14]. Briefly, we conducted a population-based case–control study where all women 20–44 years of age diagnosed with invasive breast cancer between June 2004 and June 2010 in the three county Seattle–Puget Sound metropolitan area were eligible as cases. These patients were identified through our local population-based cancer registry. Of the 1,359 eligible cases identified, 1,056 (78 %) were interviewed. Data on tumor characteristics were obtained from the cancer registry and from a centralized review of pathology reports including data on ER, PR, and HER2 status. ER and PR positivity were defined as positive staining of $\geq$1 % of cells and negativity as 0 or <1 % positive staining of cells. HER2 positivity was based on an immunohistochemistry (IHC) score of 3+ and/or a FISH-positive result, and negativity was defined as an IHC score of 0 or 1+ and/or a FISH-negative result. This information was used to group cases into three groups approximating the different molecular subtypes of breast cancer: ER+ (approximating the luminal subtypes), ER−/PR−/HER2− (this triple-negative group approximates the basal-like subtype), and ER−/HER2+ (approximating the HER2-overexpressing subtype). This approach has been used in several other studies focused on characterizing risk factors for different molecular subtypes of breast cancer [7, 8, 11, 12, 15–17]. The 28 cases for whom data on ER, PR, and/or HER2 status were missing could not be classified by subtype and were therefore excluded from all analyses.

A population-based control group, frequency matched within 5-year age groups to the cases, was identified and recruited using random digit dialing. We used a combination of list-assisted (purchased randomly generated telephone numbers) and Mitofsky–Waksberg (telephone numbers randomly generated ourselves using a clustering factor of 5) [18] random digit dialing methodologies. Of the 1,489 eligible controls identified, 943 (63 %) were interviewed.

Data collection

The study protocol was approved by the Fred Hutchinson Cancer Research Center Institutional Review Board, and written informed consent was obtained from all study subjects. Cases and controls were interviewed in-person and asked about a variety of exposures. In particular, comprehensive reproductive histories were obtained including details relating to each pregnancy participants ever had such as their age at each pregnancy, the pregnancy's outcome, and if the pregnancy was a live birth their breastfeeding history. Using this information, we assessed the relationship between age at menarche, parity, number of live births, age at first live birth, age at last birth, and breastfeeding in relation to risks of ER+, triple-negative, and HER2-overexpressing breast cancers. In addition, we estimated risks associated with the time interval between age at menarche and age at first live birth. All our questions were limited to exposures that occurred before each participant's reference date. The reference date used for each woman with breast cancer was her diagnosis date, and controls were assigned reference dates that reflected the distribution of reference dates among the cases. Data on one or more reproductive factors were missing for two controls and three cases. These participants were excluded from all analyses and thus our final analytic data set consisted of 941 control women, 781 ER+ cases, 184 triple-negative cases, and 60 HER2-overexpressing cases.

Statistical analysis

Polytomous logistic regression was used to simultaneously estimate the risks associated with a particular aspect of reproductive history in relation to each of the three breast cancer subtypes in comparison to controls within a single statistical model. These models calculated odds ratios (OR), which approximate relative risks, and their associated 95 % confidence intervals (CI) [19]. *P* values for trend where appropriate were calculated by treating categorical variables as ordered continuous variables. *P* values comparing risks across case types were performed in analyses that excluded the control group and used the ER+ case

Table 1 Distribution of selected characteristics among controls, ER+ cases, triple-negative cases, and HER2-overexpressing cases

Characteristic	Controls ($n = 941$)		Cases					
			ER+ ($n = 781$)		Triple-negative ($n = 184$)		HER2-overexpressing ($n = 60$)	
	n	%	*n*	%	*n*	%	*n*	%
Age (years)								
20–29	25	2.7	15	1.9	7	3.8	2	3.3
30–34	86	9.1	56	7.2	23	12.5	6	10.0
35–39	268	28.5	201	25.7	59	32.1	22	36.7
40–44	562	59.7	509	65.2	95	51.6	30	50.0
Reference (years)								
2004–2005	308	32.7	214	27.4	62	33.7	17	28.3
2006–2007	361	38.4	273	35.0	58	31.5	25	41.7
2008–2010	272	28.9	294	37.6	64	34.8	18	30.0
Race/ethnicity								
Non-Hispanic white	766	81.8	606	78.6	142	78.0	48	80.0
African American	34	3.6	32	4.2	17	9.3	4	6.7
Asian/Pacific Islander	82	8.8	98	12.7	14	7.7	6	10.0
Native American	19	2.0	19	2.5	7	3.8	1	1.7
Hispanic White	35	3.7	16	2.1	2	1.1	1	1.7
Missing	5		10		2		0	
Education								
High school or less	97	10.4	89	11.5	24	13.2	8	13.3
Post high school/some	305	32.6	251	32.3	65	35.7	16	26.7
College graduate	354	37.8	283	36.5	69	37.9	23	38.3
Post college	181	19.3	153	19.7	24	13.2	13	21.7
Missing	4		5		2		0	
Annual household in come								
<$25,000	74	7.9	59	7.7	13	7.2	7	11.7
$25,000–49,999	122	13.1	111	14.5	31	17.2	12	20.0
$50,000–89,999	348	37.4	253	33.0	48	26.7	20	33.3
≥$90,000	387	41.6	343	44.8	88	48.9	21	35.0
Missing	10		15		4		0	
First-degree family history of breast cancer								
No	816	89.9	605	80.2	142	78.9	48	81.4
Yes	92	10.1	149	19.8	38	21.1	11	18.6
Missing	33		27		4		1	
Body mass index 1 year prior to reference age (kg/m^2)								
<25.0	531	56.9	472	61.1	98	54.1	38	63.3
25.0–29.9	234	25.1	181	23.4	44	24.3	8	13.3
≥30.0	169	18.1	120	15.5	39	21.5	14	23.3
Missing	7		8		3		0	
Duration of oral contraceptive use (years)								
Never	102	10.9	91	11.7	15	8.3	11	18.3
<5.0	339	36.2	274	36.6	61	33.7	22	36.7
5.0–9.9	218	23.3	157	20.2	39	21.5	11	18.3
≥10.0	278	29.7	245	31.5	66	36.5	16	26.7
Missing	4		4		3		0	

Table 2 Relationship between reproductive factors and risk of invasive breast cancer by subtype

Risk factor	Controls ($n = 941$)		ER+ cases ($n = 781$)				Triple-negative ($n = 184$)				HER2-overexpressing cases ($n = 60$)			
	n	%	*n*	%	OR*	95 % CI	*n*	%	OR*	95 % CI	*n*	%	OR*	95 % CI
Age at menarche (years)														
<12	191	20.3	171	21.9	1.0	Ref	44	23.9	1.0	Ref	11	18.3	1.0	Ref
12–13	523	55.6	441	56.5	0.9	0.7–1.2	102	55.4	0.8	0.6–1.3	42	70.0	1.4	0.7–2.7
≥14	227	24.1	169	21.6	0.8	0.6–1.1	38	20.7	0.7	0.5–1.2	7	11.7	0.5	0.2–1.4
P value for trend:			0.219				0.199				0.221			
							P value versus ER+ cases: 0.594				*P* value versus ER+ cases: 0.441			
Parity (ever had a live birth)														
Nulliparous	188	20.0	207	26.5	1.0	Ref	51	27.7	1.0	Ref	11	18.3	1.0	Ref
Parous	753	80.0	574	73.5	0.7	0.5–0.8†	133	72.3	0.7	0.5–1.0†	49	81.7	1.1 R+	0.6–2.2
							P value versus ER+ cases: 0.960				*P* value versus ER+ cases: 0.110			
Number of live births (parous women only)														
1	192	25.5	161	28.0	1.0	Ref	33	24.8	1.0	Ref	14	28.6	1.0	Ref
2	363	48.2	282	49.1	0.9	0.7–1.1	68	51.1	1.0	0.6–1.6	23	46.9	0.8	0.4–1.6
≥3	198	26.3	131	22.8	0.7	0.5–0.9†	32	24.1	0.7	0.4–1.2	12	24.5	0.6	0.2–1.4
P value for trend:					0.015				0.172				0.220	
							P value versus ER+ cases: 0.425				*P* value versus ER+ cases: 0.779			
Age at first live birth, years (parous women only)														
<20	59	7.8	56	9.8	1.4	0.9–2.2	21	15.8	1.6	0.9–3.1	5	10.2	1.2	0.4–3.5
20–24	162	21.5	117	20.4	1.0	Ref	37	27.8	1.0	Ref	12	24.5	1.0	Ref
25–29	228	30.3	188	32.8	1.1	0.8–1.5	35	26.3	0.6	0.4–1.0	20	40.8	1.1	0.5–2.4
30–34	204	27.1	143	24.9	0.8	0.6–1.2	30	22.6	0.5	0.3–0.9†	8	16.3	0.5	0.2–1.2
≥35	100	13.3	70	12.2	0.7	0.5–1.1	10	7.5	0.4	0.2–0.8†	4	8.2	0.4	0.1–1.5
Per 5 years					0.94	0.85–1.03			0.77	0.65–0.91			0.85	0.65–1.10
P value for trend:					0.201				0.001				0.210	
							P value versus ER+ cases: 0.020				*P* value versus R+ cases: 0.230			
Interval between age at menarche and age at first live birth, years (parous women only)														
<10	141	18.7	109	19.0	1.0	Ref	40	30.1	1.0	Ref	14	28.6	1.0	Ref
10–14	200	26.6	163	28.4	1.0	0.7–1.4	36	27.1	0.6	0.4–1.0	8	16.3	0.4	0.2–1.0†
15–19	237	31.5	157	27.4	0.8	0.5–1.1	29	21.8	0.4	0.2–0.6†	17	34.7	0.7	0.3–1.5
>20	175	23.2	145	25.3	0.9	0.6–1.2	28	21.1	0.5	0.3–0.9†	10	20.4	0.5	0.2–1.4
P value for trend:					0.102				0.006				0.114	
							P value versus ER+ cases: 0.051				*P* value versus ER+ cases: 0.337			

Table 2 continued

Risk factor	Controls ($n = 941$)		ER+ cases ($n = 781$)				Triple (negative cases ($n = 184$)				HER2 expressing cases ($n = 60$)			
	n	%	*n*	%	OR*	95 % CI	*n*	%	OR*	95 % CI	*n*	%	OR*	95 % CI
Age at most recent live birth, years (parous women only)														
<25	79	10.5	62	10.8	1.0	Ref	23	17.3	1.0	Ref	6	12.2	1.0	Ref
25–29	151	20.1	132	23.0	1.2	0.8–2.0	30	22.6	0.9	0.5–1.9	14	28.6	1.5	0.4–4.8
30–34	282	37.5	207	36.2	1.1	0.7–2.0	56	42.1	1.2	0.5–2.6	18	36.7	1.5	0.4–5.7
≥35	241	32.0	173	30.1	1.2	0.7–2.3	24	18.0	0.6	0.2–1.7	11	22.4	1.6	0.3–8.0
P value for trend:					0.679				0.516				0.701	
							P value versus ER+ cases: 0.378				*P* value versus ER+ cases: 0.822			
Time since last live birth (years) (parous women only)														
<5	265	35.2	161	28.0	1.0	Ref	41	30.8	1.0	Ref	16	32.7	1.0	Ref
5–9.9	243	32.3	182	31.7	1.2	0.9–1.6	41	30.8	1.1	0.6–1.8	12	24.5	0.8	0.3–1.8
≥10	245	32.5	231	40.2	1.5	1.0–2.2	51	38.3	1.0	0.5–2.0	21	42.9	1.2	0.5–3.4
P value for trend:					0.062				0.884				0.712	
							P value versus ER+ cases: 0.338				*P* value versus ER+ cases 0.735			
Breastfeeding (parous women only)														
Never	60	8.0	53	9.3	1.0	Ref	19	14.3	1.0	Ref	4	8.2	1.0	Ref
Ever	692	92.0	519	90.7	0.9	0.6–1.4	114	85.7	0.6	0.4–1.1	45	91.8	1.2	0.4–3.9
<6 months	190	25.3	143	25.0	0.9	0.6–1.4	45	33.8	0.9	0.5–1.6	14	28.6	1.2	0.4–3.9
6–11 months	111	14.8	93	16.3	1.1	0.7–1.7	17	12.8	0.6	0.3–1.2	9	18.4	1.5	0.4–5.4
>12 months	389	51.9	283	49.5	1.0	0.6–1.5	52	39.1	0.5	0.3–0.9†	22	44.9	1.1	0.3–3.6
P value for trend:					0.606				0.018				0.086	
							P value versus ER+ cases: 0.009				*P* value versus ER+ cases: 0.713			

* All odds ratios (OR) are adjusted for 5-year age group and reference year. Number of live births is additionally adjusted for age at first live birth, the interval between age at menarche and age at first live birth is additionally adjusted for number of live births, and age at most recent live birth, time since last live birth, and breastfeeding history is additionally adjusted for age at first live birth and number of live births

† *P* value <0.05

group as the reference category. All analyses were adjusted for age (in 5-year groups) and reference year (continuous) as controls were matched to cases on these factors. We a priori adjusted our analysis of number of live births for age at first live birth, our analysis of the interval between age at menarche and age at first live birth for number of live births, and our analysis of breastfeeding for age at first live birth and number of live births. 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 statistical models. In particular, first-degree family history of breast cancer was neither a confounder nor an effect modifier (based on likelihood ratio testing). All analyses were conducted using Stata/SE version 11.2 (StataCorp LP, College Station, TX, USA).

Results

Compared to controls, ER+ cases were somewhat older and more likely to be Asian/Pacific Islander, and triple-negative and HER2-overexpressing cases were somewhat younger and more likely to be African American (Table 1). Triple-negative cases were also somewhat more likely to be less highly educated, to have higher annual household incomes, and to have used oral contraceptives compared to controls.

Age at menarche was not statistically significantly related to risk of any of the three breast cancer subtypes (Table 2). Parity was associated with a 30 % reduction in risk of both ER+ (95 % CI 0.5–0.8) and triple-negative (95 % CI 0.5–1.0) breast cancer, but not with risk of HER2-overexpressing disease (OR = 1.1, 95 % CI 0.6–2.2). Increasing number of live births was similarly associated with reduced risks of all three breast cancer subtypes although the only statistically significant association was in relation to ER+ breast cancer (P for trend = 0.015). While there was some suggestion that increasing age at first birth was associated with reduced risks of all three breast cancer subtypes, this relationship was only statistically significant for triple-negative breast cancer (P for trend = 0.002). Furthermore, the association with triple-negative disease was statistically different from the one between age at first live birth and risk of ER+ breast cancer (P value for comparison between these case groups = 0.034). The interval between age at menarche and age at first live birth was inversely related to risk of triple-negative breast cancer (P for trend = 0.006) but not to risk of ER+ (P value for the ER+ vs. triple-negative cases = 0.051). Finally, breastfeeding was not associated with risk of either ER+ or HER2-overexpressing breast cancer, but was associated with a reduced risk of triple-negative disease. This association was statistically different from the relationship between breastfeeding and ER+ breast cancer (P values for difference 0.009).

Discussion

The most notable differences in risk we observed by breast cancer subtype were with age at first live birth, the interval between age at menarche and age at first live birth, and breastfeeding. With respect to age at first birth, a pooled analysis of much of the world's literature suggests that risk of premenopausal breast cancer is increased by 5 % for each additional year age at first birth is delayed [1]. The results presented here suggest that increasing age at first birth was associated with a reduced risk of triple-negative breast cancer that was stronger in magnitude than the non-statistically significant reduced risks observed with respect to both ER+ and HER2-overexpressing breast cancers. Only six prior studies have assessed the relationship between age at first birth and breast cancer risk according to molecular subtype [7–12]. Four found that age at first birth was not related to risk of any of these three subtypes of breast cancer [7, 10–12], including the only previous study to present data specific to younger women (35–44 years of age) [7]. The other two studies found that age at first live birth was positively associated with risk of luminal A breast cancer, but was not associated with risk of any other breast cancer subtype [8, 9]. Of note, in all these studies there were relatively few women with later ages at first birth. In three studies, 90 % [11], 92 % [12], and 79 %[7] of the controls, respectively had an age at first birth of <30, in another 76 % had an age at first birth of <26 [9], and in two others the mean ages at first birth were 23.6 [10] and 22.5 [8] years. In contrast, in our study which was more recently conducted, only 59 % of parous controls had their first live birth at ≤30 years of age and the mean age at first birth was 27.8 years. It is possible that the comparatively smaller proportions of women with later ages at first birth in previous studies may have limited their statistical power.

The interval between age at menarche and age at first live birth is a metric that has only been assessed by a handful of studies, but it is of interest because it represents the period of time over which postpubertal breast tissue is relatively undifferentiated and potentially more susceptible to carcinogenic insults until the differentiation induced by pregnancy confers a long-term reduction in breast cancer risk occurs. Prior studies suggest that this interval is positively associated with breast cancer risk, but none has assessed risk according to joint ER/PR/HER2 status [20–23]. The novel finding here is that this interval was inversely associated with risk of triple-negative breast cancer. There was also a similar non-statistically significant suggestion that this interval was inversely associated with risk of HER2-overexpressing breast cancer, but this analysis was hampered by the comparatively few number of HER2-overexpressing cases included. These relationships with triple-negative and

HER2-overexpressing breast cancers are in the opposite direction of what has been observed for breast cancer overall in prior studies, but as this is the first report of these relationships these findings require confirmation.

A pooled analysis of 47 studies estimated that breast cancer risk is reduced by 4 % with each additional 12 months of breastfeeding [2]. Here, we observed that breast feeding is associated with a substantial reduction in risk of triple-negative breast cancer only, as it did not influence risk of either ER+ or HER2-overexpressing breast cancer. Five more recently published studies have evaluated this relationship by breast cancer subtype [7–9, 11, 12]. Three found that breastfeeding was statistically significantly associated with a reduced risk of triple-negative or basal-like breast cancer but was not associated with risk of ER+ or luminal A breast cancer [8, 9, 12], one study restricted to only postmenopausal women observed similar relationships though the trend for triple-negative breast cancer was not statistically significant [11], and one study found that breastfeeding was associated with reduced risks of similar magnitudes for both triple-negative and luminal A type breast cancers among young women 35–44 years of age [7]. The magnitude and direction of the relationship between breastfeeding and triple-negative breast cancer and the lack of an association with ER+ breast cancer observed here are consistent with the results of the majority of the studies that have assessed these relationships. Our results therefore add to the growing body of evidence that breastfeeding may indeed confer a lower risk of triple-negative breast cancer, a finding that here is supported by both our case–control (P for trend in the case–control comparison = 0.02) and case–case comparisons (P for comparison to the ER+ case group = 0.01). With the addition of our results, at present breastfeeding is the most consistently identified factor to be differentially associated with risk of triple-negative breast cancer compared to the other major molecular subtypes of the disease.

The biological mechanisms through which a late age at first birth, a longer interval between age at menarche and age at first live birth, and breastfeeding could preferentially confer a lower risk of triple-negative or basal-like breast cancer are largely unknown. These exposures are thought to influence breast cancer risk through the structural changes and differentiation of terminal ductal lobular units in breast tissue they are related to, rather than to be due to hormonal effects [24, 25]. Parous women experience differentiation of breast tissue that nulliparous women never do, and breastfeeding results in even greater differentiation. Further studies are required to replicate our findings with respect to age at first birth and the interval between age at menarche and age at first live birth as the relationships observed here between these two exposures and risk of triple-negative breast cancer are in the opposite direction from what has been observed for breast cancer overall. Why these exposures would have an opposite effect on triple-negative tumors remains unknown making replication critical. Alternatively, given the remarkable consistency across diverse populations with respect to the relationship between breastfeeding and triple-negative breast cancer further mechanistic studies to better understand how breastfeeding may confer a lower risk of this specific subtype of breast cancer are warranted. Such studies are not only of etiologic interest but also point to new approaches to prevent this particular aggressive form of breast cancer.

The potential protective effects of age at first birth and breastfeeding in relation to triple-negative breast cancer could in part also explain some of the demographic differences in the occurrence of triple-negative breast cancers observed in the United States. Specifically, it has been well characterized that higher proportions of breast cancer diagnosed among African American women are triple-negative compared to proportions among white women [5, 8, 9, 26–29]. It has also been shown that African American women are more likely to have a younger age at first birth and to never have breastfed compared to white women. In one study of women <40 years of age, 78 % of African Americans and 59 % of whites had their first birth before age 26 (P for difference = 0.04) and 82 % of parous African American women never breastfed compared to 61 % of white women (P for difference = 0.01) [9]. There were too few African American women in the study conducted here to construct the models needed to formally assess the extent to which differences in these reproductive characteristics could account for the observed higher risks of triple-negative breast cancer that African American women experience. While further work is needed, these data do suggest that differences in risk factor distributions may be of equal or greater relevance than biological or genetic differences with respect to explaining the greater burden of triple-negative disease among African Americans.

There is inconsistency in the literature on the relationship between parity and risk of different breast cancer subtypes. Our observation that parous women have reduced risks of both ER+ and triple-negative breast cancer is consistent with the only two published studies presenting analyses restricted to women <45 years of age that have evaluated this relationship [7, 8]. In contrast, two studies, one including similar numbers of premenopausal and postmenopausal women and one of exclusively postmenopausal women, found that while parity was associated with a reduced risk of luminal A/ER+ breast cancer it was associated with an increased risk of triple-negative breast cancer [9, 11]. So while parity has been consistently associated with a reduced risk of ER+ breast cancer, its relationship to triple-negative breast cancer remains uncertain though it may vary according to menopausal status.

The primary limitation of this study relates to its case–control design. Recall bias is always a theoretical concern; however, this study was restricted to younger women and focused on noteworthy life events regarding timing of full-term pregnancies and breastfeeding that should be recalled similarly and accurately by both cases and controls. Selection bias is also a concern. Our response rates for cases and controls were reasonable, though response rates were higher among cases compared to controls. Further counteracting both potential recall and selection biases and enhancing the validity of our findings are the statistically significant results from our case–case comparisons as response rates did not vary by case type and recall of these exposures is unlikely to vary according to breast cancer subtype. Another limitation is that we lacked data on *BRCA1* and *BRCA2* mutation status. However, our results of first-degree family history were neither a confounder nor an effect modifier and the proportion of young breast cancer patients who carry *BRCA1* or *BRCA2* mutations is relatively low, ranging 1.3–6.8 and 2.0–4.0 %, respectively, based on the results of prior population-based studies [30–33].

There is a small but growing body of literature characterizing differences in the relationships between established breast cancer risk factors and risk of different molecular subtypes of breast cancer. The risk factor that has most consistently emerged thus far as being differentially associated with risk according to subtype is breastfeeding, as now five out of six studies have shown that breastfeeding is more strongly associated with a reduced risk of triple-negative/basal-like breast cancer than it is with ER+/luminal A breast cancer. Adding to the potential validity and generalizability of this relationship is the fact that it has been observed across studies conducted in different regions of the United States and that have included disparate age ranges. With respect to other reproductive factors, the picture is less clear, but variations by age, menopausal status, and demographic factors may also be highly relevant. The studies published thus far have each included relatively few triple-negative/basal-like cases (ranging from 78 to 335 cases) limiting statistical power for stratified analyses. Given the comparatively poor prognoses of triple-negative/basal-like breast cancers compared to ER+/luminal breast cancers, additional studies further characterizing their etiologic differences are needed with the hope that they can inform novel subtype-specific prevention strategies. Additional work is also needed to characterize factors that influence the risk of HER2-overexpressing breast cancer as this somewhat rarer subtype also carries a relatively poor prognosis. This study is consistent with other studies in finding that no reproductive factor appears to be related either positively or negatively to risk of HER2-overexpressing disease.

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